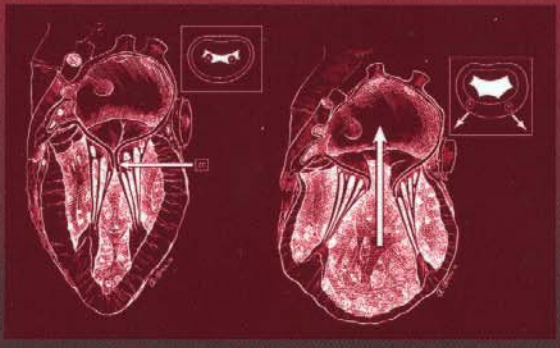
Surgical Management of Congestive Heart Failure

Edited by

James C. Fang, MD
Gregory S. Couper, MD



HUMANA PRESS

Surgical Management of Congestive Heart Failure

CONTEMPORARY CARDIOLOGY

CHRISTOPHER P. CANNON, MD

SERIES EDITOR

Surgical Management of Congestive Heart Failure, edited by *James C. Fang, MD and Gregory S. Couper, MD, 2005*

Interventional Cardiology: Percutaneous Noncoronary Intervention, edited by *Howard C. Herrmann, MD, 2005*

Principles of Molecular Cardiology, edited by *Marschall S. Runge, MD, and Cam Patterson, MD, 2005*

Heart Disease Diagnosis and Therapy: *A Practical Approach, Second Edition,* edited by *Gabriel M. Khan, MD, FRCP, FRCP (C), FACC, 2005*

Cardiovascular Genomics: *Gene Mining for Pharmacogenomics and Gene Therapy,* edited by *Mohan K. Raizada, PhD, Julian F. R. Paton, PhD, Michael J. Katovich, PhD, and Sergey Kasparov, MD, PhD, 2005*

Cardiopulmonary Resuscitation, edited by *Joseph P. Ornato, MD, FACP, FACC, FACEP and Mary Ann Peberdy, MD, FACC, 2005*

CT of the Heart: Principles and Applications, edited by *U. Joseph Schoepf, MD, 2005*

Cardiac Transplantation: The Columbia University Medical Center/New York-Presbyterian Hospital Manual, edited by *Niloo M. Edwards, MD, Jonathan M. Chen, MD, and Pamela A. Mazzeo, 2004*

Heart Disease and Erectile Dysfunction, edited by *Robert A. Kloner, MD, PhD, 2004*

Coronary Disease in Women: *Evidence-Based Diagnosis and Treatment,* edited by *Leslee J. Shaw, PhD and Rita F. Redberg, MD, FACC, 2004*

Complementary and Alternate Cardiovascular Medicine, edited by *Richard A. Stein, MD and Mehmet C. Oz, MD, 2004*

Nuclear Cardiology, The Basics: *How to Set Up and Maintain a Laboratory,* by *Frans J. Th. Wackers, MD, PhD, Wendy Bruni, BS, CNMT, and Barry L. Zaret, MD, 2004*

Minimally Invasive Cardiac Surgery, Second Edition, edited by *Daniel J. Goldstein, MD, and Mehmet C. Oz, MD 2004*

Cardiovascular Health Care Economics, edited by *William S. Weintraub, MD, 2003*

Platelet Glycoprotein IIb/IIIa Inhibitors in Cardiovascular Disease, Second Edition, edited by *A. Michael Lincoff, MD, 2003*

Heart Failure: *A Clinician's Guide to Ambulatory Diagnosis and Treatment,* edited by *Mariell L. Jessup, MD and Evan Loh, MD, 2003*

Management of Acute Coronary Syndromes, Second Edition, edited by *Christopher P. Cannon, MD 2003*

Aging, Heart Disease, and Its Management: *Facts and Controversies,* edited by *Niloo M. Edwards, MD, Mathew S. Maurer, MD, and Rachel B. Wellner, MPH, 2003*

Peripheral Arterial Disease: *Diagnosis and Treatment,* edited by *Jay D. Coffman, MD and Robert T. Eberhardt, MD, 2003*

Surgical Management of Congestive Heart Failure

Edited by

James C. Fang, MD
Gregory S. Couper, MD

Brigham and Women's Hospital, Harvard Medical School, Boston, MA

Foreword by

Lynne W. Stevenson, MD

Brigham and Women's Hospital, Harvard Medical School, Boston, MA

Humana Press
Totowa, New Jersey

999 Riverview Drive, Suite 208
Totowa, New Jersey 07512

humanapress.com

For additional copies, pricing for bulk purchases, and/or information about other Humana titles, contact Humana at the above address or at any of the following numbers: Tel.: 973-256-1699; Fax: 973-256-8341, E-mail: humana@humanapr.com; or visit our Website: www.humanapress.com

Production Editor: Robin B. Weisberg
Cover Illustration: From Fig. 2 in Chapter 4, "Mitral Valve Surgery With Severe Left Ventricular Dysfunction," by Vinay Badhwar and Steven F. Bolling.
Cover design by Patricia F. Cleary

This publication is printed on acid-free paper. ∞
ANSI Z39.48-1984 (American National Standards Institute) Permanence of Paper for Printed Library Materials.

Printed in the United States of America. 10 9 8 7 6 5 4 3 2 1

eISBN 1-59259-842-0

Library of Congress Cataloging-in-Publication Data

Surgical management of congestive heart failure / edited by James C. Fang, Gregory S. Couper.
p. ; cm. -- (Contemporary cardiology)
Includes bibliographical references and index.
ISBN 1-58829-034-4 (alk. paper)
1. Heart--Surgery. 2. Congestive heart failure.
[DNLM: 1. Cardiac Surgical Procedures--methods. 2. Heart Failure, Congestive--surgery. WG 169 S9615 2005] I. Fang, James C. II. Couper, Gregory S. III. Sereis: Contemporary cardiology (Totowa, N.J. : Unnumbered)
RD598.S854 2005
616.1'29--dc22

2004004129

Foreword

There are 4 to 5 million people with heart failure in the United States alone. Included in this diagnosis are patients who have decreased left ventricular contractility and ejection fraction but no symptoms, and patients who have "preserved" ejection fraction, even supernormal in hypertrophic cardiomyopathy, in whom an impairment of ventricular filling leads to exercise intolerance and elevated venous pressures. However, the majority of patients currently diagnosed have left ventricular ejection fraction 20–40% and mild to moderate symptoms of heart failure.

Medical Therapy for Heart Failure

For these patients, there have been major advances in pharmacologic therapy since the late 1980s, since the demonstration that vasodilator therapy improves outcome in heart failure. Subsequent trials showed that inhibition of the renin-angiotensin system enzyme bestows additional benefit, decreasing recurrent ischemic events and improving outcomes for patients with diabetes, as well as decreasing the left ventricular dilation, or "remodeling" that characterizes heart failure progression. Even more striking for survival benefit has been the addition of β-adrenergic blocking agents. The complexity of initiation and uptitration of β-blocking agents has highlighted the chasm between the recommended therapeutic regimen and the limited experience and resources available to establish and maintain that regimen in the community. The true impact of the therapies proven in clinical trials has not yet been realized, but may be less than anticipated when those therapies are provided without clinical trial-level surveillance to populations on average 10 years older and with more co-morbidities.

Although inhibition of the renin-angiotensin system and β-receptors of the sympathetic nervous system have provided the cornerstones of our pharmacologic therapy, it is not clear whether more benefit can be derived from further neurohormonal modulation. Trials of central sympatholysis, angiotensin receptor blockers, cytokine inhibitors, and endothelin antagonists may even be deleterious on top of the known therapies. Furthermore, as heart failure progresses, an increasing proportion of patients are unable to tolerate reflex inhibition, first showing intolerance to β-blockers, then to angiotensin-converting enzyme (ACE) inhibitors. Symptoms of con-

gestion can be relieved at most stages of heart failure until close to the end stage, when the cardiorenal syndrome often becomes limiting before there is other evidence of refractory low output states. Oral inotropic therapy to improve cardiac output was abandoned owing to a small but significant increase in mortality. Paradoxically, intravenous inotropic therapy is increasingly used to provide palliation at the end stage of heart failure. Expected survival is less than 50% at 6 months for patients who are dependent on chronic inotropic therapy.

Surgery for Heart Failure: Repair, Remodeling, and Replacement

Since medical therapy for heart failure has delayed but not prevented disease progression, there is increasing interest in more definitive therapy. Many previous surgical approaches were tried and subsequently abandoned, whereas transplantation became an accepted therapy without any controlled experiment. More recently, the template of the double-blind randomized clinical trial that has validated drug therapies has been superimposed with some awkwardness on investigation of procedures and devices. After initial feasibility has been shown, systematic performance and documentation of outcomes with a new therapy without randomization can provide conclusive evidence of lack of sufficient efficacy to merit a controlled trial, as with the commendable experience of the Cleveland Clinic with the left ventriculectomy procedure. For cardiomyo-plasty, the limited functional improvement observed was not sufficient to maintain enthusiasm for the courageously planned randomized trial, subsequently plagued with slow enrollment. For benefit, it remains possible that early experience carefully recorded with a new procedure could be sufficiently positive to constitute a "breakthrough" development, after which equipoise could not then be established for a randomized trial. More often, there are encouraging results that warrant further investigation with a prospective control arm. It should be recognized, however, that inability to provide an ethical double blind limits both patient enrollment and the interpretation of results for such trials. These limitations and the inherently greater cost and risk of surgical procedures mandate a higher bar of obvious benefit before acceptance of a new surgical procedure for heart failure.

Inherent in consideration of surgery for heart failure is the recognition that some patients are more likely to benefit than others. In this respect, the surgical approaches are already advanced beyond the medical approaches, which have been hindered by the assumption of homogeneity of the heart failure populations. In *Surgical Management of*

Congestive Heart Failure, multiple different procedures for heart failure are presented, together with careful description of the candidate populations for each. For procedures such as revascularization and valve repair or replacement, the benefit has been well established for some populations. The challenge here is to push the envelope to identify when such procedures may offer meaningful benefit for patients once considered to be "too late" in the stage of their disease. Other procedures under active investigation for advanced stages of disease, such as ventricular reconstruction or external constraint devices, may eventually be introduced earlier in the course of disease to limit disease progression. At the end of the road, the goal of effective cardiac replacement looms large. Cardiac transplantation at this time remains the greatest success story for truly end-stage disease, with more than 50,000 patients now transplanted worldwide. The breadth of its impact far exceeds the actual recipients, however, because the lure of cardiac transplantation called attention to the newly defined population of advanced heart failure, whereas the restricted donor supply inspired the development of better heart failure management and of new strategies for replacement, such as mechanical cardiac devices and xenotransplantation.

The Right Therapy for Each Patient

Heart failure has legitimately moved into a field of its own. After a barren period in the mid-1990s when medical therapy was ACE inhibitors and surgical therapy was transplantation, better understanding of the physiology of heart failure has yielded a cornucopia of potential options. At the same time, survival alone is no longer the only count of success. The implanted defibrillators have decreased the cloud of sudden death, and biventricular pacing has shown larger improvement in symptoms than seen with neurohormonal therapy, but issues of functional capacity and quality of life are increasingly relevant. Heart failure is not one disease, and the heart failure patient is not a composite of averages. The individual patient has developed heart failure uniquely through injury and adaptation, suffers the limitations of heart failure uniquely, and seeks therapy with unique expectations regarding length and quality of survival, tempered by risk-taking preferences that can be honored but not predicted. This book seeks to encompass both the large studies and the vital experiences. Improved outcome in heart failure must be calibrated and tracked for populations, but will ultimately be provided by individual physicians for individual patients.

Lynne W. Stevenson, MD

PREFACE

Congestive heart failure (CHF) is one of the leading causes of hospitalization in the United States and is associated with significant morbidity and mortality. Pharmacologic therapies have had a significant impact on the disease, but have been primarily limited to angiotensin-converting enzyme inhibitors and β-blockers. Inotropic agents and other vasodilators are available and effective for the acute management of heart failure, but are associated with poor long-term outcomes. Until recently, few surgical therapies were available for severe end-stage CHF short of cardiac transplantation. With the advent of better surgical techniques and improved pre- and postoperative medical management, traditional surgeries for severe left ventricular dysfunction can now be performed with reasonable success. Furthermore, the advances in mechanical circulatory support devices have made the concept of bridging to transplant and bridging to recovery a reality. Even permanent mechanical circulatory support is now available. Finally, other novel approaches using various devices are constantly being investigated.

The surgical options for the end-stage heart failure patient are now numerous and effective. The aim of *Surgical Management of Congestive Heart Failure* is to bring together the latest clinical, scientific, and investigational surgical approaches to improve the lives of this challenging group of patients. The book is written by leading authorities in both cardiovascular surgery and cardiology as the management of these patients has necessitated an increasingly multidisciplinary approach. We hope that the readers will get a broad yet in-depth understanding of the options that can be offered to their patients and what the future holds for the surgical and device-oriented treatment of heart failure.

James C. Fang, *MD*
Gregory S. Couper, *MD*

CONTENTS

CONTRIBUTORS

MICHAEL A. ACKER, MD, *Division of Cardiothoracic Surgery, University of Pennsylvania School of Medicine, Philadelphia, PA*

FRANCISCO A. ARABIA, MD, *Department of Surgery, Sarver Heart Center, University of Arizona College of Medicine, Tucson, AZ*

VINAY BADHWAR, MD, *Section of Cardiac Surgery, University of Michigan, Ann Arbor, MI*

STEVEN F. BOLLING, MD, *Section of Cardiac Surgery, University of Michigan, Ann Arbor, MI*

JOHN G. BYRNE, MD, *Division of Cardiac Surgery, Department of Surgery, Brigham and Women's Hospital, Harvard Medical School, Boston, MA*

BLASÉ A. CARABELLO, MD, FACC, *Department of Medicine, Baylor College of Medicine, Veterans Affairs Medical Center, Houston, TX*

JACK G. COPELAND, MD, *Section of Cardiovascular and Thoracic Surgery, Department of Surgery, Sarver Heart Center, University of Arizona College of Medicine, Tucson, AZ*

GREGORY A. COUPER, MD, *Division of Cardiac Surgery, Department of Surgery, Brigham and Women's Hospital, Harvard Medical School, Boston, MA*

TERESA DE MARCO, MD, *Division of Cardiology, University of California at San Francisco, San Francisco, CA*

PAUL L. DIGIORGI, MD, *Division of Cardiothoracic Surgery, Department of Surgery, Columbia University College of Physicians and Surgeons, New York, NY*

VINCENT DOR, MD, *Cardio Thoracic Center of Monaco, Monaco*

JAMES C. FANG, MD, *Cardiovascular Division, Brigham and Women's Hospital, Harvard Medical School, Boston, MA*

JAMES P. GREELISH, MD, *Department of Cardiac Surgery, Vanderbilt University Medical Center, Nashville, TN*

RUEDIGER HOERBELT, MD, *Division of Cardiac Surgery and Transplantation Biology Research Center, Department of Surgery, Massachusetts General Hospital, Harvard Medical School, Boston, MA*

KATHERINE J. HOERCHER, RN, *George M. and Linda H. Kaufman Center for Heart Failure, Cleveland Clinic, Cleveland, OH*

JOHN ADAMS JARCHO, MD, *Cardiovascular Division, Department of Medicine, Brigham and Women's Hospital, Harvard Medicine School, Boston; and UpToDate Inc., Wellesley, MA*

UDAY N. KUMAR, MD, *Department of Medicine, University of California, San Francisco, CA*

RICHARD LEE, MD, MBA, *Division of Cardiothoracic Surgery, Department of Surgery, St. Louis University School of Medicine, St. Louis, MO*

PATRICK M. MCCARTHY, MD, *Cardiovascular Institute, Northwestern University Medical School, Chicago, IL*

JOREN C. MADSEN, MD, DPhil, *Division of Cardiac Surgery and Transplantation Biology Research Center, Department of Surgery, Massachusetts General Hospital, Harvard Medical School, Boston, MA*

YOSHIFUMI NAKA, MD, PhD, *Division of Cardiothoracic Surgery, Department of Surgery, Columbia University College of Physicians and Surgeons, New York, NY*

MEHMET C. OZ, MD, *Division of Cardiothoracic Surgery, Department of Surgery, Columbia University College of Physicians and Surgeons, New York, NY*

BRADLEY J. PHILLIPS, MD, *Division of Cardiac Surgery, Brigham and Women's Hospital, Harvard Medical School, Boston, MA*

MOHAMMED A. QUADER, MD, *Division of Cardiothoracic Surgery, Department of Surgery, Nebraska Heart Institute, Lincoln, NE*

HARRY RAKOWSKI, MD, *Division of Cardiovascular Surgery, University of Toronto, Toronto, Ontario, Canada*

ANTHONY C. RALPH-EDWARDS, MD, *Division of Cardiovascular Surgery, University of Toronto, Toronto, Ontario, Canada*

LESLIE A. SAXON, MD, *Division of Cardiovascular Medicine, Department of Medicine, Keck School of Medicine, University of Southern California, Los Angeles, CA*

LEONARD SCHWARTZ, MD, *Division of Cardiovascular Surgery, University of Toronto, Toronto, Ontario, Canada*

RICHARD G. SMITH, MSEE, CEE, *Marshall Foundation Artificial Heart Program, University of Arizona Sarver Heart Center, Tucson, AZ*

LYNNE W. STEVENSON, MD, *Cardiovascular Division, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA*

JEFFREY J. TEUTEBERG, MD, *Cardiovascular Division, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA*

E. Douglas Wigle, md, *Division of Cardiovascular Surgery, Department of Medicine, University of Toronto, Toronto, Ontario, Canada*

William G. Williams, md, *Division of Cardiovascular Surgery, Department of Medicine, The Hospital for Sick Children, University of Toronto, Toronto, Ontario, Canada*

1 Recent Advances in Cardiac Allotransplantation

John Adams Jarcho, MD
and James C. Fang, MD

CONTENTS

INTRODUCTION

Heart transplantation has become a routine approach to the management of severe cardiac failure *(1)*. Indeed, given the excellent survival statistics for heart transplant recipients, heart transplant outcomes are now an important standard against which the success of other therapies is routinely measured. There are more than 200 institutions currently performing heart transplants worldwide, two-thirds of them in the United States. In 1995, there were 4049 heart transplants reported to the International Society for Heart and Lung Transplantation (ISHLT);

From: *Contemporary Cardiology: Surgical Management of Congestive Heart Failure*
Edited by: J. C. Fang and G. S. Couper © Humana Press Inc., Totowa, NJ

2359 of these took place in the United States. The same figures for the year 2000 were 3175 and 2197, respectively *(2)*. It is clear that more patients would benefit from heart transplantation if more donor organs were available; in 2000, there were 3452 new registrations on US waiting lists, according to data from the United Network for Organ Sharing (UNOS). In that same year, the median waiting time for a heart transplant in the United States, considering all patients regardless of waiting list priority, was 346 days *(3)*.

Over the last decade, the field of heart transplantation has evolved in response to many changes, including the following:

- Rapid improvements in heart failure management
- Increasing availability of mechanical ventricular assist devices (VADs)
- Better appreciation of the risk factors influencing transplant outcome
- Shortage of suitable donor organs
- Increasingly competitive behavior between transplant centers
- Advances in the science of immunology, with the development of new approaches to immunosuppression
- Improved management of posttransplant complications, including especially posttransplant coronary artery disease (CAD)
- Increasing number of long-lived heart transplant recipients

This chapter focuses on recent developments in cardiac transplantation and relates them to current clinical practice.

THE HEART TRANSPLANT CANDIDATE

Heart transplantation is generally considered the choice of last resort in heart failure management, which means that all other feasible approaches, whether medical or surgical, should have been exhausted. Furthermore, the standard of practice has required the demonstration of a survival advantage—that is, the expectation that a heart transplant recipient will benefit, not only by the resolution of symptoms, but also by an improvement in life expectancy. This strict standard has grown harder to meet as the medical management of congestive heart failure has improved.

Data from the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS) trial, published in 1987, showed that patients with New York Heart Association class III to IV heart failure had an anticipated 1-year survival of less than 50% without angiotensin-converting enzyme (ACE) inhibitor therapy *(4)*. A decade and a half later, in the COPERNICUS trial, a similar population of patients achieved a 1-year survival of 89% with ACE inhibitors and β-blockade

(5). This prognosis is comparable to that of heart transplant recipients; in a review from Stanford University, patients transplanted between 1987 and 1998 had a 1-year survival of 85% *(6)*.

Thus, it has become progressively more important to define the survival of patients with heart failure precisely. Although many variables influence prognosis, the single variable most frequently used to estimate prognosis in heart transplant candidates is the peak oxygen uptake with exercise. In a study that did much to establish this approach, Mancini et al. *(7)* performed exercise tests on 114 patients with advanced heart failure. Those with a peak oxygen uptake less than or equal to 14 mL/kg/min had a survival rate of 47% at 1 year, suggesting that such patients would derive a survival benefit from heart transplantation. It was on the basis of this and similar studies that the American College of Cardiology's 24th Bethesda Conference recommended the use of a peak oxygen uptake of 14 mL/kg/min as a threshold in selecting transplant candidates *(8)*.

However, the results of a single test are an inadequate indication for heart transplantation because no one measurement can be expected to capture all of the individual variability in prognosis. In practice, a combination of test data and clinician judgment are typically used to evaluate potential recipients. Efforts have been made to derive a multivariate risk score, such as the Heart Failure Survival Score *(9)*, that would permit a more accurate prediction of survival in advanced heart failure and thus improve the accuracy of candidate selection. Some centers have used the Heart Failure Survival Score as a criterion in selecting patients for transplant. An important limitation to such scoring systems is that they were developed and validated in the era before β-blockers were shown to be beneficial in patients with heart failure, and therefore may not reflect the significant impact this medical therapy has had on survival.

Heart transplant candidates must also be free of other medical problems that could be expected to jeopardize the success of the transplant or reduce the likelihood of a satisfactory long-term outcome *(10)*. The contraindications to transplantation, unlike the indications, are based primarily on a combination of empiricism and clinical experience (*see* Table 1). Absolute contraindications are those considered sufficient to exclude transplantation; relative contraindications are evaluated on a case-by-case basis.

The application of these contraindications, and the "unacceptable" values for measurements such as pulmonary vascular resistance and creatinine clearance, vary somewhat from institution to institution. New data have influenced judgment about many of these clinical issues:

Table 1
Contraindications to Heart Transplantation

Absolute contraindications
Current malignancy other than skin cancer
Hepatatis B or C infection with active hepatitis
AIDS (acquired immunodeficiency syndrome)
Fixed pulmonary hypertension
Relative contraindications
Age over 65 years
Diabetes mellitus with end-organ damage
Significant renal, liver, or lung disease
Severe peripheral or carotid vascular disease or abdominal aortic aneurysm
HIV infection
Hepatitis B or C infection
Previously treated malignancy other than skin cancer
Reversible pulmonary hypertension
Recent pulmonary embolus
Active peptic ulcer disease
Infiltrative myocardial disease
Collagen vascular disease
Major psychiatric disorder
History of persistent noncompliance with medical care
Drug, alcohol, or tobacco addiction

- The age limit for heart transplantation, once as low as 55 years, has continued to extend upward. In one report comparing 15 patients aged 70 years and older with 98 younger patients, all undergoing transplantation between 1994 and 1999, there were no significant differences between the two groups in 1-year or 4-year survival *(11)*.
- Although diabetes with end-organ damage is considered a contraindication to transplantation, selected patients may have outcomes as good as those without the disease. In an analysis of 374 cardiac transplant recipients, 76 with diabetes, the 1-year and 3-year survival rates of the two groups were comparable *(12)*.
- Pulmonary hypertension has been demonstrated to be a risk factor for early posttransplant mortality in data from the ISHLT *(2)* and from the Cardiac Transplant Research Database (CTRD) *(13)*. However, there is a significant difference between *reversible* pulmonary hypertension (i.e., pulmonary hypertension that can be reduced with acute vasodilator therapy) and *fixed* or *irreversible* pulmonary hypertension in this regard. In one study of 293 cardiac transplant candidates, those with a pulmonary vascular resistance (PVR) less than 2.5 Wood units

(200 dynes-s/cm^5) at baseline had a 3-month mortality rate of 6.9% *(14)*. Those who had an elevated PVR at baseline that could be reduced below 2.5 Wood units using nitroprusside had a 3-month mortality of only 3.8%; those with a fixed elevation in PVR had a 3-month mortality of 40.6%.

Although fixed pulmonary hypertension is a contraindication to transplantation, the evolution of newer approaches to reduce PVR has made this criterion somewhat more flexible. Continuous intravenous infusion of a vasodilator such as dobutamine *(15)*, milrinone *(16)*, prostaglandin E1 *(17)*, or prostacyclin *(16)* during the weeks or months prior to transplant may reduce PVR significantly. For transplant candidates with persistent mild-to-moderate pulmonary hypertension, the decision is often made to accept only a heart from a donor who weighs more than the recipient; larger hearts are less likely to develop right ventricular failure in response to elevated PVR *(18)*. The implantation of a VAD to reduce an elevated PVR has been reported *(19,20)*, although this approach is not typically employed in the absence of other indications for VAD support. Additional management strategies for elevated PVR in the posttransplant setting are discussed in another section (*see* The Immediate Posttransplant Course).

- Patients with a history of malignancy may be appropriate candidates for transplantation if they have been successfully treated and if enough time has passed to have a reasonable certainty of cure. In the reported experience of two large transplant centers, 31 of 1388 patients (2%) had a history of malignancy *(21,22)*. Of these 31 patients, 4 had recurrence of the original malignancy after transplantation. The recurrent cancers included a uterine leimyosarcoma that had previously required treatment for distant metastases, a malignant melanoma (which was presumably incurable), an adenocarcinoma of the bladder that was not actually resected until after transplantation, and a renal hypernephroma resected only 3 months before transplantation. These data suggest that recurrent malignancy tends to occur primarily in patients with metastatic or untreatable disease or in those treated within a short time of the transplant.
- The hepatitis B and hepatitis C viruses are of particular concern in cardiac transplantation because they can produce chronic infection, liver disease, and cirrhosis. In a study using data from the Joint ISHLT/UNOS Thoracic Registry, 30 patients were identified who were known to have a positive serologic test for hepatitis B surface antigen (HBsAg) prior to transplant *(23)*. Of these, 11 developed active hepatitis or cirrhosis, and 5 died of hepatitis B. The authors suggested caution in accepting HBsAg-positive heart transplant candidates. However, a study of heart transplant recipients in Taiwan, where hepatitis B is endemic, found that lamivudine was effective in controlling hepatitis B

virus reactivation in six of seven patients, suggesting that newer antiviral agents may make heart transplantation in HBsAg-positive patients feasible *(24)*. Similar improvements are evolving in the management of hepatitis C *(25)*.

- Human immunodeficiency virus (HIV) infection has been regarded as an absolute contraindication to organ transplantation because of the expectation that the immunological consequences would be unpredictable and likely fatal. However, limited experience has demonstrated that, in the era of highly active antiretroviral drug therapy, organ transplantation is feasible in HIV-positive patients *(26,27)*. The experience with this approach is still too limited to make any firm statements about the anticipated outcome for such patients, however.

Heart transplant candidates must also be evaluated for evidence of immune sensitization against non-self tissue types. Human leukocyte antigen (HLA) tissue types are determined by cell surface molecules that are highly heterogeneous; exposure to non-self HLA molecules typically produces a vigorous immune response *(28)*. Such exposure can occur as a result of blood product transfusions or, for women, exposure to nonidentical fetal HLA molecules during pregnancy. Anti-HLA sensitization is of concern in transplantation because it can cause an aggressive immune response against the transplanted organ, termed *hyperacute rejection*, which can destroy the organ and potentially cause the death of the patient *(29,30)*. Evaluation for anti-HLA sensitization typically involves testing of the transplant candidate's serum for the presence of anti-HLA antibodies by any one of several methods, including a complement-dependent cytotoxicity assay, an enzyme-linked immunosorbent assay, or flow cytometry *(31)*. These tests all result in a quantitative measurement called the percent reactive antibody.

If the PRA is elevated, donor-specific crossmatching (testing of the recipient's serum for antibodies against donor tissue) is generally performed. Although crossmatching has typically been performed using a complement-dependent cytotoxicity assay, more sensitive flow cytometric crossmatching has been shown to correlate with clinical outcomes after transplantation *(32–34)*.

The advent of VAD technology has complicated the problem of anti-HLA sensitization. Patients supported with a VAD have a significantly increased likelihood of developing anti-HLA sensitization; some series suggested that this occurs in one-third to two-thirds of VAD recipients *(35,36)*. Women and recipients of multiple blood transfusions are at greater risk of sensitization, just as is seen among transplant candidates without VADs *(37)*. The mechanism for this increase in sensitization in VAD recipients appears to be T-cell activation as a result of contact

between circulating blood elements and the material components of the device itself, leading to B-cell stimulation and increased production of immunoglobulins by existing B-cell clones *(38)*. Hence, the device "turns on" latent anti-HLA sensitization.

The increase in elevated PRA results seen in VAD patients has led to the development of a number of approaches to decrease anti-HLA sensitization. Efforts are routinely made to limit blood product use as much as possible and to use leukocyte-depleted blood for transfusion, although these approaches do not prevent sensitization completely *(39)*. More aggressive strategies for decreasing sensitization have included the use of plasmapheresis to remove bulk immunoglobulins *(40,41)*, immunoadsorption columns specifically designed to remove anti-HLA antibodies *(42,43)*, the administration of exogenous intravenous immunoglobulin to inhibit native antibody production and function *(44,45)*, and the use of chemotherapeutic agents (typically cyclophosphamide) *(46)* to inhibit antibody production. Reports of the use of anti-CD20 monoclonal antibody (rituximab) for treatment of "humoral rejection" have suggested that this agent might also be beneficial in decreasing anti-HLA sensitization *(47,48)*.

THE HEART TRANSPLANT WAITING LIST

In the United States, patients who are accepted as suitable candidates for heart transplantation are registered with UNOS and are placed on the candidate waiting list. At the time of listing, each patient is assigned one of three priority status codes based on acuity of illness (*see* Table 2). The rationale for this status system is the expectation that it ranks patients fairly according to urgency; status 1A patients are presumably at a higher risk of death in the near term than status 1B or status 2 patients and are thus entitled to priority for the next available donated heart *(49)*. Additional policies intended to help ensure fair organ allocation include

- The requirement that the transplanting institution provide clinical information to justify all status 1A listings
- A time limit on all status 1A listings (in most cases, 14 days), with automatic downgrading to status 1B unless the transplanting center provides new justification to extend the listing
- A regional review board for each UNOS-defined geographic region of the United States, appointed to review all clinical justification information and approve or deny status 1A listings; the decisions of the regional review board may be appealed to the national Thoracic Organ Committee of UNOS

Table 2
Status Priorities for Heart Transplantation

1A. A patient listed as status 1A is admitted to the listing transplant center hospital and has at least one of the following devices or therapies in place:
  (a) Mechanical circulatory support for acute hemodynamic decompensation that includes at least one of the following:
    (i) Left and/or right VAD implanted for a maximum of 30 days at any point after being implanted
    (ii) Total artificial heart
    (iii) Intraaortic balloon pump
    (iv) Extracorporeal membrane oxygenator
  (b) Mechanical circulatory support with objective medical evidence of significant device-related complications, such as thromboembolism, device infection, mechanical failure, and/or life-threatening ventricular arrhythmias.
  (c) Mechanical ventilation.
  (d) Continuous infusion of a single high-dose intravenous inotrope (e.g., dobutamine ≥ 7.5 μg/kg/min, or milrinone ≥ 0.50 μg/kg/min), or multiple intravenous inotropes, in addition to continuous hemodynamic monitoring of left ventricular filling pressures.

1B. A patient listed as status 1B has at least one of the following devices or therapies in place:
  (a) Left and/or right VAD implanted (beyond the 30 days of status 1A allotted to such patients)
  (b) Continuous infusion of intravenous inotropes

2. A patient who does not meet the criteria for status 1A or 1B is listed as status 2.

- A provision for exceptional cases in which patients with highly urgent need who do not meet formal status criteria may be granted a status 1A or 1B listing on approval of the regional review board

Despite the considerable effort devoted to creating and enforcing these policies, it is evident that unresolved inequities persist in the allocation system for heart transplantation. In a study conducted by UNOS in 1999, data on heart transplants taking place between 1994 and 1996 were analyzed separately for each of the 11 geographical UNOS regions. The number of patients placed on the waiting list during that interval in the different UNOS regions ranged from 11.5 to 33 per million population; the number of transplants varied from 5.3 to 10.7 per million *(50)*. With such disparities from region to region, it is not

surprising to find that the wait for a donor organ across the country varies widely. During 2000 and 2001, the median waiting time for status 1A candidates varied from 25 days in Region 1 (New England) to 67 days in Region 7 (the northern Midwest). During the same period, the median waiting time for status 2 candidates varied from 248 days in Region 4 (Texas and Oklahoma) to 945 days in Region 9 (New York) *(51)*.

Disparities encountered from region to region of the country may be explained as arising from differences in organ procurement rates, because most hearts are transplanted locally within the relatively limited geographic area served by a single organ bank or organ procurement organization (OPO). However, inequalities have also been demonstrated among transplanting institutions served by the same OPO. An analysis of heart transplants performed within the Delaware Valley OPO (now called the Gift of Life Donor Program) reviewed 662 transplants that were performed between 1992 and 1995 (before status 1 had been separated into status 1A and 1B). Significant differences in waiting times and mortality rates were found among the four institutions performing heart transplants in the OPO service area (Hahnemann University Hospital, Hershey Medical Center, Temple University Hospital, and Hospital of the University of Pennsylvania) *(52)*. The median waiting time for status 1 patients varied by institution from 18 to 42 days, and the mortality rate on the waiting list for status 1 patients varied from 9 to 25%. The likelihood that a status 1 patient would be transplanted within 30 days varied from 17 to 53%.

These disparities in waiting time and mortality rates within a local organ allocation unit raise the concern that differences in institutional clinical practice may be significant enough to alter a patient's likelihood of undergoing a heart transplant or of dying while waiting. Clinical management variables that could contribute to the observed disparities include

- How long and how vigorously medical alternatives are pursued before the decision is made to list a patient for transplant
- Whether exclusion criteria are applied strictly or loosely
- Which approach to therapy is taken while the patient is waiting, including the choice of medications, the doses, and the clinical follow-up
- How ill the patient must be before the decision is made to make management changes that result in the patient's advancing to a higher status
- How often and how readily the clinicians at an institution resort to the use of mechanical cardiac support

In many cases, these management decisions have no right or wrong answers, and experts may disagree about the best course of action in a given clinical situation. Certainly, such decisions could not be successfully policed or regulated without impeding the flexibility that is critical to good medical care. Unfortunately, such differences in practice do have a direct influence on the likelihood that a patient will survive to undergo a heart transplant. The public availability of institutional statistics (on the UNOS Internet website, for example) makes it likely that patients will take these data into account in making their own decisions about where to seek treatment for advanced heart disease.

An additional strategy to increase donor organ availability is the development of an "alternate" waiting list that matches less-ideal transplant candidates with less-optimal organs. The largest experience with an alternate recipient waiting list is that of the University of California at Los Angeles *(53)*. In a report of 62 patients transplanted from the alternate list, the survival rate at 90 days posttransplant was 82% (compared with 91% for 401 contemporaneous transplants from the standard list). After 90 days, the death rates per 1000 patient-months were 4.3 for the alternate list and 3.6 for the standard list. The authors concluded that the satisfactory long-term survival of patients transplanted from the alternate list supports the use of this approach, although it is not clear whether the data would not also support the use of a single waiting list with broader acceptance criteria for both donors and recipients.

THE CARDIAC DONOR

In the fields of kidney, lung, and even liver transplantation, the shortage of donor organs has to some extent been mitigated by the use of living organ donors. In heart transplantation alone, this approach is not a possibility; all cardiac donors are cadaveric donors who have suffered brain death but maintain cardiopulmonary function. In 2000 and 2001, the cause of brain death for most cadaveric donors was either a cerebrovascular event (43%) or head trauma (42%), with the remainder mostly caused by cerebral anoxia or central nervous system tumors *(54)*.

Organ transplantation from brain-dead donors is complicated by the fact that physiological stability is not maintained after brain death. Initially, the increase in intracranial pressure that often accompanies brain death (because of cerebral edema and herniation) causes an abrupt increase in catecholamine release, with blood levels increasing 10-fold over baseline values. This catecholamine surge is accompanied by a

sudden rise in systolic and diastolic blood pressure; in one animal model, the mean systolic blood pressure rose from 125 to 402 mmHg during this phase *(55)*. The heart rate often slows initially (the "Cushing reflex"), but then accelerates; the baseline heart rate may double. The severity of the hemodynamic and neurohormonal changes appears to be influenced by how rapidly intracranial pressure rises *(56)*.

The sudden catecholamine release that occurs with brain death causes ischemic injury to the myocardium. Histologically, contraction band necrosis and focal myocyte necrosis are seen, with neutrophil infiltration and subendocardial hemorrhage. Myocardial lactate production increases, and a significant decrease in adenosine triphosphate has been demonstrated by nuclear magnetic resonance spectroscopy *(57)*. β-Adrenergic receptors are decoupled from adenylyl cyclase, and contractility is impaired *(58)*.

Brain death also causes injury to the coronary vascular endothelium *(59)*. Endothelium-dependent vasodilation is impaired *(60)*, and there is an increase in the cell-surface expression of adhesion molecules and HLA antigens *(61)*. As a result, the allograft is more immunogenic; in animal studies, hearts from brain-dead donors suffered more rapid rejection than hearts obtained without the induction of brain death *(62)*.

These effects of brain death may have clinical consequences for the allograft recipient, depending on how severe the catecholamine surge is. One study compared the outcomes when donors had died of an intracranial bleed, typically associated with an abrupt rise in intracranial pressure (group I) with outcomes when donors had died by other means, possibly associated with less-significant catecholamine release (group II). Compared with group II, group I had a higher mortality rate by discharge posttransplant (14 vs 5%) *(63)*.

Once the catecholamine surge accompanying brain death recedes, the loss of central nervous system function results in progressive physiological instability. Respiration by definition ceases and must be supported by artificial ventilation. Blood pressure, having risen acutely during brain death, now declines progressively as a result of decreasing circulating levels of catecholamines *(64)* and vasopressin *(65)*. Diabetes insipidus occurs in about half of cases, also because of the decrease in vasopressin levels; left untreated, diabetes insipidus results in hypernatremia and volume depletion. Declines in other hormone levels, including adrenocorticotropic hormone, cortisol, thyroxine, triiodothyronine, and glucagon, have also been described *(66)*.

Given these physiological events in the setting of brain death, it is evident that the clinical evaluation of a potential cardiac donor is complex (*see* Table 3) *(67)*.

Table 3
Optimal Assessment of the Organ Donor

- The inciting event, including cause of brain death, any information about possible chest trauma, and cardiac arrest with cardiopulmonary resuscitation.
- Past history, focusing on cardiac disease, hypertension, and other coronary risk factors; high-risk behaviors for hepatitis or HIV infection (intravenous drug use, incarceration, etc.); and history of malignancy.
- Clinical course from the inciting event until the present examination, including sequential data regarding vital signs, central venous pressure, cardiac rhythm, and fluid intake and output, as well as medications (especially inotropes and/or pressors).
- Examination for chest trauma, cardiac rubs, murmurs or gallops, peripheral pulses, and perfusion.
- Laboratory data, including blood gases, electrocytes, blood counts, hepatic and renal function, cardiac enzymes, and bacterial cultures.
- Consideration of pulmonary artery catheterization for more complete hemodynamic monitoring.
- An echocardiogram to evaluate cardiac structure and function, including evidence of left ventrical hypertrophy, valvular abnormalities, and global and regional wall motion.
- Cardiac catheterization in patients with risk factors for coronary artery disease.

The ideal donor is young; has no cardiac history; did not require resuscitation; has had stable hemodynamics since brain death, with an optimal volume status and a minimum of inotropes; and has a normal echocardiogram (and angiogram, if necessary). Unfortunately, such donors are rare, and the pressing need for more organs has led to questions about what departures from the "ideal" are acceptable and can be tolerated without endangering the transplant recipient. As with the selection of the acceptable transplant candidate, the identification of the acceptable cardiac donor has varied from institution to institution. A survey from the Association of Organ Procurement Organizations in 1999 found that the "donor yield" for hearts (i.e., the number of hearts procured and transplanted divided by the total number of potential donors in a given OPO) ranged from 19 to 62% *(68)*.

Such statistics clearly indicate the need for defined criteria for donor acceptability. In 2001, a committee of experts at a conference in Crystal

City, Virginia, suggested that the following donor characteristics were compatible with successful heart transplantation *(69)*:

- Age greater than 55 years (the upper end of the acceptable donor age spectrum is uncertain)
- Small donor size relative to the transplant candidate; an adult male donor weighing 70 kg or more is suitable for most recipients
- Hepatitis B or C seropositivity
- Modest cardiac enzyme elevation without left ventricular dysfunction
- Mild left ventricular hypertrophy (wall thickness less than or equal to 13 mm)
- Minor cardiac structural abnormalities, including mild mitral or tricuspid regurgitation, bicuspid aortic valve, secundum atrial septal defect
- In some cases, the presence of mild coronary disease on angiography

Single-institution studies have demonstrated that donors with such relative contraindications ("marginal" donors) can be used successfully with an acceptable posttransplant outcome *(70)*, although an analysis from the CTRD confirmed that the mortality rate for the recipients of hearts from marginal donors is higher *(71)*. Institutional experience is likely to be a critical factor in determining the success of such efforts to expand the donor pool.

One of the most frequently encountered donor problems is distinguishing acceptable from unacceptable donor hemodynamic instability. The Papworth Hospital in Cambridge, UK, was one of the first institutions to examine this issue systemically. They evaluated 150 organ donors on whom hemodynamic data were collected between 1990 and 1993. Of these, 52 (35%) were found to be unacceptable initially because of hypotension, elevated filling pressures, a low left ventricular stroke work index, or a high inotrope requirement. However, with optimal hemodynamic and hormonal management, including optimization of volume status and the judicious use of vasopressin, triiodothyronine, steroids, insulin, and glucose, 44 of the 52 originally unacceptable donors yielded transplantable organs. At follow-up 13 to 48 months later, 37 of the 44 recipients (84%) were alive and well *(72)*. Based on this experience and the comparable experience of a few other institutions, a consensus conference in Crystal City, Virginia, recommended an approach to optimal donor management to improve organ yield (*see* Table 4) *(71)*. It is anticipated that the widespread use of such a protocol would greatly increase the number of cardiac transplants nationally, but this outcome remains to be demonstrated.

Table 4
Recommended Approach to Optimal Donor Management

Conventional management prior to the initial echocardiogram
- a. Adjust volume status (target central venous pressure 6–10 mmHg).
- b. Correct metabolic perturbations, including
  Acidosis (target pH 7.40 to 7.45)
  Hypoxemia (target pO_2 > 80 mm Hg, O_2 saturation > 95%)
  Hypercarbia (target pCO_2 ≥ 30 to 35 mmHg)
- c. Correct anemia (target hematocrit > 30%, hemoglobin > 10 g/dL)
- d. Adjust inotropes to maintain mean arterial pressure ≥ 60 mmHg. Norepinephrine and epinephrine should be tapered off rapidly in favor of dopamine or dobutamine.
- e. Target dopamine < 10 g/kg/min or dobutamine < 10 g/kg/min.

Initial echocardiogram
- a. Rule out structural abnormalities (substantial left ventricular hypertrophy, valvular dysfunction, congenital lesions).
- b. If left ventricular ejection fraction is ≥ 45%, proceed with recovery (consider aggressive management as shown below to optimize cardiac function before recovery), with final evaluation in the operating room.
- c. If left ventricular ejection fraction is < 45%, aggressive management with placement of a pulmonary arterial catheter and hormonal resuscitation is strongly recommended.

Hormonal resuscitation
- a. Triiodothyronine: 4 g bolus, then infusion at 3 g/h.
- b. Arginine vasopressin: 1-U bolus, then infusion at 0.5 to 4 U/h, titrated to a systemic vascular resistance of 800 to 1200 dyne/s/cm^5.
- c. Methylprednisolone: 15-mg/kg bolus.
- d. Insulin: 1 U/h minimum. Titrate to maintain blood sugar 120 to 180 mg/dL.

Aggressive hemodynamic management
- a. Initiated simultaneously with hormonal resuscitation.
- b. Placement of pulmonary artery catheter.
- c. Duration of therapy ≥ 2 h.
- d. Adjustment of fluids, inotropes, and pressors every 15 min based on serial hemodynamic measurements to minimize use of α-agonists and meet the following target (Papworth) criteria:
  Mean arterial pressure > 60 mmHg.
  Central venous pressure 4 to 12 mmHg.
  Pulmonary capillary wedge pressure 8 to 12 mmHg.
  Systemic vascular resistance 800 to 1200 dyne/s/cm^5.
  Cardiac index > 2.4 L/min/m^2.
  Dopamine < 10 g/kg/min or dobutamine < 10 g/kg/min.

Follow-up echocardiogram may be useful to reassess ventricular function, although data are currently limited on this issue.

THE TRANSPLANT OPERATION

The cardioplegia solution that is used to perfuse the heart during donor harvest and to transport the heart from donor to recipient is intended to optimize myocardial preservation and minimize the amount of ischemic injury the heart sustains. Myocardial injury during ex vivo ischemia results from several distinct phenomena, including cellular swelling, extracellular edema, intracellular acidosis, depletion of metabolic substrate, calcium overload, endothelial injury, and reperfusion injury *(73)*. Therefore, most cardioplegia solutions include osmotic agents, buffering agents, antioxidants, a metabolic substrate, and magnesium to retard calcium influx.

Unfortunately, the best composition for cardioplegia is unclear. Two broad categories of cardioplegia solutions have been developed: "intracellular" solutions, with a high potassium concentration and a low sodium concentration, such as the University of Wisconsin, Collins, and Stanford solutions; and "extracellular" solutions, with a low potassium concentration and a high sodium concentration, such as Celsior and the St. Thomas solution.

A survey of heart transplant programs in the United States published in 1997 retrospectively evaluated 9401 heart transplants performed between 1987 and 1992 and concluded that intracellular solutions were superior to extracellular solutions in their effect on mortality at 1 month posttransplant (odds ratio 0.85; $p < 0.05$) *(74)*. However, the survey also found that 167 different solutions were in current use—a number equivalent to the number of heart transplant programs—suggesting that experimental proof of superiority has not been a prerequisite for the use of any given formulation.

It has been proposed that continuous perfusion of the donor heart should be a more effective way of preventing ischemic injury than cold storage alone. This has been confirmed in animal studies, in which viable organ function is markedly prolonged by perfusion techniques *(75–77)*. However, the acceptable results for most cardiac transplant recipients with cold ischemic storage, and the cost and logistical difficulties associated with continuous perfusion systems, have thus far precluded clinical adoption of a continuous perfusion approach.

There are two commonly employed approaches to the implantation of the donor heart. In the first, the standard or Shumway technique, the left and right atria of the donor heart are anastomosed to cuffs of left and right atrium created in the recipient *(78)*. With this technique, the left and right atria of the recipient are divided during

the excision of the native heart, leaving a cuff of atrial tissue on each side. The donor atria are opened posteriorly to create corresponding left and right atrial cuffs.

In the second, the bicaval or Wythenshawe technique, the superior and inferior vena cavae of the recipient are anastomosed to an intact donor right atrium; the left atrial anastomosis is created in the same way as in the standard technique *(79)*. For the bicaval approach, the recipient right atrium is divided to create superior and inferior vena caval cuffs. No incisions are made in the donor right atrium. A third technique, designated "total" orthotopic heart transplantation, involves the anastomosis of left and right pulmonary vein cuffs to a nearly intact left atrium; this approach is used infrequently *(80)*.

Comparative studies have suggested that there are at least two disadvantages to the standard technique that are overcome by the bicaval technique *(81–83)*:

- Significant tricuspid regurgitation may occur after heart transplantation, in part because of distortion of right atrial geometry with the standard technique; this occurs less often with the bicaval approach.
- Sinus node dysfunction may occur with the standard technique because of injury to the sinus node; this is also less common with bicaval transplantation.

These advantages have led to a progressive increase in the use of the bicaval technique. In a worldwide survey of heart transplant programs reported in 1999, the bicaval technique was preferred by 54% of centers, the standard technique by 23%, and the total technique by 6%; the remaining 17% had no consistent preference *(84)*.

THE IMMEDIATE POSTTRANSPLANT COURSE

The immediate postoperative period after heart transplantation is dominated by concern for hemodynamic stability. Early graft failure accounts for the majority of the operative mortality and for 20 to 25% of deaths in the first posttransplant year, a figure that has not changed in the last decade *(85)*. Optimal hemodynamics require good intrinsic function of the right and left ventricles of the allograft, acceptable systemic and pulmonary vascular resistance, and appropriate cardiac filling pressures.

There is a close correlation between total ischemic time and the function of any allograft organ; however, the time constraints are strictest in heart transplantation, with the optimal ischemic time less than 4 hours. In a study of 911 heart transplant recipients from the CTRD, patients

with an ischemic time of less than 4 hours had a 1-month survival of 85%, compared to those with longer ischemic times, who had a 1-month survival of 71% *(86)*. Analyses of data from the ISHLT also demonstrated that ischemic time has a statistically significant, linear relationship to mortality at 1 year posttransplant (odds ratios for ischemic times of 0, 3, 7, and 10 hours are 0.6, 1.0, 2.1, and 3.5, respectively) *(87)*. The impact on survival at 5 years, although still statistically significant, is much less pronounced.

Right ventricular function is possibly of even greater concern than left ventricular function after heart transplantation. Several factors contribute to a significant incidence of right ventricular dysfunction in this setting, including the following:

- Most cardiac transplant recipients have some degree of pulmonary hypertension, as noted in The Heart Transplant Candidate section.
- Pulmonary vascular resistance may be further elevated during cardiopulmonary bypass by several factors. Atelectasis, hypoxic pulmonary vasoconstriction, and microemboli probably all play a role. In addition, cardiopulmonary bypass induces a systemic inflammatory response, with cytokine and protease release and activation of leukocytes and complement *(88,89)*. Direct injury to the pulmonary vascular endothelium, with the loss of endothelium-dependent vasodilation, has also been demonstrated *(90)*.
- The right ventricle appears to be more vulnerable than the left ventricle to the cardiac injury that occurs with brain death, as suggested by animal models *(91)*.

As described regarding the management of pulmonary hypertension in the pretransplant setting, a variety of intravenous agents with vasodilatory and/or inotropic properties have been used postoperatively to reduce pulmonary vascular resistance and support right heart function. Dobutamine *(92)* and milrinone *(93)* are effective in this setting, combining inotropic support for both the left and the right ventricle with pulmonary vasodilation. The utility of nonspecific vasodilators like dobutamine, milrinone, and isoproterenol may be limited by systemic vasodilation and hypotension, especially if the systemic vascular resistance is already low (*see* below). Intravenous prostaglandin E1 *(94)*, intravenous or inhaled prostacyclin *(95,96)*, and inhaled nitric oxide *(97)* all have greater specificity for the pulmonary vascular bed and are effective in reducing pulmonary vascular resistance. Nitric oxide in particular has seen increasing use in the immediate postoperative period, although it can only be administered to an intubated patient.

Severe right ventricular dysfunction with consequent cardiogenic shock occurs in 2 to 3% of patients after heart transplantation. Mechanical support with a right VAD can be life-saving *(98–100)*. Unfortunately, only about 25 to 30% of such patients recover, usually because, by the time mechanical support is instituted, secondary complications such as sepsis, coagulopathy, or renal failure have supervened. Close observation of hemodynamics in the immediate postoperative period and rapid intervention in the event of progressive right heart failure are necessary for right VAD support to be successful.

It has been recognized that as many as 10% of patients undergoing cardiopulmonary bypass experience vasodilatory shock in the postoperative period; in many cases, this vasodilatory state persists despite high levels of endogenous or exogenous catecholamines *(101)*. It is possible that patients receiving high doses of long-lasting vasodilators (such as angiotension-converting enzyme inhibitors) are at increased risk of this complication. In addition, however, an improved understanding of the pathogenesis of shock has led to the recognition that, with prolonged hypotension, neurohypophyseal stores of the vasoconstrictor vasopressin are depleted *(102)*. A lack of vasopressin may underlie many cases of vasodilatory shock in the postbypass setting. In one study of 145 patients undergoing cardiopulmonary bypass, 11 had vasodilatory shock. All of these patients had inappropriately low serum arginine vasopressin concentrations, and all responded to low-dose arginine vasopressin infusions *(103)*.

Finally, the use of mechanical cardiac assistance (if appropriately timed) for catastrophic early graft failure is often preferable to high doses of vasoconstricting catecholamines as the sole means of hemodynamic support and allows for patient stability while issues of urgent relisting for transplantation are considered.

IMMUNOSUPPRESSION

Calcineurin Inhibitors

Most patients receive some form of triple-drug therapy (a calcineurin inhibitor, an antiproliferative agent, and a corticosteroid) for maintenance immunosuppression with or without the addition of antilymphocyte antibody therapy during the initiation of treatment *(104)*. The calcineurin inhibitors cyclosporine and tacrolimus are a mainstay of the triple-drug regimen *(105,106)*. The advent of this class of drugs (cyclosporine was first introduced for clinical use in the United States in 1983) resulted in a rapid improvement in posttransplant survival from approx 50% at 1 year to above 80% at 1 year *(107)*. The inhibition of

calcineurin decreases the transcription of interleukin-2 (IL-2), an essential cytokine for the activation and proliferation of T lymphocytes *(108)*.

Several small studies have compared the efficacy and side-effect profile of cyclosporine with that of tacrolimus, but even the largest of these studies included only 243 patients *(109)*. None was able to detect a significant difference in acute rejection or in patient survival; there were reported differences in side-effect profile, but they were not consistent from study to study. As a result, there are no compelling data to support the choice of one of these two agents over the other in most instances. In some cases, switching from cyclosporine to tacrolimus may be effective for a specific patient in improving control of rejection or in ameliorating specific side effects, such as hyperlipidemia, hypertension, and hirsutism. Data from the ISHLT Registry indicate that 72% of patients transplanted between 1999 and 2001 were receiving cyclosporine and 25% were receiving tacrolimus; 3% were not receiving a calcineurin inhibitor *(2)*.

Antiproliferative Agents

The second component of most heart transplant drug regimens is an antiproliferative agent. For many years (since the advent of clinical heart transplantation), azathioprine was virtually the only drug used for this purpose. Mycophenolate mofetil was introduced as an alternative antiproliferative agent in 1992. It is metabolized to mycophenolic acid, which is a noncompetitive inhibitor of the enzyme inosine monophosphate dehydrogenase. This enzyme converts inosine monophosphate to guanosine monophosphate, which is an essential step in *de novo* purine biosynthesis. Proliferating lymphocytes are uniquely dependent on the *de novo* pathway *(110)*.

After initial trials in renal transplant patients suggested that mycophenolate might be more effective than azathioprine for preventing rejection, a randomized trial was undertaken comparing the two drugs in heart transplant recipients *(111)*. A total of 650 patients were enrolled, but 72 of these patients (11%) were withdrawn from the study before receiving the study drug because of inability to take oral medication within a prespecified time limit of 6 days after transplant. When the results of the study were analyzed by intention to treat, there was no beneficial effect of mycophenolate compared with azathioprine. However, by received-treatment analysis, patients receiving mycophenolate had a significant reduction in rejection-requiring treatment (65.7 vs 73.7%) and in mortality at 1 year (6.2 vs 11.4%).

Despite several methodological problems with this study, the results were generally interpreted to suggest that mycophenolate may

be superior to azathioprine for the prevention of cardiac allograft rejection. A subsequent report from the ISHLT Registry also compared mycophenolate with azathioprine and found a significant improvement in survival at 1 year (96 vs 93%) and 3 years (91 vs 86%), providing further support for the superiority of mycophenolate in a larger (although retrospective) analysis *(112)*. Data from the ISHLT Registry indicated that 70% of patients transplanted between 1999 and 2001 were receiving mycophenolate, and 15% were receiving azathioprine *(2)*.

Two newer drugs, sirolimus (also called rapamycin) and its derivative everolimus, are also antiproliferative agents; they are collectively referred to as TOR (target of rapamycin) inhibitors. Sirolimus was first identified as an immunosuppressive agent in the 1970s, but was not introduced into clinical organ transplantation until the 1990s. This agent has a structure similar to that of tacrolimus, and like tacrolimus, it binds to FK506-binding protein (FKBP) in the cell. However, rather than inhibiting calcineurin, the complex of sirolimus and FKBP then binds to another intracellular protein, TOR. Although the effects of TOR have not been completely defined, it is known to play a central role in the G1 phase of the cell cycle and IL-2-stimulated cell growth and proliferation *(113)*.

The place of TOR inhibitors in the immunosuppressive regimen is still not clearly established. In studies in renal transplant recipients, sirolimus has been used in place of a calcineurin inhibitor (with mycophenolate or azathioprine) or in place of mycophenolate or azathioprine (with cyclosporine). Sirolimus was an effective immunosuppressant in both settings. However, when sirolimus is substituted for cyclosporine, there is an increase in the incidence of acute rejection, and when sirolimus is combined with cyclosporine, there is an increase in the frequency of significant nephrotoxicity *(114)*.

Only one major randomized trial to date has evaluated the efficacy of TOR inhibitor therapy for preventing rejection in heart transplant recipients *(115)*. In this study, 634 patients were randomly assigned to receive either azathioprine or one of two doses of everolimus in combination with cyclosporine and prednisone. At 6 months, there was a significant reduction in the incidence of rejection with everolimus. In both this study and a single-center trial of sirolimus *(116)*, TOR inhibitor therapy was also found to reduce the severity of allograft vasculopathy (*see* Cardiac Allograft Vasculopathy). Data from the ISHLT Registry indicated that only 3% of patients transplanted between 1999 and 2001 were treated with sirolimus, although this figure is undoubtedly increasing *(2)*.

Corticosteroids

Although corticosteroids form the third cornerstone of the immunosuppressive regimen, their side effects can be unacceptably morbid. As a result, during the late 1980s and early 1990s several large centers attempted, using a variety of different approaches, to withdraw patients from steroids after transplantation *(117–121)*. These studies demonstrated that rapid steroid tapering (within the first 2 months) results in the greatest reduction in steroid morbidity, but two-thirds of patients have recurrent rejection and require the resumption of steroid therapy. Slower steroid weaning (after the first 6 months) is associated with a higher rate of successful steroid withdrawal, but the reduction in steroid side effects is more modest. Patients who are successfully weaned from steroids appear to have better long-term survival than those who are not. However, it is not clear whether this is a consequence of the reduction in steroid morbidity or whether successful steroid weaning merely identifies a subset of patients with a less severe response to their allograft who would be likely to have a better long-term survival in any case.

Induction Therapy

Antilymphocyte antibody therapy is initiated at the time of transplantation at some centers as an adjunct to triple-drug immunosuppression. The earliest antilymphocyte antibody preparations were crude sera derived from the immunization of animals (horses, rabbits, etc.) with human lymphocytes. Progressive refinement of these sera, with isolation of the globulin fraction and with use of pure T-cell populations for immunization, led to the development of commercial preparations. A monoclonal antibody directed against the T-cell surface molecule CD3 (OKT3) was introduced for clinical use in kidney transplantation in 1981 and in heart transplantation in 1987. Numerous small trials have compared these preparations to one another and to initiation of immunosuppression without antilymphocyte antibodies, but there has been no conclusive evidence that one approach is superior to another *(122)*. In the most recent survey of transplant programs, less than 50% use any sort of induction therapy, and this proportion is falling.

There may be certain clinical indications for which such therapy is warranted. For example, in the patient who is at high-risk for rejection, this more potent immunosuppression may be advantageous. Antilymphocyte therapy also has sufficient immunosuppressive potency that it may permit postponement of the initiation of calcineurin inhibitor therapy, which may be especially useful in patients who have early

postoperative renal dysfunction. However, these indications have not been prospectively studied in cardiac transplantation.

These advantages of antilymphocyte therapy must be balanced against potential disadvantages. The administration of OKT3 is associated with a risk of an acute inflammatory process called the cytokine release syndrome, thought to be caused by release of tumor necrosis factor from the targeted lymphocytes *(123)*. This syndrome is characterized by high fever, headache, elevated blood pressure, and in severe cases, pulmonary edema. The cytokine release syndrome is not seen with other antilymphocyte preparations. Increases in infection rates and decreased effectiveness with repeated use (because of an allogeneic response against these nonhuman antibodies) also occur with antilymphocyte therapy.

The anti-IL-2 receptor antibodies daclizumab and basiliximab are a new class of immunoglobulins introduced in the 1990s *(124,125)*. Unlike earlier antilymphocyte antibodies, these agents specifically target only activated T cells, that is, T cells that have been specifically stimulated in response to foreign antigen. They do so because they are directed against the high-affinity form of the IL-2 receptor, which is expressed only on activated T cells. Initial experience in renal transplantation demonstrated that both daclizumab and basiliximab significantly reduced the incidence of rejection during the first 6 months after transplant compared to placebo without a significant increase in side effects or adverse events.

The success of these agents in renal transplantation led to a cardiac transplant study conducted at Columbia-Presbyterian Medical Center and reported in 2000 *(126)*. Individuals in a group of 55 patients undergoing heart transplantation were randomly assigned to receive five doses of either daclizumab or placebo. All patients also received triple-drug immunosuppression with cyclosporine, mycophenolate mofetil, and prednisone. During the "induction period" (the first 3 months after transplantation, based on the dosing regimen and the half-life of daclizumab), the proportion of patients experiencing acute rejection was significantly greater in the daclizumab group than the placebo group (63 vs 18%). There was no difference between the two groups during the subsequent 3 months (43 vs 37%). The use of daclizumab was not associated with an increased risk of adverse events, and there were no episodes of cytokine release syndrome.

The data from this study and the renal transplant studies suggested that anti-IL-2 receptor antibodies may have efficacy similar to other antilymphocyte antibodies with a more benign side effect profile. There are insufficient data at present to determine whether these antibodies

truly reduce rejection frequency over the longer term or merely postpone rejection, as with other induction agents. There are also no data on other long-term effects, such as malignancy.

THE POSTTRANSPLANT CLINICAL COURSE

Rejection

Rejection is a significant cause of mortality after heart transplantation, accounting for approx 15% of deaths in the first posttransplant year; fortunately, it declines in frequency over time *(127)*. However, the incidence of rejection-related deaths is declining; approx 6% of patients transplanted in 1990, but fewer than 2% of those transplanted in 2000, died of rejection within the first 3 years after transplantation *(128)*. Improvements in immunosuppression (*see* Immunosuppression) are likely responsible for this decline.

The diagnosis of rejection is still based on invasive procurement of myocardial tissue and histological examination. Although noninvasive strategies, such as echocardiographic diastolic abnormalities, biomarkers such as troponin I and T, and magnetic resonance imaging, have been studied, they have not proven reliable enough to permit confident early diagnosis *(129)*.

The management of cellular rejection (i.e., the presence of lymphocytic infiltration) is relatively uniform, although there is debate for certain histological pictures. There is some variation from institution to institution in the treatment approach. For example, there is debate about whether an ISHLT biopsy grade 2 requires treatment; studies suggest that a grade 2 biopsy early after transplant may progress to more severe rejection, while late grade 2 episodes (more than 6 months to 1 year after transplant) typically resolve spontaneously *(130)*. Whenever a biopsy finding is thought to require treatment, a follow-up biopsy is obtained within the subsequent few weeks to confirm resolution of rejection.

In 1989, Hammond et al. described a distinct form of rejection without histological evidence of a lymphocyte infiltrate *(131)*. This entity has been called *humoral rejection* or *vascular rejection* and has been the subject of extended debate, including disagreement about its existence, its clinical features, its pathologic characteristics, its etiology, and its management. A general characterization of humoral rejection has evolved gradually; in 2003, a panel of pathologists, cardiologists, cardiac surgeons, and other scientists published a summary description of the current understanding of this entity, although no consensus diagnostic criteria have yet emerged *(132)*.

Humoral rejection occurs early after transplantation (usually within the first month). As its name indicates, it is thought to be a humorally mediated, rather than cell-mediated, form of rejection. Clinically, it often presents with an abrupt decline in cardiac function; some patients present with cardiogenic shock. Histologically, a cellular infiltrate is not present. However, immunofluorescence studies can detect the deposition of immunoglobulin and complement (such as C4d) within the myocardium, especially in the capillaries and other small vessels. In severe cases, light microscopic changes may be seen, including endothelial cell swelling, interstitial edema and hemorrhage, and a perivascular inflammatory infiltrate (vasculitis). Ischemic damage to the myocardium may be seen, perhaps as a result of vascular inflammation and subsequent occlusion by thrombus.

Treatment of humoral rejection has been unsatisfactory. One moderately successful approach is to use plasmapheresis for removal of immunoglobulin with or without high-dose cyclophosphamide to eliminate B cells responsible for the production of antibodies targeting the allograft *(133)*. The use of rituximab, a monoclonal antibody against the CD20 molecule expressed on B cells, has also been described *(134)*. Despite aggressive treatment, the mortality rate of humoral rejection remains high (13% in one recent series) *(135)*. Those who survive have a significantly increased incidence of cardiac allograft vasculopathy (CAV).

Infection

Infection is the counterpart to rejection in the heart transplant recipient *(136)*. The aggressive immunosuppression necessary to prevent rejection leads to a significant risk of infectious complications. Infection causes 25% of deaths in the first posttransplant year. Unlike rejection, which has become a less frequent cause of posttransplant mortality over the last decade, infection has consistently accounted for approx 4.5% of deaths within the first 3 years after transplantation *(134)*.

One of the most important infectious pathogens in the heart transplant setting is cytomegalovirus (CMV) *(137)*. The CMV virus is latent (as a result of prior, often inapparent, infection) in about two-thirds of adults. Usually, CMV does not cause significant clinical illness except in the immunosuppressed patients. After transplantation, reactivation of the CMV virus, or *de novo* infection, can cause an acute febrile illness as well as gastroenteritis, hepatitis, pneumonia, and even myocarditis.

The incidence of clinical CMV disease after heart transplantation is approx 20 to 25%, but varies depending on whether the transplant recipient and/or the organ donor have previously been infected (as demonstrated by positive or negative CMV serology). Recipients who are CMV negative and receive an organ from a CMV-positive donor are at highest risk (in one report, 85% of such patients developed clinical CMV illness requiring treatment) *(138)*.

In addition to the acute manifestations of CMV disease, CMV infection can have an immunosuppressive effect, increasing the risk of fungal, bacterial, and other superinfection *(139)*. Furthermore, CMV infection increases the incidence of rejection and has been implicated as a risk factor for the development of CAV *(140)*. It has also been suggested that CMV infection contributes to the pathogenesis of posttransplant lymphoproliferative disease (*see* below).

The drug of choice for treating CMV disease is ganciclovir or valganciclovir. Although such antiviral therapy is typically effective in the treatment of active CMV illness, the morbidity associated with CMV infection has led most transplant centers to adopt a strategy of prophylaxis after transplantation with either an antiviral agent or CMV immune globulin *(141)*. Such prophylactic therapy is usually given to CMV-negative recipients of CMV-positive donor hearts. In another approach, referred to as *preemptive therapy*, patients are screened repeatedly for evidence of CMV viremia by polymerase chain reaction and are treated only if active viral replication is detected. Whether CMV prophylaxis will influence the later development of CAV is still under investigation.

Cardiac Allograft Vasculopathy

CAV is a form of CAD unique to heart transplant recipients. CAV differs from typical coronary atherosclerosis in that it is a diffuse process involving the entire coronary arterial tree. The lesions of CAV are concentric rather than eccentric, resulting in a progressive circumferential narrowing of the vessel. Histologically, CAV lacks the lipid accumulation and cholesterol crystal formation seen in native coronary disease; smooth muscle cell proliferation and macrophage infiltration predominate *(142)*.

CAV also develops and progresses much more rapidly than typical coronary disease. Angiographically, CAV is detectable in 40 to 50% of heart transplant recipients by 5 years posttransplant *(143)*. However, angiography underestimates the frequency of CAV because the diffuse, concentric nature of the disease process makes it difficult to be certain of the "normal" luminal diameter. Intravascular ultrasound (IVUS)

studies have demonstrated that CAV is detectable in more than 80% of patients as early as 1 year after transplantation *(144)*.

Once CAV is evident by angiography, the prognosis is poor, with progressive vascular narrowing, diffuse myocardial ischemic injury, and cardiac failure. Revascularization, including percutaneous coronary intervention and coronary artery bypass grafting, is usually not feasible in patients with advanced CAV because of the diffuse nature of the disease process, which extends to the arteriolar level. Cardiac retransplantation is an option for some patients, but most heart transplant recipients with CAV die of their disease. Although rejection and infection are the predominant causes of death in the first year after transplantation, CAV is responsible for 20 to 25% of subsequent mortality *(134)*.

Because CAV is very difficult to treat once it is established, efforts to manage this serious condition have focused on prevention. The first breakthrough in reducing the incidence of CAV was described in 1995 by Kobashigawa et al. *(145)* in their report of a randomized trial of pravastatin in 97 heart transplant recipients. Patients taking pravastatin at a dose of 40 mg per day had a significant reduction in the frequency of angiographically detectable coronary disease at 1 year posttransplant when compared to controls not taking the drug (6 vs 20%). In addition, survival at 1 year was significantly better in the pravastatin group (94 vs 78%). Because most of the deaths in the study patients were caused by rejection, it has been suggested that pravastatin may also have an immunological effect on heart transplant recipients, although a mechanism for such an effect has not been established. A similar study of simvastatin also found reductions in both CAV and mortality *(146)*.

The pathogenesis of CAV is multifactorial, but it is clear that the immune response to the allograft is one important variable. As a result, various maintenance immunosuppressive regimens have been studied for their potential ability to reduce the development of graft coronary disease. The first agents for which such a beneficial effect has been clearly demonstrated are the TOR inhibitors sirolimus and everolimus. In the study of everolimus for rejection prophylaxis described in the Immunosuppression section, IVUS studies were also performed at baseline (within 6 weeks after transplantation) and at 1 year. Measurements were made of the maximal intimal thickness from both studies, and CAV was considered to have developed if the maximal intimal thickness had increased by at least 0.5 mm between the baseline and 1-year studies. Patients taking azathioprine had a higher incidence of CAV than those taking either the 1.5 mg or 3.0 mg dose of everolimus (52.8 vs 35.7 and 30.4%) *(147)*. In another trial, sirolimus was substituted for either azathioprine or mycophenolate in patients

with established, severe CAV. After 2 years, adverse cardiac events and angiographic worsening of disease were seen less often than in patients who continued previous therapy *(148)*.

Antioxidant vitamins, although they have not been shown to be beneficial in typical CAD, may be effective in the posttransplant setting. This was illustrated in a trial of 40 heart transplant recipients randomly assigned to either vitamin C and E supplementation or placebo. IVUS was performed at baseline and 1 year later, and measurements of average intimal index (plaque area divided by vessel area) were made. Patients treated with antioxidants had no significant change in intimal index; there was an 8% increase in intimal index among the placebo group *(149)*.

The calcium channel blocker diltiazem was also found to reduce the progression of CAV in a randomized trial of 106 heart transplant recipients. Angiography was used to evaluate changes in mean coronary artery diameter. The average coronary diameter decreased in the control group, from 2.41 mm at baseline to 2.19 and 2.22 mm at 1 and 2 years, respectively, but was unchanged in the diltiazem-treated group *(150)*.

Malignancy

The chronic use of immunosuppressive agents in heart transplant recipients increases the risk of malignancy approx 80 to 100 times that in the general population *(151)*. The most common cancers in this setting are skin cancers (primarily squamous cell carcinoma), lymphoma, lung cancer (especially among smokers), and Kaposi's sarcoma *(152,153)*. Malignancy, like CAV, is responsible for 20 to 25% of posttransplant deaths after the first year. Unlike CAV, however, the incidence of malignancy as a cause of death has not fallen over the past decade, but has remained constant *(134)*.

Most posttransplant malignancies are treated in the same way as in nonimmunosuppressed patients, with standard surgical resection, chemotherapy, and radiotherapy. The dose of immunosuppression is usually reduced; a common approach is to discontinue the antiproliferative agent (azathioprine or mycophenolate) and to decrease the calcineurin inhibitor dose substantially. Surgically, resection can cure carcinoma *in situ*, including skin cancer, colon cancer, renal cell carcinoma, and other solid tumors. However, the prognosis is poor in patients with advanced disease, and the clinical course tends to be more aggressive in the immunosuppressed host.

The term *posttransplant lymphoproliferative disorder* (PTLD) is used to encompass three different forms of disease that can occur after transplantation *(154)*:

- Benign polyclonal lymphoproliferation, which is not a true malignancy, but is an acute illness characterized by fever, malaise, fatigue, and rapidly progressive lymphadenopathy; it is responsible for about 55% of cases.
- Polyclonal B-cell proliferation with evidence of early malignant transformation, which is similar to the first disorder, but with the development of clonal cytogenetic abnormalities; it is responsible for about 30% of cases.
- True monoclonal malignant lymphoma, which is usually an extranodal disease that often involves the gastrointestinal tract, lungs, central nervous system, and sometimes the allograft organ; it is responsible for about 15% of cases.

The overall incidence of these disorders in heart transplant recipients is approx 4% *(164)*, although it is much higher (>10%) in patients who have received OKT3 (*see* Immunosuppression) *(156)*. The pathogenesis of PTLD in most cases is *de novo* infection or reactivation of Epstein-Barr virus (EBV), with consequent B-cell proliferation and transformation *(157)*. In one study of 381 nonrenal transplant recipients, the risk of PTLD was 24 times higher for EBV-seronegative transplant recipients than for seropositive recipients, suggesting that primary EBV infection carries a much greater risk than reactivation of latent virus from previous infection *(158)*.

Treatment of PTLD depends on the type of disease present, as outlined above. Patients with benign polyclonal lymphoproliferation are often treated with reduction in immunosuppression alone. Although antiviral therapy with acyclovir or ganciclovir has been suggested as an option, there is no solid evidence of the efficacy of this approach *(159)*. In patients who have true malignant lymphoma, standard chemotherapy regimens such as CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) or the more aggressive ProMACE-CytaBOM (cyclophosphamide, doxorubicin, etoposide, cytarabine, bleomycin, vincristine, methotrexate, and prednisone) have been used successfully *(160)*. The use of the anti-CD20 monoclonal antibody rituximab has also been described in this setting *(161)*.

CONCLUSION

Because of the complexity of their clinical condition, heart transplant patients require lifelong follow-up care at an institution with expertise in the field. Nonetheless, despite the risks posed by the immune attack on the allograft and the immunosuppression necessary to control it, an increasing number of heart transplant recipients are enjoying extended survival. The patient half-life (time to 50% survival)

and 1-year conditional half-life (time to 50% survival for patients who live more than 1 year) for all patients in the ISHLT Registry are 9.3 and 11.8 years, respectively; prognosis tends to be better at institutions that perform a larger number of transplants annually *(2)*. Recipients tend to report excellent functional status, with more than 90% having no activity limitation.

Although heart transplantation is an option for only a small number of patients, it is an effective form of therapy that continues to evolve with new advances in both basic science and clinical medicine. Furthermore, the creation of heart transplantation as a field of expertise, both in medicine and in surgery, has had the consequence of dramatically increasing the understanding of advanced heart failure and has led directly to the development of other approaches (such as ventricular assist) to manage this common and mortal disease.

REFERENCES

1. Hunt SA. Current status of cardiac transplantation. JAMA 1998;280:1692.
2. Hertz MI, Taylor DO, Trulock EP, et al. The Registry of the International Society for Heart and Lung Transplantation: 19th Official Report—2002. J Heart Lung Transplant 2002;21:950.
3. 2001 Annual Report of the US Organ Procurement and Transplantation Network and the Scientific Registry for Transplant Recipients: Transplant Data 1991–2000. Rockville, MD: Department of Health and Human Services, Health Resources and Services Administration, Office of Special Programs, Division of Transplantation; Richmond, VA: United Network for Organ Sharing; Ann Arbor, MI: University Renal Research and Education Association, Ann Arbor, MI.
4. Effects of enalapril on mortality in severe congestive heart failure. Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). The CONSENSUS Trial Study Group. N Engl J Med 1987;316:1429.
5. Packer M, Coats AJ, Fowler MB, et al. Effect of carvedilol on survival in severe chronic heart failure. N Engl J Med 2001;344:1651.
6. Robbins RC, Barlow CW, Oyer PE, et al. Thirty years of cardiac transplantation at Stanford University. J Thorac Cardiovasc Surg 1999;117:939.
7. Mancini DM, Eisen H, Kussmaul W, et al. Value of peak exercise oxygen consumption for optimal timing of cardiac transplantation in ambulatory patients with heart failure. Circulation 1991;83:778.
8. Mudge GH, Goldstein S, Addonizio LJ, et al. Twenty-fourth Bethesda conference: cardiac transplantation: Task Force 3: recipient guidelines/prioritization. J Am Coll Cardiol 1993;22:21.
9. Aaronson KD, Schwartz JS, Chen TM, et al. Development and prospective validation of a clinical index to predict survival in ambulatory patients referred for cardiac transplant evaluation. Circulation 1997;95:2660.
10. Cimato TR, Jessup M. Recipient selection in cardiac transplantation: contraindications and risk factors for mortality. J Heart Lung Transplant 2002;21:1161.
11. Blanche C, Blanche DA, Kearney B, et al. Heart transplantation in patients 70 years of age and older: a comparative analysis of outcome. J Thorac Cardiovasc Surg 2001;121:532.

12. Mancini D, Beniaminovitz A, Edwards N, et al. Survival of diabetic patients following cardiac transplant. J Heart Lung Transplant 2001;20:168.
13. Bourge RC, Kirklin JK, Naftel DC, et al. Predicting outcome after cardiac transplantation: lessons from the Cardiac Transplant Research Database. Curr Opin Cardiol 1997;12:136.
14. Costard-Jackle A, Fowler MB. Influence of preoperative pulmonary artery pressure on mortality after heart transplantation: testing of potential reversibility of pulmonary hypertension with nitroprusside is useful in defining a high risk group. J Am Coll Cardiol 1992;19:48.
15. Stanek B, Sturm B, Frey B, et al. Bridging to heart transplantation: prostaglandin E1 vs prostacyclin vs dobutamine. J Heart Lung Transplant 1999;18:358.
16. Canver CC, Chanda J. Milrinone for long-term pharmacologic support of the status 1 heart transplant candidates. Ann Thorac Surg 2000;69:1823.
17. Frey B, Zuckermann A, Koller-Strametz J, et al. Effects of continuous, long-term therapy with prostaglandin E1 preoperatively on outcome after heart transplantation. Transplant Proc 1999;31:80.
18. Yeoh TK, Frist WH, Lagerstrom C, et al. Relationship of cardiac allograft size and pulmonary vascular resistance to long-term cardiopulmonary function. J Heart Lung Transplant 1992;11:1168.
19. Petrofski JA, Hoopes CW, Bashore TM, et al. Mechanical ventricular support lowers pulmonary vascular resistance in a patient with congential heart disease. Ann Thorac Surg 2003;75:1005.
20. Adamson RM, Dembitsky WP, Jaski BE, et al. Left ventricular assist device support of medically unresponsive pulmonary hypertension and aortic insufficiency. ASAIO J 1997;43:365.
21. Koerner MM, Tenderich G, Minami K, et al. Results of heart transplantation in patients with preexisting malignancies. Am J Cardiol 1997;79:988.
22. Goldstein DJ, Seldomridge A, Addonizio L, et al. Orthotopic heart transplantation in patients with treated malignancies. Am J Cardiol 1995;75:968.
23. Hosenpud JD, Pamidi SR, Fiol BS, et al. Outcomes in patients who are hepatitis B surface antigen-positive before transplantation: an analysis and study using the joint ISHLT/UNOS thoracic registry. J Heart Lung Transplant 2000;19:781.
24. Ko WJ, Chou NK, Hsu RB, et al. Hepatitis B virus infection in heart transplant recipients in a hepatitis B endemic area. J Heart Lung Transplant 2001;20:865.
25. Nguyen MH, Wright TL. Therapeutic advances in the management of hepatitis B and hepatitis C. Curr Opin Infect Dis 2001;14:593.
26. Fishman JA, Rubin RH. Solid organ transplantation in HIV-infected individuals: obstacles and opportunities. Transplant Proc 2001;33:1310.
27. Calabrese LH, Albrecht M, Young J, et al. Successful cardiac transplantation in an HIV-1-infected patient with advanced disease. N Engl J Med 2003;348:2323–2328.
28. Abbas AK, Lichtman AH, Pober JS. Immune responses to tissue transplants. In: Abbas AK, Lichtman AH, Pober JS, eds. Cellular and Molecular Immunology, 2nd ed. WB Saunders, Philadelphia, PA: 1994.
29. Smith JD, Danskine AJ, Laylor RM, et al. The effect of panel reactive antibodies and the donor specific crossmatch on graft survival after heart and heart-lung transplantation. Transplant Immunol 1993;1:60.
30. Baid S, Saidman SL, Tolkoff-Rubin M, et al. Managing the highly sensitized transplant recipient and B cell tolerance. Curr Opin Immunol 2001;13:577.
31. Betkowski AS, Graff R, Chen JJ, Hauptman PJ. Panel-reactive antibody screening practices prior to heart transplantation. J Heart Lung Transplant 2002;21:644.

32. Bishay ES, Cook DJ, Starling RC, et al. The clinical significance of flow cytometry crossmatching in heart transplantation. Eur J Cardiothorac Surg 2000;17:362.
33. Przybylowski P, Balogna M, Radovancevic B, et al. The role of flow cytometry-detected IgG and IgM anti-donor antibodies in cardiac allograft recipients. Transplantation 1999;67:258.
34. Aziz S, Hassantash SA, Nelson K, et al. The clinical significance of flow cytometry crossmatching in heart transplantation. J Heart Lung Transplant 1998;17:686.
35. McKenna DH Jr, Eastlund T, Segall M, et al. HLA alloimmunization in patients requiring ventricular assist device support. J Heart Lung Transplant 2002;21:1218.
36. Massad MG, McCarthy PM, Smedira NG, et al. Does successful bridging with the implantable left ventricular assist device affect cardiac transplantation outcome? J Thorac Cardiovasc Surg 1996;112:1275.
37. Massad MG, Cook DJ, Schmitt SK, et al. Factors influencing HLA sensitization in implantable LVAD recipients. Ann Thorac Surg 1997;64:1120.
38. Itescu S, Ankersmit J-H, Kocher AA, Schuster MD. Immunobiology of left ventricular assist devices. Prog Cardiovasc Dis 2000;43:67.
39. Stringham JC, Bull DA, Fuller TC, et al. Avoidance of cellular blood product transfusions in LVAD recipients does not prevent HLA allosensitization. J Heart Lung Transplant 1999;18:160.
40. Ratkovec RM, Hammond EH, O'Connell JB, et al. Outcome of cardiac transplant recipients with a positive donor-specific crossmatch—preliminary results with plasmapheresis. Transplantation 1992;54:651.
41. Pisani BA, Mullen GM, Malinowska K, et al. Plasmapheresis with intravenous immunoglobulin G is effective in patients with elevated panel reactive antibody prior to cardiac transplantation. J Heart Lung Transplant 1999;18:701.
42. Ruiz JC, de Francisco AL, Vazquez de Prada JA, et al. Successful heart transplantation after anti-HLA antibody removal with protein-A immunoadsorption in a hyperimmunized patient. J Thorac Cardiovasc Surg 1994;107:1366.
43. Robinson JA. Apheresis in thoracic organ transplantation. Ther Apher 1999;3:34.
44. Dowling RD, Jones JW, Carroll MS, Gray LA Jr. Use of intravenous immunoglobulin in sensitized LVAD recipients. Transplant Proc 1998;30:1110.
45. John R, Lietz K, Burke E, et al. Intravenous immunoglobulin reduces anti-HLA alloreactivity and shortens waiting time to cardiac transplantation in highly sensitized left ventricular assist device recipients. Circulation 1999;100: II229.
46. Itescu S, Burke E, Lietz K, et al. Intravenous pulse administration of cyclophosphamide is an effective and safe treatment for sensitized cardiac allograft recipients. Circulation 2002;105:1214.
47. Aranda JM Jr, Scornik JC, Normann SJ, et al. Anti-CD20 monoclonal antibody (rituximab) therapy for acute cardiac humoral rejection: a case report. Transplantation 2002;73:907.
48. Garrett HE Jr, Groshart, K, Duvall-Seaman D, et al. Treatment of humoral rejection with rituximab. Ann Thorac Surg 2002;74:1240.
49. Renlund DG, Taylor DO, Kfoury AG, Shaddy RS. New UNOS rules: historical background and implications for transplantation management. United Network for Organ Sharing. J Heart Lung Transplant 1999;18:1065.
50. Kauffman HM, McBride MA, Shield CF, et al. Determinants of waiting time for heart transplants in the United States. J Heart Lung Transplant 1999;18:414.
51. Data from the Organ Procurement and Transplantation Network Web site at http://www.optn.org/latestData/stateData.asp?type=region.

52. Whellan DJ, Tudor G, Denofrio D, et al. Heart transplant center practice patterns affect access to donors and survival of patients classified as status 1 by the United Network of Organ Sharing. Am Heart J 2000;140:443.
53. Laks H, Marelli D, Fonarow GC, et al. Use of two recipient lists for adults requiring heart transplantation. J Thorac Cardiovasc Surg 2003;125:49.
54. Data from the Organ Procurement and Transplantation Network Web site at http://www.optn.org/latestData/step2.asp.
55. Chen EP, Bittner HB, Kendall SW, Van Trigt P. Hormonal and hemodynamic changes in a validated animal model of brain death. Crit Care Med 1996; 24:1352.
56. Shivalkar B, Van Loon J, Wieland W, et al. Variable effects of explosive or gradual increase of intracranial pressure on myocardial structure and function. Circulation 1993;87:230.
57. Pinelli G, Mertes PM, Carteaux JP, et al. Myocardial effects of experimental acute brain death: evaluation by hemodynamic and biological studies. Ann Thorac Surg 1995;60:1729.
58. White M, Wiechmann RJ, Roden RL, et al. Cardiac beta-adrenergic neuroeffector systems in acute myocardial dysfunction related to brain injury. Evidence for catecholamine-mediated myocardial damage. Circulation 1995;92:2183.
59. Stoica SC, Goddard M, Large SR. The endothelium in clinical cardiac transplantation. Ann Thorac Surg 2002;73:1002.
60. Szabo G, Buhmann V, Bahrle S, et al. Brain death impairs coronary endothelial function. Transplantation 2002;73:1846.
61. Koo DD, Welsh KI, McLaren AJ, et al. Cadaver vs living donor kidneys: impact of donor factors on antigen induction before transplantation. Kidney Int 1999; 56:1551.
62. Wilhelm MJ, Pratschke J, Beato F, et al. Activation of the heart by donor brain death accelerates acute rejection after transplantation. Circulation 2000;102: 2426–2433.
63. Tsai FC, Marelli D, Bresson J, et al. Use of hearts transplanted from donors with atraumatic intracranial bleeds. J Heart Lung Transplant 2002;21:623.
64. Schnuelle P, Berger S, de Boer J, et al. Effects of catecholamine application to brain-dead donors on graft survival in solid organ transplantation. Transplantation 2001;72:455.
65. Chen JM, Cullinane S, Spanier TB, et al. Vasopressin deficiency and pressor hypersensitivity in hemodynamically unstable organ donors. Circulation 1999; 100:II244.
66. Chen EP, Bittner HB, Kendall SW, Van Trigt P. Hormonal and hemodynamic changes in a validated animal model of brain death. Crit Care Med 1996;24:1352.
67. Hunt SA, Baldwin J, Baumgartner W, et al. Cardiovascular management of a potential heart donor: a statement from the Transplantation Committee of the American College of Cardiology. Crit Care Med 1996;24:1599.
68. Ozcan YA, Begun JW, McKinney MM. Benchmarking organ procurement organizations: a national study. Health Serv Res 1999;34:855.
69. Zaroff JG, Rosengard BR, Armstrong WF, et al. Consensus conference report: maximizing use of organs recovered from the cadaver donor: cardiac recommendations, March 28–29, 2001, Crystal City, Virginia. Circulation 2002;106:836.
70. Jeevanandam V, Furukawa S, Prendergast TW, et al. Standard criteria for an acceptable donor heart are restricting heart transplantation. Ann Thorac Surg 1996;62:1268.

71. Young JB, Naftel DC, Bourge RC, et al. Matching the heart donor and heart transplant recipient: clues for successful expansion of the donor pool: a multivariable, multiinstitutional report. J Heart Lung Transplant 1994;13:353.
72. Wheeldon DR, Potter CD, Oduro A, et al. Transforming the "unacceptable" donor: outcomes from the adoption of a standardized donor management technique. J Heart Lung Transplant 1995;14:734.
73. Jahania MS, Sanchez JA, Narayan P, et al. Heart preservation for transplantation: principles and strategies. Ann Thorac Surg 1999;68:1983.
74. Demmy TL, Biddle JS, Bennett LE, et al. Organ preservation solutions in heart transplantation—patterns of usage and related survival. Transplantation 1997;63:262.
75. Hassanein WH, Zellos L, Tyrrell TA, et al. Continuous perfusion of donor hearts in the beating state extends preservation time and improves recovery of function. J Thorac Cardiovasc Surg 1998;116:821.
76. Nickless DK, Rabinov M, Richards SM, et al. Continuous perfusion improves preservation of donor rat hearts: importance of the implantation phase. Ann Thorac Surg 1998;65:1265.
77. Jones BU, Serna DL, Beckham G, et al. Recovery of cardiac function after standard hypothermic storage vs preservation with Peg-hemoglobin. ASAIO J 2001: 47:197.
78. Shumway NE, Lower RR, Stouffer RC. Transplantation of the heart. Adv Surg 1966;2:265.
79. Sarsam MA, Campbell CS, Yonan NA, et al. An alternative surgical technique in orthotopic cardiac transplantation. J Cardiac Surg 1993; 8:344.
80. Dreyfus G, Jebara V, Mihaileanu S, et al. Total orthotopic heart transplantation: an alternative to the standard technique. Ann Thorac Surg 1991;52:1181.
81. Blanche C, Nessim S, Quartel, A, et al. Heart transplantation with bicaval and pulmonary venous anastomoses. A hemodynamic analysis of the first 117 patients. J Cardiovasc Surg 1997;38:561.
82. Aziz T, Burgess M, Khafagy R, et al. Bicaval and standard techniques in orthotopic heart transplantation: medium-term experience in cardiac performance and survival. J Thorac Cardiovasc Surg 1999;118:115.
83. Milano CA, Shah AS, Van Trigt P, et al. Evaluation of early postoperative results after bicaval vs standard cardiac transplantation and review of the literature. Am Heart J 2000;140:717.
84. Aziz TM, Burgess MI, El-Gamel A, et al. Orthotopic cardiac transplantation technique: a survey of current practice. Ann Thorac Surg 1999;68:1242.
85. Kirklin JK, Naftel DC, Bourge RC, et al. Evolving trends in risk profiles and causes of death after heart transplantation: a ten-year multi-institutional study. J Thorac Cardiovasc Surg 2003;125:881.
86. Bourge RC, Naftel DC, Costanzo-Nordin MR, et al. Pretransplantation risk factors for death after heart transplantation: a multiinstitutional study. J Heart Lung Transplant 1993;12:549.
87. Hosenpud J, Bennett L, Keck B, et al. The Registry of the International Society for Heart and Lung Transplantation: 17th Official Report—2000. J Heart Lung Transplant 2000;19:909.
88. Asimakopoulos G, Smith PL, Ratnatunga CP et al. Lung injury and acute respiratory distress syndrome after cardiopulmonary bypass. Ann Thorac Surg 1999; 68:1107.
89. Butler J, Rocker GM, Westaby S. Inflammatory response to cardiopulmonary bypass. Ann Thorac Surg 1993;55:552.

90. Wessel D, Adatia I, Giglia T, et al. Use of inhaled nitric oxide and acetylcholine in the evaluation of pulmonary hypertension and endothelial function after cardiopulmonary bypass. Circulation 1993;88:2128–2138.
91. Bittner HB, Chen EP, Kendall SW, et al. Brain death alters cardiopulmonary hemodynamics and impairs right ventricular power reserve against an elevation of pulmonary vascular resistance. Chest 1997;111:706.
92. De Broux E, Lagace G, Dumont L, et al. Efficacy of dobutamine in the failing transplanted heart. J Heart Lung Transplant 1992;11:1133.
93. Levy JH, Bailey JM, Deeb GM. Intravenous milrinone in cardiac surgery. Ann Thorac Surg 2002;73:325.
94. Vincent JL, Carlier E, Pinsky MR, et al. Prostaglandin E1 infusion for right ventricular failure after cardiac transplantation. J Thorac Cardiovasc Surg 1992; 103:33.
95. Kieler-Jensen N, Lundin S, Ricksten SE. Vasodilator therapy after heart transplantation: effects of inhaled nitric oxide and intravenous prostacyclin, prostaglandin E1, and sodium nitroprusside. J Heart Lung Transplant 1995; 14:436.
96. Haraldsson A, Kieler-Jensen N, Ricksten S-E. Inhaled prostacyclin for treatment of pulmonary hypertension after cardiac surgery or heart transplantation: a pharmacodynamic study. J Cardiothorac Vasc Anesth 1996;10:864.
97. Rajek A, Pernerstorfer T, Kastner J, et al. Inhaled nitric oxide reduces pulmonary vascular resistance more than prostaglandin E(1) during heart transplantation. Anesth Analg 2000;90:523.
98. Chen JM, Levin HR, Rose EA, et al. Experience with right ventricular assist devices for perioperative right-sided circulatory failure. Ann Thorac Surg 1996; 61:305.
99. Barnard SP, Hasan A, Forty J, et al. Mechanical ventricular assistance for the failing right ventricle after cardiac transplantation. Eur J Cardiothorac Surg 1995; 9:297.
100. Kaul TK, Fields BL. Postoperative acute refractory right ventricular failure: incidence, pathogenesis, management and prognosis. Cardiovasc Surg 2000;8:1.
101. Albright TN, Zimmerman MA, Selzman CH. Vasopressin in the cardiac surgery intensive care unit. Am J Crit Care 2002;11:326.
102. Landry DW, Oliver JA. The pathogenesis of vasodilatory shock. N Engl J Med 2001;345:588.
103. Argenziano M, Chen JM, Choudhri AF, et al. Management of vasodilatory shock after cardiac surgery: identification of predisposing factors and use of a novel pressor agent. J Thorac Cardiovasc Surg 1998;116:973.
104. Taylor DO. Cardiac transplantation: drug regimens for the 21st century. Ann Thorac Surg 2003;75:S72.
105. Valantine H. Neoral use in the cardiac transplant recipient. Transplant Proc 2000; 32:S27.
106. Taylor DO, Barr ML, Meiser BM, et al. Suggested guidelines for the use of tacrolimus in cardiac transplant recipients. J Heart Lung Transplant 2001; 20:734.
107. Opelz G. Multicenter evaluation of immunosuppressive regimens in heart transplantation. Transplant Proc 1997;29:617.
108. Wiederrecht G, Lam E, Hung S, et al. The mechanism of action of FK-506 and cyclosporin A. Ann NY Acad Sci 1993;696:9.
109. Kobashigawa JA. Controversies in heart and lung transplantation immunosuppression: tacrolimus vs cyclosporine. Transplant Proc 1998;30:1095.

110. Allison AC, Kowalski WJ, Muller CD, et al. Mechanism of action of mycophenolic acid. Ann NY Acad Sci 1990;696:63.
111. Kobashigawa J, Miller L, Renlund D, et al. A randomized active-controlled trial of mycophenolate mofetil in heart transplant recipients. Transplantation 1998; 66:507–515.
112. Hosenpud JD, Bennett LE. Mycophenolate mofetil vs azathioprine in patients surviving the initial cardiac transplant hospitalization: an analysis of the Joint UNOS/ISHLT Thoracic Registry. Transplantation 2001;72:1662.
113. Schmelzle T, Hall MN. TOR, a central controller of cell growth. Cell 2000; 103:253.
114. Saunders RN, Metcalfe MS, Nicholson ML. Rapamycin in transplantation: a review of the evidence. Kidney Int 2001;59:3.
115. Eisen HJ, Tuzcu EM, Dorent R, et al. Everolimus for the prevention of allograft rejection and vasculopathy in cardiac-transplant recipients. N Engl J Med 2003; 349:847.
116. Mancini D, Pinney S, Burkhoff D, et al. Use of rapamycin slows progression of cardiac transplantation vasculopathy. Circulation 2003;108:48.
117. Prieto M, Lake KD, Pritzker MR, et al. OKT3 induction and steroid-free maintenance immunosuppression for treatment of high-risk heart transplant recipients. J Heart Lung Transplant 1991;10:901.
118. Miller LW, Wolford T, McBride LR, et al. Successful withdrawal of corticosteroids in heart transplantation. J Heart Lung Transplant 1992;11(2 part 2):431.
119. Olivari MT, Jessen ME, Baldwin BJ, et al. Triple-drug immunosuppression with steroid discontinuation by 6 months after heart transplantation. J Heart Lung Transplant 1995;14(1 part 1):127.
120. Kobashigawa JA, Stevenson LW, Brownfield ED, et al. Corticosteroid weaning late after heart transplantation: relation to HLA-DR mismatching and long-term metabolic benefits. J Heart Lung Transplant 1995;14:963.
121. Taylor DO, Bristow MR, O'Connell JB, et al. Improved long-term survival after heart transplantation predicted by successful early withdrawal from maintenance corticosteroid therapy. J Heart Lung Transplant 1996;15:1039.
122. Taylor DO, Kfoury AG, Pisani B, et al. Antilymphocyte-antibody prophylaxis: review of the adult experience in heart transplantation. Transplant Proc 1997;29 (suppl 8A):13S.
123. Norman DJ, Chatenoud L, Cohen D, et al. Consensus statement regarding OKT3-induced cytokine-release syndrome and human antimouse antibodies. Transplant Proc 1993;25(2 suppl 1):89.
124. Nashan B, Moore R, Amlot P, et al. Randomised trial of basiliximab vs placebo for control of acute cellular rejection in renal allograft recipients. CHIB 201 International Study Group. Lancet 1997;350:1193.
125. Vincenti F, Kirkman R, Light S, et al. Interleukin-2-receptor blockade with daclizumab to prevent acute rejection in renal transplantation. Daclizumab Triple Therapy Study Group. N Engl J Med 1998;338:161.
126. Beniaminovitz A, Itescu S, Lietz K, et al. Prevention of rejection in cardiac transplantation by blockade of the interleukin-2 receptor with a monoclonal antibody. N Engl J Med 2000;342:613.
127. Kirklin JK, Naftel DC, Bourge RC, et al. Rejection after cardiac transplantation: a time-related risk factor analysis. Circulation 1992;86(suppl II):II-236.
128. Kirlin JK, Naftel DC, Bourge RC, et al. Evolving trends in risk profiles and causes of death after heart transplantation: a 10-year multi-institutional study. J Thorac Cardiovasc Surg 2003;125:881.

129. Valantine HA, Yeoh TK, Gibbons R, et al. Sensitivity and specificity of diastolic indexes for rejection surveillance: temporal correlation with endomyocardial biopsy. J Heart Lung Transplant 191;10 (5 part 1):757.
130. Winters GL, Loh E, Schoen FJ. Natural history of focal moderate cardiac allograft rejection: is treatment warranted? Circulation 1995;91:1975.
131. Hammond EH, Yowell RL, Nunoda S, et al. Vascular (humoral) rejection in heart transplantation: pathologic observations and clinical implications. J Heart Lung Transplant 1989;8:430.
132. Rodriguez ER. The pathology of heart transplant biopsy specimens: revisiting the 1990 ISHLT working formulation. J Heart Lung Transplant 2003;22:3.
133. Grauhan O, Knosalla C, Ewert R, et al. Plasmapheresis and cyclophosphamide in the treatment of humoral rejection after heart transplantation. J Heart Lung Transplant 2001;20:316.
134. Garrett HE, Groshart K, Duvall-Seaman D, et al Treatment of humoral rejection with rituximab. Ann Thorac Surg 2002;74:1240.
135. Michaels PJ, Espejo ML, Kobashigawa J, et al. Humoral rejection in cardiac transplantation: risk factors, hemodynamic consequences and relationship to transplant coronary artery disease. J Heart Lung Transplant 2003;22:58.
136. Fishman JA, Rubin RH. Infection in organ-transplant recipients. N Engl J Med 1998;338:1741.
137. Rubin RH. Prevention and treatment of cytomegalovirus disease in heart transplant recipients. J Heart Lung Transplant 2000;19:731.
138. Madden BP, Reynolds L, Tryhorn Y, et al. Is routine post-operative surveillance for cytomegalovirus infection following heart transplantation necessary? Eur J Cardiothorac Surg 1998;14:15.
139. Avery RK. Prevention and treatment of cytomegalovirus infection and disease in heart transplant recipients. Curr Opin Cardiol 1998;13:122.
140. Koskinen PK, Kallio EA, Tikkanen JM. Cytomegalovirus infection and cardiac allograft vasculopathy. Transpl Infect Dis 1999;1:115.
141. Valantine HA, Luikart H, Doyle R, et al. Impact of cytomegalovirus hyperimmune globulin on outcome after cardiothoracic transplantation: a comparative study of combined prophylaxis with CMV hyperimmune globulin plus ganciclovir vs ganciclovir alone. Transplantation 2001;72:1647.
142. Billingham ME. Histopathology of graft coronary disease. J Heart Lung Transplant 1992;11(3 part 2):S38.
143. Costanzo MR, Naftel DC, Pritzker MR, et al. Heart transplant coronary artery disease detected by coronary angiography: a multiinstitutional study of preoperative donor and recipient risk factors. Cardiac Transplant Research Database. J Heart Lung Transplant 1998;17:744.
144. Rickenbacher PR, Pinto FJ, Chenzbraun A, et al. Incidence and severity of transplant coronary artery disease early and up to 15 years after transplantation as detected by intravascular ultrasound. J Am Coll Cardiol 1995;25:171.
145. Kobashigawa JA, Katznelson S, Laks H, et al. Effect of pravastatin on outcomes after cardiac transplantation. N Engl J Med 1995;333:621.
146. Wenke K, Meiser B, Thiery J, et al. Simvastatin reduces graft vessel disease and mortality after heart transplantation: a 4-year randomized trial. Circulation 1997;96:1398.
147. Eisen HJ, Tuzcu EM, Dorent R, et al. Everolimus for the prevention of allograft rejection and vasculopathy in cardiac-transplant recipients. N Engl J Med 2003; 349:847.

148. Mancini D, Pinney S, Burkhoff D, et al. Use of rapamycin slows progression of cardiac transplantation vasculopathy. Circulation 2003;108:48.
149. Fang JC, Kinlay S, Beltrame J, et al. Effect of vitamins C and E on progression of transplant-associated atherosclerosis: a randomized trial. Lancet 2002;359:1108.
150. Schroeder JS, Gao SZ, Alderman EL, et al. A preliminary study of diltiazem in the prevention of coronary artery disease in heart-transplant recipients. N Engl J Med 1993;328:164.
151. Penn I. Cancers complicating organ transplantation. N Engl J Med 1990;323:1767.
152. Penn I. Solid tumors in cardiac allograft recipients. Ann Thorac Surg 1995; 60:1559.
153. Rinaldi M, Pellegrini C, D'Armini AM, et al. Neoplastic disease after heart transplantation: single center experience. Eur J Cardiothorac Surg 2001;19:696.
154. Nalesnik MA, Jaffe R, Starzl TE, et al. The pathology of posttransplant lymphoproliferative disorders occurring in the setting of cyclosporine A-prednisone immunosuppression. Am J Pathol 1988;133:173.
155. Armitage JM, Kormos RL, Stuart RS, et al. Posttransplant lymphoproliferative disease in thoracic organ transplant recipients: 10 years of cyclosporine-based immunosuppression. J Heart Lung Transplant 1991;10:877.
156. Swinnen LJ, Costanzo-Nordin MR, Fisher SG, et al. Increased incidence of lymphoproliferative disorder after immunosuppression with the monoclonal antibody OKT3 in cardiac-transplant recipients. N Engl J Med 1990;323:1723.
157. Hanto DW. Classification of Epstein-Barr virus-associated posttransplant lymphoproliferative diseases: implications for understanding their pathogenesis and developing rational treatment strategies. Annu Rev Med 195;46:381.
158. Walker RC, Marshall WF, Strickler JG, et al. Pretransplantation assessment of the risk of lymphoproliferative disorder. Clin Infect Dis 1995;20:1346.
159. Paya CV, Fung JJ, Nalesnik MA, et al. Epstein-Barr virus-induced posttransplant lymphoproliferative disorders. ASTS/ASTP Task Force and the Naymo Clinic Organized International Consensus Development Meeting. Transplantation 1999; 68:1517.
160. Swinnen LJ, Mullen GM, Carr TJ, et al. Aggressive treatment for postcardiac transplant lymphoproliferation. Blood 1995;86:3333.
161. Zilz ND, Olson LJ, McGregor CG. Treatment of post-transplant lymphoproliferative disorder with monoclonal CD20 antibody (rituximab) after heart transplantation. J Heart Lung Transplant 2001;20:770.

2 Surgical Revascularization in the Management of Heart Failure and Ischemic Left Ventricular Dysfunction

Jeffrey J. Teuteberg, MD
and James C. Fang, MD

CONTENTS

INTRODUCTION

More than 5 million Americans have congestive heart failure, and 550,000 new cases are diagnosed each year. This condition results in almost 1 million hospital discharges and more than 50,000 deaths a year at a cost of $28.8 billion *(1)*. Coronary artery disease (CAD)

From: *Contemporary Cardiology: Surgical Management of Congestive Heart Failure*
Edited by: J. C. Fang and G. S. Couper © Humana Press Inc., Totowa, NJ

remains a leading cause of heart failure. Since the early trials of surgical vs medical management of coronary artery disease in the late 1970s, there have been substantial changes in the surgical techniques and the medical management of chronic CAD, acute coronary syndromes, and heart failure.

Despite these advances, the optimal role of surgical revascularization in the management of heart failure and ischemic left ventricular (LV) dysfunction remains unclear and primarily anecdotal. There is still no large prospective randomized experience with coronary artery bypass graft (CABG) surgery for patients with heart failure in the current era of mechanical revascularization. Although retrospective surgical series have suggested benefit for this population, these studies have rarely included the most recent advances in medical, surgical, and device therapies for heart failure *(2–8)*. Furthermore, basic questions about bypass surgery and heart failure remain, including the optimal methods for assessing viability, the most appropriate end points (other than mortality) that should be targeted, and whether cost considerations and quality-of-life (QoL) measures should be paramount. Nonetheless, surgical revascularization remains one of the therapeutic cornerstones in the management of advanced heart failure from CAD.

CORONARY BYPASS SURGERY AND HEART FAILURE: THE CLINICAL EXPERIENCE

There are no randomized, controlled trials of patients with multivessel CAD and significant LV dysfunction because most early clinical trials of surgical revascularization excluded patients with advanced heart failure because of their high perioperative mortality. However, the three large randomized trials of bypass surgery vs medical management of the 1970s, the Veterans Administration Cooperative Study (VACS), the European Cooperative Coronary Study (ECSS), and the Coronary Artery Surgery Study (CASS), did include some patients with decreased LV function. Therefore, some insight into the role of CABG in these patients can be gleaned from a review of these trials (Table 1).

Randomized Trials

The VACS was the first large, multicenter, randomized controlled trial of medical therapy vs CABG for patients with stable angina. A total of 686 patients were randomized between 1972 and 1974. LV dysfunction was defined as an ejection fraction (EF) less than 50%. A minority of patients in either group had LV dysfunction, 35% in the medical arm and 31% in the CABG arm. A subgroup of patients with

Table 1
Comparison of Major Characteristics From the Three Large, Randomized Trials of Coronary Bypass Surgery vs Medical Management

	VACS	*ECSS*	*CASS*
Number of patients	686	768	780
Inclusion criteria			
Age (years)	≤65	≤65	≤65
Male sex (%)	100	100	90
EF (%)	>35	>50	>30
Significant stenosis (%)	≥50	≥50	≥70
Baseline characteristics (%)			
CHC class I/II angina	42[a]	57	74
β-Blockers	12	75	43
EF < 50%	26 (<45%)	0	21
Three-vessel disease (≥50% stenosis)	50	53[b]	51
Randomized to surgery			
Operative mortality (%)	5.8	3.3	1.4
Grafts/patient in three-vessel disease	2.3	2.4	2.8
Graft patency (%)			
12–18 months	70	75	90
60 months	67	69	82
Randomized to medical therapy (%)			
CABG by 10–12 years	38	36	38

CABG, coronary artery bypass graft surgery; CASS, Coronary Artery Surgery Study; ECSS, European Cooperative Coronary Study; EF, ejection fraction; CHC, Canadian Cardiovascular Association Classification; VACS, Veterans Administration Cooperative Study.

[a]Twenty-six percent were asymptomatic after myocardial infarction or had nonexertional chest pain.

[b]Eight percent of patients had left main coronary artery disease with lumen narrowing of 50% or more. (Adapted from ref. *16*.)

three-vessel disease and impaired LV dysfunction (but without left main CAD) was defined as having high angiographic risk. In this subgroup, the 7-year survival was 52% in the medically treated group vs 76% in the CABG group ($p = 0.002$). The survival advantage of bypass surgery was sustained at 11 years (38% medical vs 50% surgical, $p = 0.026$) *(9,10)*, but not by 18 years (23% medical vs 24% surgical, $p = 0.49$) *(11)*.

The ECSS was the second large, multicenter, randomized controlled trial of medical therapy vs CABG for patients with stable angina. It enrolled 768 patients from 1973 until 1976, but excluded any patient with an EF less than 50% *(12)*.

CASS was the third large, multi-center, randomized controlled trial of bypass surgery for stable angina. Patients in New York Heart Association (NYHA) class III/IV or with an EF less than 35% were specifically excluded. A total of 780 patients were randomly assigned from 1975 to 1979. There were, however, 160 patients with an EF less than 50%; in this subgroup, there was a survival benefit to bypass surgery at 7 years (70% medical vs 84% surgical, $p = 0.01$). Importantly, most of the survival advantage was in those patients with triple-vessel disease, whose survival was 65% with medical therapy and 88% with CABG ($p = 0.009$) *(13)*. A survival benefit was also seen in those with LV dysfunction in combination with more severe angina and left main coronary disease *(14,15)*. Although there was no difference in overall survival for all patients at 10 years, patients with an EF less than 50% had a survival benefit with surgery (61% vs 79% for the medical and CABG groups, respectively) *(16)*.

In summary, the landmark randomized trials of coronary bypass surgery did demonstrate a survival benefit to patients with advanced CAD and decreased LV function, but it is important to note that these studies were primarily trials of angina and not heart failure. Moreover, they were conducted in an era when surgical mortality was much higher than it is today, and medical therapy for both atherosclerosis and heart failure was essentially nonexistent. In fact, some have argued that the trials have no relevance in today's practice.

Contemporary Retrospective Studies

With improvements in surgical techniques and a growing perception that CABG benefits ischemic LV dysfunction, more contemporary experiences have been reported and are arguably more reflective of current practices. Duke University reported 710 patients with an EF of 40% or less, 301 of whom had CABG. After adjusting for differences between those who did and did not receive operations, the 3-year survival was 86% in the surgical group and 68% in the medical group. The benefits were greatest in the subgroup with the worst tertile of LV function *(17)*.

Yale University reported 83 consecutive patients with an EF of 30% or less who underwent CABG, half of whom had heart failure as the indication for surgery. The survival in this cohort at 3 years was 80%, with concomitant improvements in symptoms (by one NYHA functional class) and ventricular function (EF improved from a mean of 24.6 to 36%, $p < 0.001$) *(18)*.

Finally, in a review of 12 retrospective surgical series, bypass surgery improved 3-year survival by 30 to 50% in patients with LV

dysfunction *(19)*, but at the cost of a higher surgical mortality. This increase in surgical mortality was, not surprisingly, consistent across studies. In a study of 12,471 patients undergoing bypass surgery, the operative mortalities with an EF above 40%, from 20 to 40%, and less than 20% were 2.3, 4.8, and 9.8%, respectively ($p < 0.001$) *(20)*. In fact, this surgical mortality paradox is often the clinical dilemma of whether to accept the high perioperative mortality for the potential long-term mortality benefit.

ISCHEMIC HEART DISEASE AND HEART FAILURE: PATHOPHYSIOLOGY

Historically, the prevailing perception was that LV dysfunction was the consequence of nonviable scar from myocardial infarction. Yet, early surgical revascularization experience with advanced CAD and concomitant LV dysfunction resulted in improvements in overall ventricular performance, and this improvement was not easily explained by the concept of a scarred hypocontractile ventricle. By the early to mid-1980s, the phenomenon of painless ischemia at rest and myocardial viability began to supplant the previous notion of an irreversibly scarred heart *(21)*. This concept that chronic resting hypoperfusion could result in resting wall motion abnormalities without infarction and was reversible with revascularization was termed *hibernating myocardium (22,23)*.

In a related manner, some areas of myocardium, although well perfused at rest (therefore not hibernating), may easily become ischemic because of a tenuous blood supply from severe epicardial CAD. With repeated bouts of episodic ischemia, the myocardium may become dysfunctional, a process referred to as *stunning*. Although these entities are thought of as clinically distinct (stunning in acute ischemic events and hibernation in chronic stable coronary disease), they often coexist in the same patient and even in the same myocardial territory *(24)*. Most important, both conditions are potentially reversible with revascularization.

Hibernation is an adaptive response of the myocyte to a level of perfusion sufficient for the preservation of the low-energy demands of maintaining cellular integrity, but inadequate for the high-energy demands of contractile function *(25)*. Although the myocyte can maintain cellular integrity when blood flow is reduced by 40–60%, greater reductions in blood flow usually result in membrane dysfunction *(26)*. In the setting of hypoxia, the myocyte shifts to glucose utilization to meet its metabolic demands. However, glycolysis can only be maintained if there is enough

blood flow to ensure the supply of glucose and the removal of inhibitory metabolites, such as lactate *(27,28)*. Thus, hibernating myocardium exists in a delicate balance between blood flow adequate enough to avert cellular death, but insufficient for contractile function.

Although cellular integrity may be maintained, intracellular functions may be altered. Hibernating myocardium at the time of bypass surgery demonstrates characteristics of dedifferentiation with loss of contractile elements and an increase in the interstitial space *(29)*. Subsequent investigations have shown cytoskeletal disorganization, interstitial fibrosis, and markers of apoptosis, but not signs of ischemic cell death. Therefore, the hibernating myocyte is not merely a normal cell with reduced metabolic activity *(30)*. It eventually undergoes a process of architectural disorganization and extracellular fibrosis that may lead to apoptotic signaling. Hence, the time from restoration of flow to clinically detectable improvement in contractile function depends on the severity of the intracellular alterations that have occurred. If hypoperfusion is allowed to persist long enough, there may be myocyte loss, irreversible cell damage, or an unfavorable extracellular matrix that may diminish the magnitude of any potential improvement in contractile function *(31)*. However, if hibernation (and/or stunning) can be identified before irreversible cell damage or death, restoring adequate blood flow by revascularization should improve myocardial function. This concept of recoverable myocardial function in the setting of compromised blood flow is known as *myocardial viability.*

ASSESSMENT OF MYOCARDIAL VIABILITY

Early techniques to assess myocardial viability were primitive but important because perioperative morbidity and mortality could be prohibitive if clinical improvement was not likely. Early strategies included the use of ventriculography or echocardiography to assess improvements in regional ventricular contractility after nitrate administration *(32–34)* or after provoked extrasystoles *(35,36)*. Other provocative methods have used inotropic agents *(37)* and exercise *(38)*. In contemporary practice, detection of myocardial viability employs one of three strategies: (1) identifying metabolically active myocardium (i.e., radionuclide perfusion imaging), (2) assessing contractile reserve (i.e., dobutamine echo), or (3) quantifying myocardial scar (i.e., cardiac magnetic resonance imaging [MRI]).

Positron Emission Tomography

The determination of viability with positron emission tomography (PET) scanning involves the independent assessments of myocardial

blood flow and cell viability. Blood flow to the myocardium is most commonly measured with ^{13}N-ammonium, but ^{15}O-water, ^{82}Rb, and other single-photon emission computed tomography (SPECT) perfusion tracers have been employed *(39)*. Metabolically active myocytes, especially hypoperfused myocytes that rely more heavily on glycolysis, will transport glucose intracellularly; thus, myocardial cell viability is inferred by uptake of ^{18}F-deoxyglucose (FDG) *(40)*. The perfusion scan is then matched with the metabolism scan. Normal myocardium will have normal perfusion and metabolism. Scar will have both decreased perfusion and decreased metabolism. Hibernating and viable myocardium will have decreased perfusion, but normal metabolism *(41)*. For these reasons, PET is often considered the gold standard for the noninvasive assessment of viability. Unfortunately, the lack of wide availability of this technology has limited its clinical utility.

A landmark study by Tillisch et al. in 1986 first applied PET to the assessment of myocardial viability and found an accuracy of 92% for the prediction of postoperative improvements in LV wall motion *(42)*. Their observations have been confirmed in numerous subsequent studies of PET in the prediction of viability. A meta-analysis of 17 such studies (including 462 patients) demonstrated an overall positive predictive accuracy of 76% and a negative predictive accuracy of 82% for improvement of wall motion after revascularization *(41)*. Furthermore, in a multivariate model for predicting improvement in LV function, PET viability was a strong independent predictor of recovery *(43)*.

Thallium Perfusion Imaging

There are two basic protocols for assessing viability with thallium 201 (Tl 201), rest–redistribution and stress–redistribution–reinjection. Thallium 201, a potassium analogue, is actively transported into the myocardium by a sodium–potassium pump. After injection, the tracer initially distributes into viable cells based on the distribution of blood flow. After several hours, thallium can be redistributed into myocardium independent of blood flow and thus is a marker of preserved cellular metabolism and hence viability *(44)*. During a rest–redistribution scan, Tl 201 is injected at rest, and baseline images are obtained. Hypoperfusion is manifested by a defect on the resting scan. The redistribution images are obtained 3 or 4 hours later. The resting scan is then compared to the redistribution scan. Viability is inferred by defects in Tl 201 uptake at rest that "fill in" on the redistribution scan.

However, this technique may incorrectly identify scar as viable myocardium. Both hibernating myocardium and nontransmural scar

Fig. 1. Improvement in dysfunctional segments after revascularization based on the level of Tl 201 uptake after 4 hours of redistribution. (Adapted with permission from ref. *53*.)

can produce an area of decreased perfusion that redistributes (fills in) and is associated with a resting wall motion abnormality *(45)*. Conversely, the lack of uptake after redistribution does not necessarily equate with scar *(26,46,47)*. When the redistribution phase is lengthened from several hours to as long as 8–48 hours, there is greater distinction between scar and hibernating myocardium *(48)*. Unfortunately, longer intervals between rest and redistribution scans lead to poor image quality because of tracer decay or washout *(49)*. A second injection of Tl 201 has been used to overcome this loss of tracer intensity and substantially improves viability detection *(50–52)*. As many as half of fixed defects in a redistribution scan can show enhancement after reinjection *(51)*.

Because Tl 201 activity in the myocardium is present across a continuum of values, a minimum value is often arbitrarily used as a cutoff to determine clinical viability. Myocardial defects with counts below this cutoff are therefore labeled "irreversible." Although there is no ideal single value, 50% of the maximal tracer uptake is commonly used as this cutoff. However, viability is not binary at a prespecified cutoff value, although the chance of functional recovery decreases progressively as thallium counts fall (Fig. 1) *(53)*. Moreover, the ability of thallium techniques to predict functional recovery at a particular activity value for viability is worse in areas of akinesis than hypokinesis *(53)*. Therefore, it is possible that irreversible defects by TI 201 may still be viable, especially when assessed by PET. Only the most severe perfusion defects correlate well with PET nonviability *(54)*. These cutoff values are important to note and

may account for the variable diagnostic accuracy of this technique in the literature.

The diagnostic accuracy of Tl 201 scintigraphy can be improved with exercise. In areas with equivocal viability by tracer uptake, the finding of reversible ischemia on stress imaging predicts recovery of function *(55)*. Exercise stress imaging also provides the additional prognostic information of exercise capacity. Finally, combining various features of Tl 201 scintigraphy, such as stress-induced ischemia, wall motion abnormalities, late redistribution activity, and the use of absolute of tracer counts, can refine the interpretation of viability.

Despite these technical issues, Tl 201 scintigraphy is sensitive. Pooled data from several studies showed that the use of Tl 201 for viability has a sensitivity of 86–90% and specificity of 47–54% for predicting improvement in postrevascularization wall motion *(40)* and compares favorably to PET *(56)*.

Technetium-99 Perfusion Imaging

The technetium-based tracers ^{99m}Tc-sestamibi and ^{99m}Tc-tetrofosmin have also been used for the assessment of myocardial viability. Technetium-based agents cross cell membranes passively and then bind to mitochondria. These tracers distribute according to perfusion and viability of the myocardium *(44,57)*, but do not redistribute as extensively as Tl 201. However, they are similar to Tl 201 in their ability to demonstrate viability and predict recovery of function *(58–61)*. Pooled data from seven studies of ^{99m}Tc-sestamibi showed a sensitivity of 81% and specificity of 60% for the detection of functional recovery after revascularization and can be improved with the administration of nitrates *(40)*. Finally, in one series, ^{99m}Tc-tetrofosmin had a sensitivity of 96% and specificity of 30% for predicting viability *(58)*.

In summary, the primary advantages to the use of thallium- or technetium-based scintigraphy are their widespread availability and high sensitivity. The tracers are generally similar in their ability to predict improvement in LV function. Drawbacks to the technology include motion artifacts, attenuation of counts from other organs, and the time to obtain, process, and interpret the data. Continuous technological improvements are helping to minimize these disadvantages.

Dobutamine Echocardiography

In early studies of myocardial viability, inotropic agents often improved the function of hypokinetic or akinetic myocardial segments. Although the hibernating myocyte may have a perturbed cytoskeletal structure and a decreased quantity of contractile fibers,

it is often still capable of responding to inotropic agents through β-receptor stimulation.

Low-dose dobutamine stress echocardiography (LDSE) can demonstrate this contractile reserve and imply viability. During infusion of low-dose dobutamine (<5 μg/kg/min), hypocontractile viable myocardium is stimulated to contract (via adrenergic β-1-receptors), but not to a level at which the increased oxygen demand outstrips its supply. The sensitivity, specificity, and diagnostic accuracies of LDSE to predict postoperative improvements in LV function are variable and range from 71 to 97%, 63 to 96%, and 70 to 91%, respectively *(62)*. When compared to Tl 201, LDSE generally shows a higher specificity and lower sensitivity for viability *(63,64)*.

The lower sensitivity may be because of the inability to deliver the substrate necessary to increase contractile function when there is advanced cytoskeletal disarray, so the dobutamine stress results in an ineffectual or absent contractile response *(24)*. Echocardiography is also better at predicting functional recovery of hypokinetic rather than akinetic segments *(65)*, although this is true of thallium imaging as well *(24)*. As noted by Bonow *(24)*, the ability of LDSE to predict postrevascularization improvements in wall motion more accurately than PET or SPECT may not be surprising because viability is typically defined by improvements in echocardiographically assessed wall motion.

The specificity of dobutamine stress echocardiography (DSE) for the detection of viability is improved by a phenomenon known as the *biphasic response*. The biphasic response is an improvement in wall motion at low doses of dobutamine, but a diminution in function with higher doses *(66)*. It was postulated that this represented a mismatch between limited perfusion because of coronary disease and the increasing metabolic demand from dobutamine, resulting in myocardial ischemia and dysfunction. Hence, at low doses there is improved contractile function (as in LDSE), but at higher doses of dobutamine, the myocardium becomes ischemic and dysfunctional as the demands of contractile function surpass the supply of metabolic substrate. The presence of a biphasic response increases the specificity of DSE for predicting functional recovery to 73% *(67)* and improves the concurrence with radionuclide imaging *(68)*.

In summary, dobutamine stress echocardiography is widely available and is generally lower in cost compared to both PET and SPECT. It also can be performed quickly and even portably. Concomitant echocardiography also provides other details about ventricular and valvular structure and function. Disadvantages include poor acoustic windows from lung disease, obesity, or immobility. Interpretation can

be difficult if the endocardium is not well delineated or if there is tethering from adjacent abnormal segments *(69)*. Some of these technical issues can be ameliorated with the use of echocontrast agents. Finally, as compared to scintigraphic techniques, it has greater specificity, although less sensitivity.

Cardiac MRI

Cardiac MRI is playing an increasingly important role in the assessment of viability. Improvements in contrast-enhanced MRI have led to the ability to detect myocardial perfusion and scar with high spatial resolution. Ischemic wall motion is detected via a dobutamine protocol similar to DSE. Quantification of a gadolinium-based contrast material in the myocardium is used to measure myocardial blood flow. Scar is manifest by hyperenhancement in the ventricular myocardium. Hyperenhancement is seen after myocardial infarction, but not in patients with nonischemic cardiomyopathies or in normal volunteers *(70)*. In the first large study of contrast-enhanced MRI by Kim et al., 78% of nonhyperenhancing dysfunctional segments improved after revascularization *(71)*. Furthermore, MRI was more predictive of improvement in ventricular segments with akinesia and dyskinesia than in areas of hypokinesia, which is just the converse of PET and SPECT. There was also an inverse relationship between the burden of hyperenhancement and the likelihood of improvement in wall motion after revascularization.

Contrast-enhanced dobutamine MRI will likely become an important tool in the detection of myocardial viability. The advantage of contrast-enhanced dobutamine stress MRI is the ability to combine measures of baseline and stress wall motion and myocardial perfusion with myocardial scar visualization. Disadvantages include lack of wide availability and the inability to accommodate patients with metallic hardware common to this population, such as pacemakers and implantable defibrillators.

In summary, PET still is considered the test to which other modalities are compared for predicting viability. The other radionuclide agents are similar to PET and provide excellent sensitivity, but dobutamine echocardiography and MRI have superior specificity (Fig. 2).

Problems in Assessing the Accuracy of Methods to Detect Myocardial Viability

If recovery of ventricular systolic function defines viability, then the gold standard for judging the accuracy of a diagnostic technique rests solely on the assessment of postrevascularization ventricular function *(72)*. However, it is not clear when to assess the impact of surgical

Fig. 2. Analysis of sensitivity and specificity of various modalities for predicting improvement in LV function after revascularization from multiple studies. The positive predictive value of each test is represented by the gray bars, and the inverse of the negative predictive value is represented by the open bars. CABG, coronary artery bypass graft surgery; Echo, echocardiography; FDG, ^{18}F-deoxyglucose; LV, left ventricular; MBF, myocardial blood flow; PET, positron emission tomography; PTCA, percutaneous transluminal coronary angioplasty; SPECT, single-photon emission tomography. (Reproduced with permission from ref. *24*.)

revascularization on ventricular function in the postoperative period, despite the fact that most studies base the accuracy of preoperative viability testing on assessments of ventricular function soon after surgery. Given the potential severity of the cytoskeletal disarray in hibernating myocardium, it is not surprising that full functional recovery may take months. Several studies have demonstrated such delayed recovery after revascularization does take place *(73,74)*. Conversely, viable segments may improve in function without a substantial impact on overall LV function *(75)*. In fact, in one series, the survival of patients undergoing bypass surgery without preoperative viability testing was independent of postoperative improvements in their EF *(76)*.

Completeness of revascularization will also have an impact on the predictive accuracy of tests for postoperative improvements in LV function (Table 2). If there is hypoperfusion of the myocardium from poor runoff, stenosis at the anastomotic site, development of graft atherosclerosis, or progression of native coronary disease distal to the anastamosis, there may not be functional recovery. Similarly, if the graft fails

Table 2
Factors Affecting Improvement in Left Ventricular Function After Coronary Artery Revascularization

1. Presence and degree of preoperative myocardial hibernation or stunning
2. Coronary anatomy
3. Completeness of revascularization
4. Presence and degree of intraoperative or postoperative myocardial infarction
5. Graft patency
6. Method for determining ventricular function
7. Left ventricular size
8. Time from revascularization to assessment of ventricular function
9. Presence of concomitant myopathy

Adapted from ref. *75.*

and the myocardium becomes infarcted, there will be a lack of functional recovery *(45)*. Trials have shown the predictive accuracy of rest–redistribution Tl 201 is improved with the exclusion of inadequately revascularized segments *(77)*. However, few trials address the completeness of revascularization.

OTHER BENEFITS OF SURGICAL REVASCULARIZATION IN HEART FAILURE

In multivariate models used to predict postrevascularization ventricular function *(43)*, preoperative myocardial viability only accounts for 36% of the variability in the postsurgical EF *(78)*. Therefore, some have questioned whether recovery of ventricular function is the most clinically relevant end point for patients with advanced CAD and heart failure. Statistical improvements in the contraction of segments of myocardium or even in total EF may not easily translate into tangible benefits unless they impact on symptom relief, QoL, or survival. Various studies have examined such end points in addition to postoperative ventricular systolic function.

Symptoms

The identification of viability may identify those most likely to derive symptomatic benefit from surgery. In a study of 36 patients with symptomatic heart failure (a third also had angina) and poor ventricular function (mean EF 28%), the total extent of PET mismatch corresponded

linearly with postoperative symptomatic improvement. In fact, those with the largest mismatch had the greatest degree of benefit *(79)*. Improvement in symptoms also paralleled an improvement in survival *(80)*.

Other techniques to identify viability also predict symptomatic improvements. Bax et al. *(81)* used DSE to assess viability in 62 patients, more than half of whom had heart failure as the indication for revascularization. For those patients with four or more viable segments by DSE, the mean NYHA functional class improved from 3.2 to 1.6 ($p < 0.01$) after revascularization and corresponded to an increase in the EF from 27 to 33% ($p < 0.01$). There were no improvements in symptoms or ventricular function in patients with less than four viable segments.

Quality of Life

QoL was investigated in a study of 73 patients (mean EF 28% and mean NYHA class 2.6) who had both PET and DSE prior to bypass surgery. Improvement in exercise capacity correlated with amount of viability by PET but not by echo. The mean NYHA functional class improved from 2.6 to 1.9, but correlated weakly with the viability assessments. Interestingly, QoL scores improved significantly with no correlation to viability *(82)*. The presence of viability contributed to improved symptoms, but QoL may be too complex a measure to be driven solely by symptomatic improvement. In fact, the contribution of the placebo effect of surgery cannot be discounted and was an important confounder in the transmyocardial laser revascularization studies of chronic medically refractory angina.

Survival

Early studies of PET showed 3-year survival was similar to cardiac transplantation with surgical revascularization when viability was present *(83)*. Revascularization of PET-viable territories also decreased nonfatal ischemic events compared to those who were treated medically *(84)*. Other studies have demonstrated decreased incidence of myocardial infarction, cardiac arrest, and death when PET viability was present before revascularization *(85)*. Tl 201 viability has also been shown to improve survival after revascularization *(86–89)* and is independent of age, EF, and number of diseased vessels *(90)*.

Scintigraphic techniques appear comparable when trying to predict survival. For example, ^{13}N-ammonia/^{18}FDG PET and stress/rest ^{99m}Tc-sestamibi SPECT were compared in 103 patients with a mean NYHA class of 2.5 and advanced LV dysfunction (a third had EF <30%). The

revascularization team was blinded to the specific test, and the patients received either percutaneous transluminal coronary angioplasty or CABG if there was demonstrable viability; otherwise, they received medical management. The cardiac event-free survival 28 months after revascularization was improved to the same degree regardless of whether SPECT or PET was used to determine viability *(91)*.

Improvements in ventricular geometry may also predict survival and make the use of echocardiographic techniques to assess viability attractive. Using LDSE, an improvement in ventricular geometry predicted a twofold increase in 4-year survival *(92)*. Along with improvements in NYHA class and EF, LDSE viability predicts survival with surgical revascularization when compared to medical management alone *(81,86,93,94)*. Furthermore, LDSE viability was the strongest predictor of survival in a multivariable analysis *(95)*. Lack of echocardiographic viability also predicts an absence of survival benefit with revascularization. In one investigation (Fig. 3), survival from cardiac death after a mean of 40 months was 97% for patients with viability who had revascularization, 69% for those with viability with medical treatment, 50% for those without viability who had revascularization, and 56% for those without viability who were treated medically *(93)*.

A meta-analysis of 24 studies of viability with PET, thallium perfusion, or dobutamine echocardiography was performed to compare the impact of viability testing on prognosis. More than 3000 patients with a mean EF of 32% were followed for more than 2 years. Annual mortality after revascularization with viable myocardium was 3.2% compared to 16% with medical treatment ($p < 0.0001$). If there was demonstrable viability, then the patients with the worst preoperative EF had the greatest degree of benefit. Last, patients with viable myocardium who were treated medically had a death rate of 16% compared with 6.2% (Fig. 4) for patients who had no viability and were treated medically *(96)*.

To conclude, testing for viability to assess suitability for subsequent revascularization of patients with CAD and LV function appears to predict not only improvements in LV function, but also improvements in symptoms and survival. However, the published data to date, as Bonow noted, are generally derived from small, single-center observational trials, with viability treated in a binary fashion and using a mix of surgical and percutaneous revascularization in patients with various degrees of heart failure and angina *(97)*. Furthermore, these studies by and large are retrospective and subject to significant bias because the decision to proceed with surgery was rarely randomized.

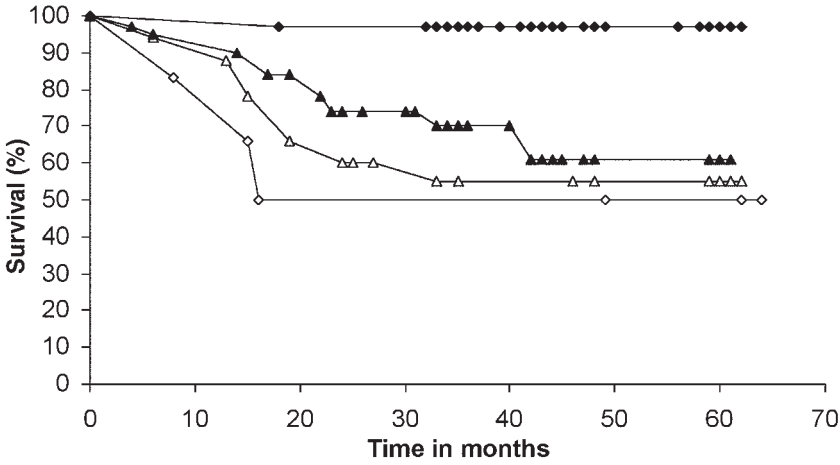


Fig. 3. Effect of myocardial viability by dobutamine echocardiography on survival in 87 consecutive patients with a mean of 2.3 diseased arteries and a mean EF of 25%. Solid diamond, viable myocardium and revascularization; solid triangle, viable myocardium and medical therapy; open triangle, no viable myocardium and medical therapy; open diamond, no viable myocardium and revascularization. (Reproduced with permission from ref. *93*.)

Nonetheless, for the patient with advanced coronary artery disease (and suitable anatomy for revascularization), LV dysfunction, and heart failure, but without angina, revascularization is likely beneficial if viability can be demonstrated. Viability demonstrated by thallium scintigraphy, PET, or dobutamine echocardiography predicts symptomatic improvement, and these modalities are similar in their ability to predict survival after revascularization (Fig. 5). Equally important, patients who lack significant myocardial viability probably do not benefit, and are potentially harmed, from surgery when compared to contemporary medical and device therapies for heart failure.

This body of evidence has contributed to the current recommendations by the American Heart Association/American College of Cardiology (AHA/ACC) for CABG *(98)* in patients with LV dysfunction (*see* Table 3). The choice of method for the preoperative assessment of myocardial viability is ultimately dependent on local expertise and familiarity because the various modalities appear to be comparable (Table 4). Some centers use more than one modality to take advantage of the high sensitivities of certain techniques (i.e., scintigraphic tests) and the high specificities of others (i.e., dobutamine echocardiography or cardiac stress MRI).

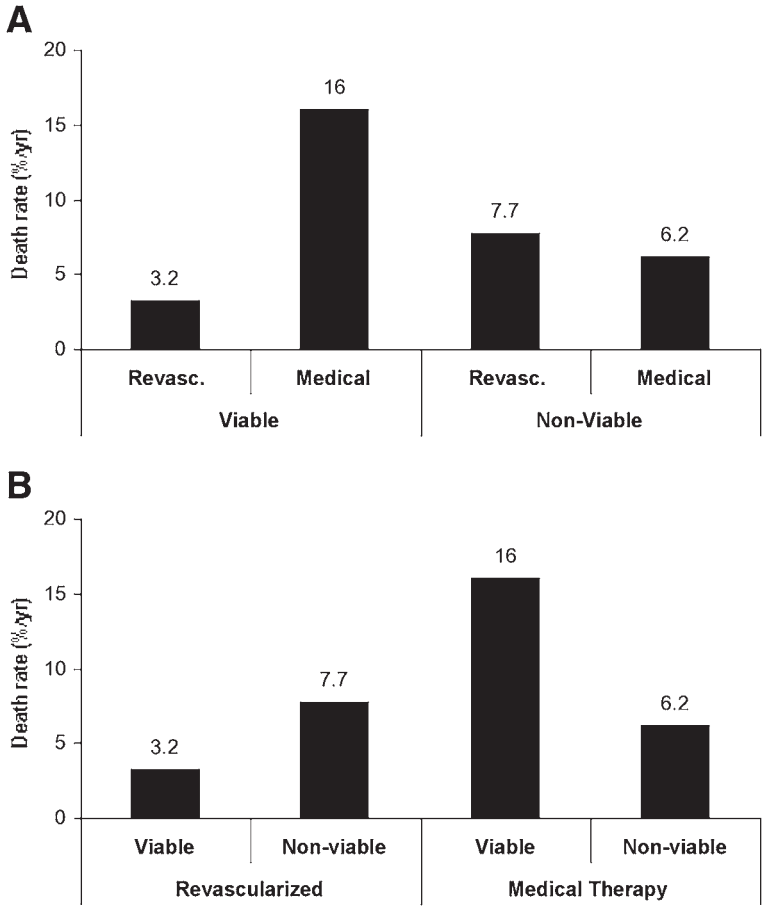


Fig. 4. The results of a meta-analysis of 24 studies using positron emission tomography, thallium 201 perfusion, or dobutamine echocardiography to assess viability in patients with coronary artery disease and left ventricular dysfunction. **(A)** Death rates for patients with and without myocardial viability treated by revascularization (Revasc.) or medical therapy. **(B)** Death rates for patients treated by revascularization or medical therapy with and without demonstrable viability. (Adapted from ref. *96*.)

SURGICAL VENTRICULAR REMODELING

Surgical remodeling of the ventricle, especially when significant ventricular distortion is present, can improve ventricular function and can be performed concomitantly with coronary bypass grafting *(99)*. This procedure, as modified by Dor, involves decreasing the scar size by apposing the surrounding viable myocardium directly or through a pericardial patch *(100)*. By maintaining LV geometry at a lower

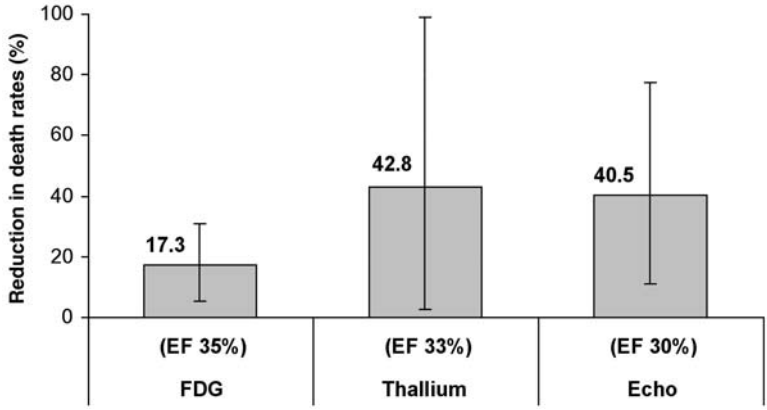


Fig. 5. The results of a meta-analysis of 11 studies of F-18 fluorodeoxyglucose (FDG) positron emission tomography, 6 studies of thallium 201 perfusion imaging, and 7 studies of dobutamine echocardiography on survival in patients with coronary artery disease and LV dysfunction. The mean EF of the patients is listed in parentheses above the modality used to assess viability. The mean decrease in mortality after the revascularization of viable myocardium is represented by the bar graph; the lines represent the 95% confidence intervals. The decrease in mortality is not statistically significantly different between the three modalities for detecting viability. (Adapted with permission from ref. *96*.)

volume, many of the adverse consequences of LV dilation can be pacified *(101,102)*. A study reviewed this approach in 439 patients, 89% of whom had simultaneous bypass surgery, from a variety of surgical centers. Both ventricular function and geometry improved, with the mean EF increasing from 29 to 39% ($p < 0.0001$), and the end systolic volume decreasing from 109 mL/m^2 to 69 mL/m^2 ($p < 0.005$). Most important, in the mortality at 18 months was an acceptable 10.8% *(103)*.

THE FUTURE OF MECHANICAL REVASCULARIZATION IN HEART FAILURE

It still remains that no prospective randomized trial exists to address the problem of revascularization for heart failure and ischemic LV dysfunction. Although current retrospective literature is supportive of surgery in this clinical situation, the evidence is far from definitive. In response to this dilemma, the National Institutes of Health is sponsoring a multicenter prospective randomized trial, the Surgical Treatment for Ischemic Heart Failure (STICH) study. It is recruiting patients with

Table 3
ACC/AHA/ASNC Consensus Recommendations for Radionuclide Techniques to Assess Myocardial Viability

Indication	*Test*	*Class*	*Level of evidence*
1. Predicting improvement in regional and global LV function after revascularization	Stress–redistribution–reinjection	I	B
	Rest–redistribution imaging	I	B
	Perfusion plus PET FDG imaging	I	B
	Resting sestamibi imaging	I	B
	Gated SPECT sestamibi imaging	IIa	B
	Late Tl 201 redistribution imaging (after stress)	IIb	B
2. Predicting improvement in heart failure symptoms after revascularization	Perfusion plus PET FDG imaging	IIa	B
3. Predicting improvement in natural history after revascularization	Tl 201 imaging (rest–redistribution and stress–redistribution–reinjection)	I	B
	Perfusion plus PET FDG imaging	I	B

ACC, American College of Cardiology; AHA, American Heart Association; ASNC, American Society of Nuclear Cardiology; LV, left ventricular; PET, positron emission tomography; FDG, ^{18}F-deoxyglucose; SPECT, single-photon emission computed tomography; Tl 201, thallium 201.

Recommendation class: I, conditions for which there is evidence for and/or general agreement that the procedure or treatment is useful and effective; IIa, the weight of evidence or opinion is in favor of the procedure or treatment. IIb, usefulness/efficacy is less well established by evidence/opinion.

Level of evidence B: Data derived from a single randomized clinical trial or nonrandomized studies. (Adapted from ref. *49*.)

Table 4
ACC/AHA Guidelines for the Indications for CABG in Patients With Poor LV Function

Class I
1. Significant left main coronary artery stenosis
2. Left main equivalent: significant (≥70%) stenosis of the proximal LAD and proximal left circumflex artery
3. Proximal LAD stenosis with two- or three-vessel disease
Class IIa
Poor LV function, with significant viable noncontracting revascularizable myocardium and without any of the above anatomic patterns
Class III
Poor LV function, without evidence of intermittent ischemia and without evidence of significant revascularizable viable myocardium

ACC, American College of Cardiology; AHA, American Heart Association; CABG, coronary artery bypass graft surgery; LV, left ventricular; LAD, left anterior descending coronary artery.

Recommendations class: I, conditions for which there is evidence for and/or general agreement that the procedure or treatment is useful and effective; IIa, the weight of evidence or opinion is in favor of the procedure or treatment; III, conditions for which there is evidence and/or general agreement that the procedure or treatment is not useful/effective and in some cases can be harmful. (Adapted from ref. *98*.)

ischemic LV dysfunction with an EF less than 35%, CAD amenable to surgical revascularization, and NYHA class 2–4 heart failure at 50 centers with a goal enrollment of 2800 patients. The overall study design is to randomly assign patients, stratified by presence or absence of angina and by the presence or absence of a large akinetic territory, either to surgery or to continued medical therapy. Those with large akinetic territories will be eligible to undergo surgical ventricular restoration (SVR; i.e., surgical remodeling).

Patients without angina will be divided into two groups: 1600 patients with SVR-ineligible anatomy and 600 patients who are SVR eligible. The SVR ineligible will be randomly assigned to medical therapy vs CABG alone. The SVR eligible will be randomly assigned to one of three arms: medical therapy, CABG alone, or CABG and SVR. Finally, in a subgroup study of 600 patients with angina, those with heart failure and a large area of akinesis will be randomly assigned to conventional CABG alone or CABG and SVR.

The trial will have a minimum follow-up of 3 years. The study has an 89% power to demonstrate a 20% reduction in the combined end point of all-cause death for CABG compared to medical therapy. For SVR-eligible patients, the study has a 90% power to detect a 20% difference in the end point of survival free of hospitalization for cardiac causes when compared to CABG alone or medical therapy. All screened patients who meet inclusion criteria for any of the trial's arms but who refuse study entry will be followed in a registry.

The study will also include an investigation of the noninvasive assessment of viability with cardiac MRI, radionuclide imaging, and echocardiography. There will be postoperative assessments of LV function at 4 months and 2 years. The modalities will be assessed for their ability to predict clinical outcomes both individually and in comparison to one another. Substudies will analyze cost, QoL, neurohormonal mediators, proinflammatory cytokines, natriuretic peptides, and polymorphisms in genotype expression. When completed, this study will surely be a landmark effort in refining the evaluation of patients with ischemic heart failure and defining the roles of medical therapy, revascularization, and surgical ventricular remodeling in their subsequent management.

REFERENCES

1. http://www.americanheart.org/downloadable/heart/1075102824882HDSStats2004UpdateREV1-23-04.pdf. American Heart Association, Heart Disease and Stroke Statistics—2004 update. Accessed 1/30/04.
2. Pitt B, Zannad F, Remme WJ, et al. for the RALES Study Investigators. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. N Engl J Med 1999;341: 709–717.
3. Packer M, Coats AJ, Fowler MB, et al. of the Carvedilol Prospective Randomized Cumulative Survival Study Group. Effect of carvedilol on survival in severe chronic heart failure. N Engl J Med 2001;344:1651–1658.
4. Hjalmarson A, Goldstein S, Fagerberg B, et al. Effects of controlled-release metoprolol on total mortality, hospitalizations, and well-being in patients with heart failure: the Metoprolol CR/XL Randomized Intervention Trial in congestive heart failure (MERIT-HF). MERIT-HF Study Group. JAMA 2000;283:1295–1302.
5. Publication Committee for the VMAC Investigators (Vasodilatation in the Management of Acute CHF). Intravenous nesiritide vs nitroglycerin for treatment of decompensated congestive heart failure: a randomized controlled trial. JAMA 2002;287:1531–1540.
6. Moss AJ, Zareba W, Hall WJ, et al. of the Multicenter Automatic Defibrillator Implantation Trial II Investigators. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. N Engl J Med 2002;346:877–883.
7. Abraham WT, Fisher WG, Smith AL, et al. of the MIRACLE Study Group. Multicenter InSync Randomized Clinical Evaluation. Cardiac resynchronization in chronic heart failure. N Engl J Med 2002;346:1845–1853.

8. Bradley DJ, Bradley EA, Baughman KL, et al. Cardiac resynchronization and death from progressive heart failure: a meta-analysis of randomized controlled trials. JAMA 2003;289:730–740.
9. The Veterans Administration Coronary Artery Bypass Surgery Cooperative Study Group. Eleven-year survival in the Veterans Administration randomized trial of coronary artery bypass surgery for stable angina. N Engl J Med 1984;311: 1333–1339.
10. Detre KM, Takaro T, Hultgren H, Peduzzi P. Long-term mortality and morbidity results of the Veterans Administration randomized trial of coronary artery bypass surgery. Circulation 1985;72(suppl):V84–V89.
11. The Veterans Administration Coronary Artery Bypass Surgery Cooperative Study Group. Eighteen-year follow-up in the Veterans Affairs cooperative study of coronary artery bypass surgery for stable angina. Circulation 1992;86:121–130.
12. European Coronary Surgery Study Group. Coronary artery bypass surgery in stable angina pectoris: survival at 2 years. Lancet 1979;1:889.
13. Passamani E, Davis KB, Gillespie MJ, Killip T, for the CASS Investigators. A randomized trial of coronary artery bypass surgery: survival of patients with a low ejection fraction. N Engl J Med 1985;312:1665–1671.
14. Myers WO, for the CASS registry. Improved survival of surgically treated patients with triple vessel coronary artery disease and severe angina pectoris. J Thorac Cardiovasc Surg 1989;97:487–495.
15. Caracciolo EA, Davis KB, Sopko G, et al. Comparison of surgical and medical group survival in patients with left main coronary artery disease. Circulation 1995;91:2325–2334.
16. Alderman EL, Bourassa MG, Cohen LS, et al. Ten-year follow-up of survival and myocardial infarction in the randomized Coronary Artery Surgery Study. Circulation 1990;82:1629–1646.
17. Bounos EP, Mark DB, Pollock BG, et al. Surgical survival benefits for coronary disease patients with left ventricular dysfunction. Circulation 1988;78(suppl): I151–I157.
18. Elefteriades JA, Tolis G, Levi E, Mills LK, Zaret BL. Coronary artery bypass grafting in severe left ventricular dysfunction: excellent survival with improved ejection fraction and functional state. J Am Coll Cardiol 1993;22:1411–1417.
19. Baker DW, Jones R, Hodges J, Massie BM, Konstam MA, Rose EA. Management of heart failure: the role of revascularization in the treatment of patients with moderate or severe left ventricular systolic dysfunction. JAMA 1994;272: 1528–1534.
20. Christakis GT, Weisel RD, Fremes SE, et al. Coronary artery bypass grafting in patients with poor ventricular function. J Thorac Cardiovasc Surg 1992;103: 1083–1092.
21. Rahimtoola SH. The hibernating myocardium. Am Heart J 1998;117:211–221.
22. Rahimtoola SH. A perspective on the three large multicenter randomized clinical trials of coronary bypass surgery for chronic stable angina. Circulation 1985;72:V-123.
23. Braunwald E, Rutherford JD. Reversible ischemic left ventricular dysfunction: evidence for the "hibernating myocardium." J Am Coll Cardiol 1986;8:1467.
24. Bonow RO. Identification of viable myocardium. Circulation 1996;94:2674–2680.
25. Ross J. Myocardial perfusion-contraction matching: implications for coronary heart disease and hibernation. Circulation 1991;83:1076.
26. Iskandrian AS, Schelbert HR. Myocardial viability assessment. J Nucl Med 1994; 35(suppl):1S–3S.

27. Dilsizian V, Bonow RO. Current diagnostic techniques of assessing myocardial viability in patients with hibernating and stunned myocardium. Circulation 1993; 87:1–20.
28. Schelbert HR. Merits and limitations of radionuclide approaches to viability and future developments. J Nucl Cardiol 1;S86–S96.
29. Ausma J, Cleutjens J, Thone F, Flameng W, Ramaekers F, Borgers M. Chronic hibernating myocardium: interstitial changes. Mol Cell Biochem 1995;147:35–42.
30. Elsässer A, Schlepper M, Klövekorn WP, et al. Hibernating myocardium: an incomplete adaptation to ischemia. Circulation 1997;96:2920–2931.
31. Braunwald E, Bristow MR. Congestive heart failure: 50 years of progress. Circulation 2000;102:IV14–IV23.
32. Helfant RH, Pine R, Meister SG, Feldman MS, Trout RG, Banka VS. Nitroglycerine to unmask reversible asynergy. Correlation with post-coronary artery bypass ventriculography. Circulation 1974;50:108.
33. Crawford MH, Amon KW, Vance WS. Exercise two-dimensional echocardiography. Quantification of left ventricular performance in patients with severe angina pectoris. Am J Cardiol 1983;51:1.
34. Stadius M, AcAnulty JH, Culter J, Rösch J, Rahimtoola SH. Specificity, sensitivity, and accuracy of the nitroglycerine ventriculogram as a predictor of surgically reversible wall motion abnormalities [abstract]. Am J Cardiol 1980;45:399.
35. Dyke SH, Cohn PF, Gorlin R, Sonnenblick EH. Detection of residual myocardial function in coronary artery disease using post-extra systolic potentiation. Circulation 1974;50:694–699.
36. Cohn LH, Collins JJ, Cohn PF. Use of the augmented ejection fraction to select patients with left ventricular dysfunction for coronary revascularization. J Thorac Cardiovasc Surg 1976;72:835–840.
37. Nesto RW, Cohn LH, Collins JJ, Wynne J, Holman L, Cohn PF. Inotropic contractile reserve: a useful predictor of increased 5 year survival and improved postoperative left ventricular function in patients with coronary artery disease and reduced ejection fraction. Am J Cardiol 1982;50:39.
38. Rozanski A, Berman D, Gray R, et al. Preoperative prediction of reversible myocardial asynergy by postexercise radionuclide ventriculography. N Engl J Med 1982;307:212–216.
39. Schelbert HR. Metabolic imaging to assess myocardial viability. J Nucl Med 1994; 35(suppl):8S–14S.
40. Bax JJ, Wijns W, Cornel JH, Visser FC, Boersma E, Fioretti PM. Accuracy of currently available techniques for prediction of functional recovery after revascularization in patients with left ventricular dysfunction due to chronic coronary artery disease: comparison of pooled data. J Am Coll Cardiol 1997;30: 1451–1460.
41. Di Carli MF, Hachamovitch R, Berman D. The art and science of predicting postrevascularization improvement in left ventricular (LV) function in patients with severely depressed LV function. Circulation 2002;40:1744–1747.
42. Tillisch J, Brunker R, Marshal R, et al. Reversibility of cardiac wall-motion abnormalities predicted by positron tomography. N Engl J Med 1986;314:884.
43. Beanlands RSB, Ruddy TD, deKemp RA, et al. Positron emission tomography and recovery following revascularization (PARR-1): the importance of scar and the development of a prediction rule for the degree of recovery of left ventricular function. J Am Coll Cardiol 2002;40:1735–1743.
44. Wackers FJ. Myocardial perfusion imaging to assess myocardial viability. J Myocardial Ischemia 1994;6:41–44.

45. McGhie AI, Weyman A. Searching for hibernating myocardium: time to reevaluate investigative strategies? Circulation 1996;94:2685–2688.
46. Manyari DE, Knudtson M, Kloiber R, Roth D. Sequential thallium-201 myocardial perfusion studies after successful percutaneous translumenal coronary angiography: delayed resolution of exercise-induced scintigraphic abnormalities. Circulation 1988;77:86–95.
47. Kiat H, Berman DS, Maddahi J, et al. Late reversibility of tomographic myocardial thallium-201 defects: an accurate marker of myocardial viability. J Am Coll Cardiol 1988;12:1456–1463.
48. Yang LD, Berman DS, Kiat H, et al. The frequency of later reversibility in SPECT thallium-201 stress-redistribution studies. J Am Coll Cardiol 1989;15:334–340.
49. Klocke FJ, Baird MG, Lorell BH, et al. ACC/AHA/ASNC guidelines for the clinical use of cardiac radionuclide imaging—executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/ASNC Committee to Revise the 1995 Guidelines for the Clinical Use of Cardiac Radionuclide Imaging). J Am Coll Cardiol. 2003; 42:1318–1333.
50. Kayden DS, Sigal S, Soufer R, Mattera J, Zaret BL, Wackers FJ. Thallium-201 for assessment of myocardial viability: quantitative comparison of 24-hour redistribution imaging with imaging after reinjection at rest. J Am Coll Cardiol 1991; 19:1121.
51. Dilsizian V, Rocco TP, Freedman NM, Leon MB, Bonow RO. Enhanced detection of ischemic but viable myocardium by the reinjection of thallium after stress-redistribution imaging. N Engl J Med 1990;323:141–146.
52. Zimmerman R, Mall G, Rauch B, et al. Residual ^{201}Tl activity in irreversible defects as a marker or myocardial viability. Circulation 1995;91:1016–1021.
53. Perrone-Filardi P, Pace L, Prastaro M, et al. Assessment of myocardial viability in patients with chronic coronary artery disease: rest-4-hour-24-hour 201Tl tomography versus dobutamine echocardiography. Circulation 1996;94: 2712–2719.
54. Bonow RO, Dilsizian V, Cuocolo A, Bacharach SL. Identification of viable myocardium in patients with chronic coronary artery disease and left ventricular dysfunction: comparison of thallium scintigraphy with reinjection and PET imaging with ^{18}F-fluorodeoxyglucose. Circulation 1991;83:26–37.
55. Kitsiou AN, Srinivasan G, Quyyumi AA, Summers RM, Bacharach SL, Dilsizian V. Stress-induced reversible and mild-to-moderate irreversible thallium defects: are they equally accurate for predicting recovery of regional left ventricular function after revascularization? Circulation 1998;98:501–508.
56. Dilsizian V, Perrone-Filardi P, Arrighi JA, et al. Concordance and discordance between stress–redistribution–reinjection and rest–redistribution thallium imaging for assessing viable myocardium: comparison with metabolic activity by positron emission tomography. Circulation 1993;88:941–952.
57. Medrano R, Lowry R, Young JB, et al. Assessment of myocardial viability with 99mTc sestamibi in patients undergoing cardiac transplantation: a scintigraphic/pathological study. Circulation 1996;94:1010–1017.
58. Matsunari I, Fujino S, Taki J, et al. Quantitative rest technetium-99m tetrofosmin imaging in predicting functional recovery after revascularization: comparison with rest-redistribution thallium-201. J Am Coll Cardiol 1997;29:1226–1233.
59. Gunning MG, Anagnostopoulos C, Knight CJ, et al. Comparison of ^{201}Tl, ^{99m}Tc-tetrofosmin, and dobutamine magnetic resonance imaging for identifying hibernating myocardium. Circulation 1998;98:1869–1874.

60. Kauffman GJ, Boyne TS, Watson DD, Smith WH, Beller GA. Comparison of rest thallium-201 imaging and rest technetium-99m sestamibi imaging for assessment of myocardial viability in patients with coronary artery disease and severe left ventricular dysfunction. J Am Coll Cardiol 1996;27:1592–1597.
61. Udelson JE, Coleman PS, Metherall J, et al. Predicting recovery of severe regional ventricular dysfunction. Comparison of resting scintigraphy with ^{201}Tl and ^{99m}Tc-sestamibi. Circulation 1994;89:2552–2561.
62. Cheitlin MD, Armstrong WF, Aurigemma GP, et al. ACC/AHA/ASE 2003 Guideline Update for the Clinical Application of Echocardiography: summary article. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/ASE Committee to Update the 1997 Guidelines for the Clinical Application of Echocardiography). J Am Soc Echocardiogr 2003;10:1091–1110.
63. Panza JA, Dilsizian V, Laurienzo JM, Curiel RV, Katsiyiannis PT. Relation between thallium uptake and contractile response to dobutamine: implications regarding myocardial viability in patients with chronic coronary artery disease and left ventricular dysfunction. Circulation 1995;91:990–998.
64. Perrone-Filardi P, Pace L, Prastaro M, et al. Assessment of myocardial viability in patients with chronic coronary artery disease: rest-4-hour-24-hour ^{201}Tl tomography vs dobutamine echocardiography. Circulation 1996;94:2712–2719.
65. Smart SC. The clinical utility of echocardiography in the assessment of myocardial viability. J Nucl Med 1994;35(suppl):49S–58S.
66. Chen C, Li L, Chen LL, et al. Incremental doses of dobutamine induce a biphasic response in dysfunctional left ventricular regions subtending coronary stenoses. Circulation 1995;92:756–766.
67. Afridi I, Kleiman NS, Raizner AE, Zoghbi WA. Dobutamine echocardiography in myocardial hibernation: optimal dose and accuracy in predicting recovery of ventricular function after coronary angioplasty. Circulation 1995;91:663–670.
68. Senior R, Lahiri A. Enhanced detection of myocardial ischemia by stress dobutamine echocardiography utilizing the "biphasic" response of wall thickening during low and high dose dobutamine infusion. J Am Coll Cardiol 1995;26:26–32.
69. Hansen TH, Segar DS. The use of dobutamine stress echocardiography for the determination of myocardial viability. Clin Cardiol 1996;19:607–612.
70. Wu E, Judd RM, Vargas JD, Klocke FJ, Bonow R, Kim RJ. Visualization of presence, location, and transmural extent of healed Q-wave and non-Q-wave myocardial infarction. Lancet 2001;357:21–28.
71. Kim RJ, Wu E, Rafael A, et al. The use of contrast-enhanced magnetic resonance imaging to identify reversible myocardial dysfunction. N Engl J Med 2000;343: 1445–1453.
72. McGhie AI, Weyman A. Searching for hibernating myocardium. Time to reevaluate investigative strategies? Circulation 1996;94:2685–2688.
73. Luu M, Stevenson LW, Brunken RC, Drinkwater DM, Schelbert HR, Tillisch JH. Delayed recovery of revascularized myocardium after referral for cardiac transplantation. Am Heart J 1990;119:668.
74. Marwick TH, MacIntyre WJ, Lafont A, Nemec JJ, Salcedo EE. Metabolic responses of hibernating and infracted myocardium to revascularization: a follow-up study of regional perfusion, function, and metabolism. Circulation 1992;85:1347–1353.
75. Iskandrian AS, Heo J, Stanberry C. When is myocardial viability an important clinical issue? J Nucl Med 1994;35(suppl):4S–7S.
76. Samady H, Elefteriades JA, Abbott BG, Mattera JA, McPherson CA, Wackers FJ. Failure to improve left ventricular function after coronary revascularization for

ischemic cardiomyopathy is not associated with worse outcome. Circulation 1999; 100:1298–1304.
77. Ragosta M, Beller GA, Watson D, Kaul S, Gimple LW. Quantitative planar rest-redistribution Tl-201 imaging in detection of myocardial viability and prediction of improvement in left ventricular function after coronary bypass surgery in patients with severely depressed left ventricular function. Circulation 1993;87: 1630–1641.
78. Di Carli MF, Hachamovitch R, Berman DS. The art and science of predicting postrevascularization improvement in left ventricular (LV) function in patients with severely depressed LV function. J Am Coll Cardiol 2002;40:1744–1747.
79. Di Carli M, Asgarzadie F, Schelbert HR, et al. Quantitative relation between myocardial viability and improvement in heart failure symptoms after revascularization in patients with ischemic cardiomyopathy. Circulation 1995;92:3436–3444.
80. Di Carli MF, Davidson M, Little R, et al. Value of metabolic imaging with positron emission tomography for evaluating prognosis in patients with left ventricular dysfunction. Am J Cardiol 1994;73:527–533.
81. Bax JJ, Poldermans D, Elhendy A, et al. Improvement of left ventricular ejection fraction, heart failure symptoms and prognosis after revascularization in patients with chronic coronary artery disease and viable myocardium detected by dobutamine stress echocardiography. J Am Coll Cardiol 1999;34:163–169.
82. Marwick TH, Zuchowski C, Lauer MS, Secknus M, Williams MJ, Lytle BW. Functional status and quality of life in patients with heart failure undergoing coronary bypass surgery after assessment of myocardial viability. J Am Coll Cardiol 1999;33:750–758.
83. Louie HW, Laks H, Milgalter E, et al. Ischemic cardiomyopathy: criteria for coronary revascularization and cardiac transplantation. Circulation 1991;84(suppl): III-290–III-295.
84. Lee KS, Marwick TH, Sevastian AC, et al. Prognosis of patients with left ventricular dysfunction, with and without viable myocardium after myocardial infarction: relative efficacy of medical therapy and revascularization. Circulation 1994;90:2687–2694.
85. Eitman D, Al-Aouar Z, Kanter HL, et al. Clinical outcome of patients with advanced coronary artery disease after viability studies with positron emission tomography. J Am Coll Cardiol 1992;20:559–565.
86. Pasquet A, Robert A, D'Hondt AM, Dio R, Melin JA, Vanoverschelde JLJ. Prognostic value of myocardial ischemia and viability in patients with chronic left ventricular ischemic dysfunction. Circulation 1999;100:141–148.
87. Gioia G, Powers J, Heo J, Iskandrian AS, Russell J, Cassell D. Prognostic value of res-redistribution tomographic thallium-201 imaging in ischemic cardiomyopathy. Am J Cardiol 1995;75:759–762.
88. Chan RKM, Raman J, Lee KJ, et al. Prediction of outcome after revascularization in patients with poor left ventricular function. Ann Thorac Surg 1996;61: 1428–1434.
89. Cuocolo A, Petretta M, Nicolai E, et al. Successful coronary revascularization improves prognosis in patients with previous myocardial infarction and evidence of viable myocardium at thallium-201 imaging. Eur J Nucl Med 1998;25:60–68.
90. Pagley PR, Beller GA, Watson DD, Gimple LW, Ragosta M. Improved outcome after coronary bypass surgery in patients with ischemic cardiomyopathy and residual myocardial viability. Circulation 1997;96:793–800.
91. Siebelink HJ, Blanksma PK, Crijns HJG, et al. No difference in cardiac event-free survival between positron emission tomography-guided and single-photon

emission computed tomography-guided patient management. Am Coll Cardiol 2001;37:81–88.
92. Senior R, Lahiri A, Kaul S. Effect of revascularization on left ventricular remodeling in patients with heart failure from severe chronic ischemic left ventricular dysfunction. Am J Cardiol 2001;88:624–629.
93. Senior R, Kaul S, Lahiri A. Myocardial viability on echocardiography predicts long-term survival after revascularization in patients with ischemic congestive heart failure. J Am Coll Cardiol 1999;33:1848–1854.
94. Afridi I, Grayburn PA, Panza JA, Oh JK, Zoghbi WA, Marwick TH. Myocardial viability during dobutamine echocardiography predicts survival in patients with coronary artery disease and severe left ventricular systolic function. J Am Coll Cardiol 1998;32:921–926.
95. Chaudry FA, Tauke JT, Alessandrini RS, Vardi G, Parker MA, Bonow RO. Prognostic implications of myocardial contractile reserve in patients with coronary artery disease and left ventricular dysfunction. J Am Coll Cardiol 1999;34: 730–738.
96. Allman KC, Shaw LJ, Hachamovitch R, Udelson JE. Myocardial viability testing and impact of revascularization on prognosis in patients with coronary artery disease and left ventricular dysfunction: a meta-analysis. J Am Coll Cardiol 2002; 39:1151–1158.
97. Bonow R. Myocardial viability and prognosis in patients with ischemic left ventricular dysfunction. J Am Coll Cardiol 2002;39:1159–1162.
98. Eagle KA, Guyton RA, Davidoff R, et al. ACC/AHA Guidelines for Coronary Artery Bypass Graft Surgery: a report of the American College of Cardiology/ American Heart Association Task Force on Practice Guidelines (Committee to Revise the 1991 Guidelines for Coronary Artery Bypass Graft Surgery). American College of Cardiology/American Heart Association. J Am Coll Cardiol 1999;34:1262–1347.
99. Cooley DA, Frazier OH, Duncan JM, Reul GJ, Krajacer Z. Intracavitary repair of ventricular aneurysm and regional dyskinesia. Ann Surg 1992;215:417–423.
100. Dor V, Saab M, Coste P, Kornaszewska M, Montiglio F. Left ventricular aneurysm: a new surgical approach. Thorac Cardiovasc Surg 1989;37:11–19.
101. Kono T, Sabbah, HN, Stein PD, Brymer JF, Khaja F. Left ventricular shape as a determinant of functional mitral regurgitation in patients with severe heart failure secondary to either coronary artery disease or idiopathic dilated cardiomyopathy. Am J Cardiol 1991;68:355–359.
102. White HD, Norris RM, Brown MA, Brandt PW, Whitlock RM, Wild CJ. Left ventricular end-systolic volume as the major determinant of survival after recovery from myocardial infarction. Circulation 1987;76:44–51.
103. Athanasuleas CL, Stanley AW Jr, Buckberg GD, Dor V, DiDonato M, Blackstone EH, and the RESTORE group. Surgical anterior ventricular endocardial restoration (SAVER) in the dilated remodeled ventricle after anterior myocardial infarction. J Am Coll Cardiol 2001;37:1199–1209.

3 Aortic Valve Surgery With Severe Left Ventricular Dysfunction

Blasé A. Carabello, MD, FACC

CONTENTS

INTRODUCTION

In most patients with severe aortic stenosis, management is relatively straightforward. Prognosis is excellent even in patients with severe valve obstruction as long as they are asymptomatic. However, once the classic symptoms of angina, syncope, dyspnea, or other symptoms of congestive heart failure (CHF) develop, prognosis dramatically worsens *(1,2)*. Because 75% of symptomatic patients will die within 3 years of the onset of the symptoms unless the aortic valve is replaced, the onset of symptoms is a compelling reason to perform aortic valve

From: *Contemporary Cardiology: Surgical Management of Congestive Heart Failure*
Edited by: J. C. Fang and G. S. Couper © Humana Press Inc., Totowa, NJ

replacement. In many asymptomatic patients, left ventricular (LV) hypertrophy normalizes wall stress, and LV systolic function is normal. However, the increase in wall thickness necessary to compensate the increased pressure term of the Laplace equation (stress equals the pressure times the radius divided by twice the thickness) results in reduced LV compliance and diastolic dysfunction *(3)*. Typically, diastolic dysfunction precedes systolic dysfunction; thus, when congestive symptoms do arise, systolic function is usually normal.

Because the general awareness of the importance of the symptoms has increased since the 1970s and because of the ease of echocardiographic surveillance, most patients with aortic stenosis develop symptoms and receive medical attention while systolic function is still normal. However, some patients still present for the first time with advanced CHF and reduced ejection fraction (EF). Because reduced ejection performance indicates poor prognosis for almost all other heart diseases, the patient with aortic stenosis presenting with CHF and systolic dysfunction often raises concerns about the risks of aortic valve replacement or even whether the patient is a surgical candidate.

CAUSES OF SYSTOLIC DYSFUNCTION

The major determinants of EF are preload, afterload, and contractility. In aortic stenosis, it is conceivable that the left ventricle might become so stiff that sarcomere stretch (preload) is reduced despite increased filling pressure. However, there is currently no evidence that reduced preload is a contributor to reduced systolic function in patients with aortic stenosis. Rather, afterload access alone or in combination with reduced contractility is the usual cause of reduced EF *(4,5)*. Huber and colleagues *(4)* suggested that, in approx 75% of patients with aortic stenosis and reduced EF, afterload mismatch plays some role, and in most patients it plays a dominant role in depressing ejection performance. It seems clear that, when afterload mismatch is the major cause for LV dysfunction, prognosis following surgery is excellent *(5,6)*. When the aortic valve is replaced, aortic orifice area increases, afterload falls, and ejection performance increases. Following surgery, symptoms abate, and lifestyle and life span improve dramatically.

Much more problematic is that group of patients with aortic stenosis and reduced ejection performance for whom contractile dysfunction, often in league with afterload mismatch, is the major cause of reduced EF. Because contractility is often irreversibly depressed in this group of patients, prognosis is much less favorable than in the group of patients for whom afterload mismatch is the prime contributor to LV dysfunction *(5)*.

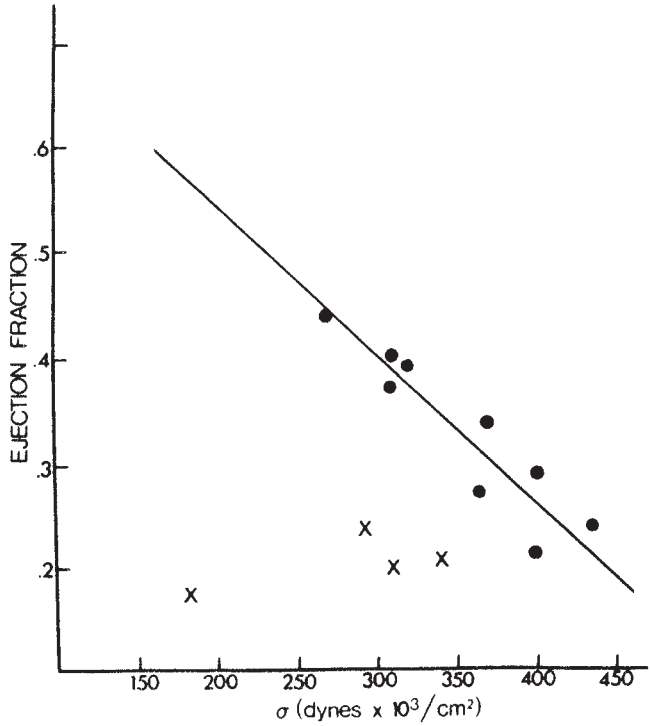


Fig. 1. Ejection fraction (EF) plotted against mean circumferential left ventricular wall stress σ for group 1 (good outcome) (●) and group 2 (bad outcome) (X). Group 2 patients fell below and to the left of group 1 patients, indicating lower EF despite less σ. This is consistent with the concept that left ventricular performance (EF) was depressed in group 1 patients because of afterload mismatch and in group 2 patients because of myocardial failure.

As shown in Fig. 1, in patients with reduced EF for whom reduced performance was primarily the result of increased afterload (increased wall stress), prognosis was excellent; in patients for whom contractile dysfunction played the predominant role, prognosis was poor *(5)*. In general, the computation of wall stress is cumbersome, which has limited its use in clinical practice and even in clinical investigations. However, as shown in Fig. 2, the transaortic pressure gradient performs as a reasonable substitute for afterload. Thus, when gradient is reduced in tandem with reduced EF, prognosis is also reduced because contractility is most severely depressed in those patients with a low gradient *(5)*.

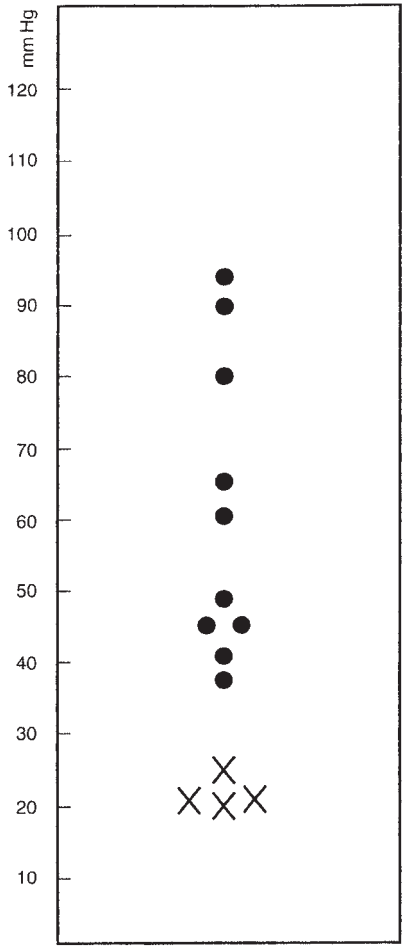


Fig. 2. Mean systolic aortic pressure gradients for patients in group 1 (●) and group 2 (X). Group 2 patients had lower systolic gradients in every case.

Virtually every study that has examined outcome in patients with aortic stenosis has demonstrated that low gradient combined with low EF has a poor prognosis *(5–8)*. A study by the Mayo Clinic demonstrated a 21% operative risk in such patients, and only 50% survived for 4 years *(8)*. Nonetheless, that study and others also demonstrated that many patients in this category do benefit from surgery. A study by the Cleveland Clinic retrospectively matched patients with low EF and low gradient who underwent aortic valve replacement to a similar group who underwent medical therapy *(9)*. Almost all patients on

medical therapy died; most patients undergoing aortic valve replacement survived for at least 3 years. This was the first study to demonstrate a survival benefit of aortic valve replacement in this group of patients with an unfavorable prognosis.

WHICH PATIENTS WITH LOW GRADIENT, LOW EJECTION FRACTION WILL BENEFIT FROM AORTIC VALVE REPLACEMENT?

Currently, it is unknown whether all patients with low EF and low gradient benefit from aortic valve replacement. However, it has become common practice to try to separate patients with severe valve stenosis with low gradient and low EF from those patients with less-severe stenosis by manipulating their hemodynamics. Logically, if severe stenosis has caused ventricular dysfunction, aortic valve replacement should be beneficial. On the other hand, if a ventricle weakened from some other cause, such as coronary disease, is unable to open a mildly stenotic valve (aortic pseudostenosis), its replacement with a prosthesis that is also inherently at least mildly stenotic should be of little advantage. Unfortunately, it has become clear that aortic valve area at rest alone cannot make this distinction. In the group with severe stenosis that has presumably led to muscle damage and LV dysfunction and in the group with aortic valve pseudostenosis, calculated aortic valve area may be reduced equally. In the Cleveland Clinic study *(9)*, no systematic attempt was made to separate these two kinds of patients. Thus, it is possible (although improbable) that patients with mild stenosis do benefit from aortic valve replacement. However, unless there is proof that patients with mild stenosis do benefit from valve replacement, it seems wise to separate those patients with true aortic stenosis and offer an aortic valve replacement to them.

As noted, it is clear that calculation of aortic valve area at rest is insufficient to divorce true aortic stenosis from aortic pseudostenosis. Thus, it has become common practice to increase forward flow, reexamine hemodynamics, and recalculate aortic valve area. Both dobutamine and nitroprusside have been used to manipulate hemodynamics pharmacologically to try to make the distinction between severe aortic stenosis and aortic pseudostenosis. When dobutamine is used, the positive inotropic response increases the force of contraction and forward output. In true stenosis, the increase in gradient is proportionate to the increase in cardiac output, and the valve area remains constant or increases only slightly *(10)*. In aortic valve pseudostenosis, increased forward flow presumably increases the aortic valve orifice such that

flow increases out of proportion to gradient, and the newly calculated valve area increases substantially (>0.3 cm or to a valve area >1.0 cm^2).

Alternatively, nitroprusside can be infused to make the distinction. As shown in Fig. 3, the concept in the use of a vasodilator is that the aortic valve and the total peripheral resistance form two resistances to flow in series *(11–13)*. If the stenotic valve is the primary and most severe resistance to outflow, infusion of a vasodilator will decrease total peripheral resistance, but flow cannot increase through the stenotic valve. As such, there will be a fall in downstream pressure and an increase in gradient with little change in output. In this case, aortic valve area does not increase or may even decrease. On the other hand, if it is the total peripheral resistance that is the major resistor (the valve is not severely stenotic, therefore it is aortic pseudostenosis), then vasodilatation decreases total peripheral resistance, resulting in increased flow through the mildly stenotic valve; the gradient changes little, and the newly calculated valve area increases substantially.

An inherent risk in the use of sodium nitroprusside to make this determination is the potential for fall in downstream pressure in patients with true stenosis. Thus, the drug must be used with caution, increasing the dose in tiny increments while monitoring hemodynamics carefully. It also should be pointed out that if dobutamine is used, there is the risk of precipitating angina in patients with concomitant coronary disease. Thus, it is helpful to know the coronary anatomy before hemodynamic manipulation.

AORTIC VALVE RESISTANCE

In cases of either true or pseudoaortic stenosis, the aortic valve area is flow dependent, increasing as flow increases, albeit the increase is small in true stenosis. Increased aortic valve area with increased flow may indicate a true increase in aperture as greater flow forces greater leaflet separation, or it may be the calculation rather than the valve area itself that is flow dependent *(14)*. One potential reason for this is that the discharge coefficients for the Gorlin formula for calculating aortic valve area were never determined for that valve *(15)*.

These problems have led investigators to use aortic valve resistance as another marker for stenosis severity *(11,12)*. Resistance is simply gradient divided by flow and utilizes no discharge coefficients. Its usefulness has been studied many times, with different investigators coming to disparate conclusions about the usefulness of valve resistance as a gage of aortic stenosis severity. In some studies, resistance was substantially less flow dependent than was valve area when transvalvular

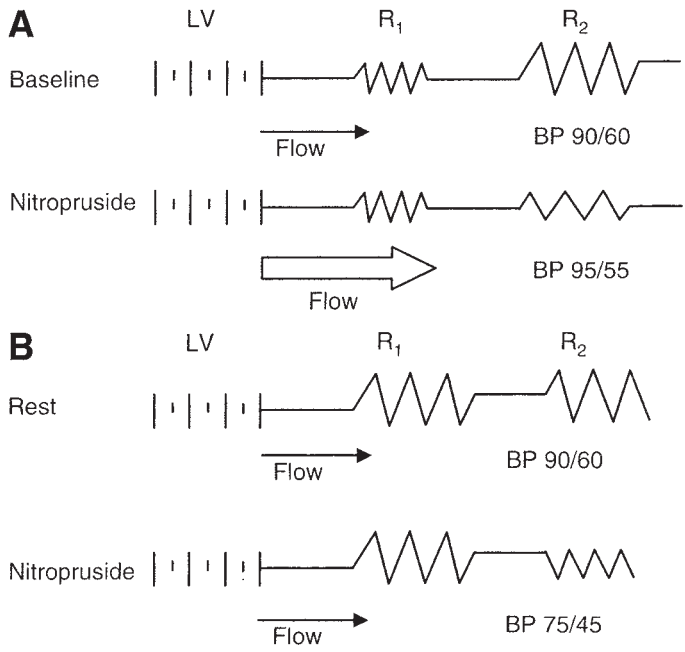


Fig. 3. (A) In this figure depicting aortic pseudostenosis, R_2 (total peripheral resistance) exceeds the resistance offered by a mildly stenotic aortic valve (R_1). When nitroprusside is infused, both resistances become low, and cardiac output increases substantially. **(B)** In the lower panel depicting true aortic stenosis, at rest both R_1 and R_2 are large. However, following nitroprusside infusion, R_2 decreases, but R_1 dose not, resulting in no increase in outflow from the left ventricle, but a fall in blood pressure (which is the product of cardiac output and total peripheral resistance).

flow was altered *(16)*. In other studies, flow dependence was quite variable *(17)*. It could be that this variability itself may be a useful tool. In separating valve types, in rigid valves with little flexibility (truly severely stenotic valves) resistance should change more with flow than valve area (gradient increases more than flow), because area is based on the square root of gradient. On the other hand, in flexible pseudostenotic valves, resistance varies less than aortic valve area *(11)*. Thus, resistance, valve area, and their respective changes to increased flow may all help separate truly stenotic from less-stenotic valves.

OVERALL DIAGNOSTIC STRATEGY

It is clear the transvalvular gradient can be measured or calculated accurately echocardiographically. If the echocardiographic approach is

pursued, patients with low EF and low gradient should be studied at rest and then following infusion of dobutamine. Valve area should be recalculated following infusion. If area increases by more than 0.3 cm^2, pseudostenosis is likely present. If infusion of dobutamine causes a substantial increase in gradient, valve area is likely to remain constant or increases only slightly, indicating the presence of truly severe aortic stenosis. If the patient's left ventricle fails to respond to dobutamine with little change in gradient or output, severe muscle dysfunction without inotropic reserve is present, and such patients have a poor prognosis irrespective of stenosis severity *(18)*.

Although the usefulness of echocardiography is unchallenged, I personally prefer cardiac catheterization in the diagnosis of this group of patients. Because dobutamine may cause myocardial ischemia and therefore decrease rather than increase cardiac function, it is (in my opinion) wise to know the coronary status prior to infusion. This is most easily judged following coronary arteriography. In addition, a right heart catheterization gives important data regarding hemodynamics and their improvement or lack of improvement following pharmacological intervention. Although not the norm, nitroprusside infusion is useful as discussed in the section on which patients benefit from aortic valve replacement. If patients respond to nitroprusside with an increase in cardiac output, a small or no increase in gradient, and an improvement in hemodynamics, severe aortic valve disease is virtually excluded. Furthermore, these results give reassurance that the patient can be treated successfully as an outpatient with vasodilator drugs, drugs usually contraindicated in patients with severe aortic stenosis.

The combined use of aortic valve resistance and aortic valve area during pharmacological manipulation should be explored further. In the patient for whom valve resistance increases dramatically with an increase in flow and the valve area remains relatively constant, it is highly likely that severe obstruction exists, and these patients should be the best candidates for aortic valve replacements. On the other hand, when resistance remains relatively unchanged but valve area increases dramatically, pseudoaortic stenosis is probably present. It should be emphasized that avoiding operation on such patients is based on logic, not fact. It is possible but unlikely that even patients with mild stenosis might improve following aortic valve replacement by relief of mild obstruction to outflow. However, it seems unlikely that the large randomized trial necessary to demonstrate the utility or futility of aortic valve replacement in pseudostenosis will occur.

SURGICAL CONSIDERATIONS

When the decision is made to perform aortic valve replacement, it seems reasonable that all other comorbidities be corrected first. Otherwise, the risk may be prohibitive. Furthermore, of major concern is the type of substitute valve that is placed. Debated in many studies is whether valve size ultimately makes a difference in outcome for patients with aortic stenosis *(8,19,20)*. Some studies have indicated higher mortality and poorer regression of LV hypertrophy when smaller valve sizes with larger gradients are inserted. The hemodynamic logic behind use of valves with the best hemodynamics is obvious, yet some studies have demonstrated that valve size has not affected the outcome.

Irrespective of this debate, it seems most unwise to leave even partial hemodynamic obstruction in patients with such weakened ventricles. If the patient begins with only a 25 mmHg transvalvular gradient, a residual gradient of 10 mmHg represents 40% of the original gradient. Alternatively, one could argue that the additional ischemic time required to implant stentless valves or homografts with better hemodynamics outweighs the hemodynamic advantages of these valves. Clearly, the decision rests with the preferences of the operating surgeon, but logic dictates that the valve with the best hemodynamic profile be implanted in this group of patients.

SUMMARY

For most patients with aortic stenosis, the onset of the symptoms of angina, syncope, or CHF indicates the need for aortic valve replacement. Following surgery in patients who have recently become symptomatic, the outcome is excellent. Although reduced systolic function is usually an indicator of worse prognosis in most types of heart disease, it is not so for patients with aortic stenosis. For those patients whose ejection performance is reduced because of the high afterload presented by the obstructing valve and for whom the left ventricle can still generate a high systolic gradient, prognosis is excellent. Following aortic valve replacement, afterload decreases, ejection performance improves, and symptoms abate.

The most problematic group of patients with aortic stenosis is that group with a low EF, low gradient, and severe LV contractile dysfunction. Although risk is clearly increased, many such patients do benefit, both symptomatically and with improved mortality, from aortic valve replacement. It seems wise (until further data are available) to separate patients with severe valvular obstruction from those with only mild obstruction prior to consideration for surgery.

Using the logic that it is those patients with the severest obstruction who should gain the most benefit from valve replacement, hemodynamic manipulation should be provided either in the echocardiographic or catheterization laboratories. Patients who have a large increase in valve area when cardiac output is increased probably have only mild stenosis and probably will not benefit from aortic valve replacement. Those patients who increase output and increase gradient have severe obstruction and should be the group most likely to benefit. Those patients who fail to augment their inotropic state apparently have the poorest LV function and reserve and poor prognosis.

REFERENCES

1. Ross J Jr, Braunwald E. Aortic stenosis. Circulation 1968;38(suppl V):V-61–V-67.
2. Kelly TA, Rothbart RM, Cooper CM, Kaiser DL, Smucker ML, Gibson RS. Comparison of outcome of asymptomatic to symptomatic patients older than 20 years of age with valvular aortic stenosis. Am J Cardiol 1988;61:123–130.
3. Hess OM, Ritter M, Schneider J, Grimm J, Turina M, Krayenbuehl HP. Diastolic stiffness and myocardial structure in aortic valve disease before and after valve replacement. Circulation 1984;69:855–865.
4. Huber D, Grimm J, Koch R, Krayenbuehl HP. Determinants of ejection performance in aortic stenosis. Circulation 1981;64:126–134.
5. Carabello BA, Green LH, Grossman W, Cohn LH, Koster JK, Collins JJ Jr. Hemodynamic determinants of prognosis of aortic valve replacement in critical aortic stenosis and advanced congestive heart failure. Circulation 1980;62: 42–48.
6. Lund O. Preoperative risk evaluation and stratification of long-term survival after valve replacement for aortic stenosis. Reasons for earlier operative intervention. Circulation 1990;82:124–139.
7. Brogan WC, Grayburn PA, Lange RA, Hillis LD. Prognosis after valve replacement in patients with severe aortic stenosis and a low transvalvular pressure gradient. J Am Coll Cardiol 1993;21:1657–1660.
8. Connolly HM, Oh JK, Schaff HV, et al. Severe aortic stenosis with low transvalvular gradient and severe left ventricular dysfunction: Result of aortic valve replacement in 52 patients. Circulation 2000;101:1940–1946.
9. Pereira JJ, Lauer MS, Bashir M, et al. Survival after aortic valve replacement for severe aortic stenosis with low transvalvular gradients and severe left ventricular dysfunction. J Am Coll Cardiol in press.
10. deFilippi CR, Willett DL, Brickner ME, et al. Usefulness of dobutamine echocardiography in distinguishing severe from nonsevere valvular aortic stenosis in patients with depressed left ventricular function and low transvalvular gradients. Am J Cardiol 1995;75:191–194.
11. Cannon JD, Zile MR, Crawford FA, Carabello BA. Aortic valve resistance as an adjunct to the Gorlin formula in assessing the severity of aortic stenosis in symptomatic patients. J Am Coll Cardiol 1992;20:1517–1523.
12. Carabello BA. Selection of patients for operation: the asymptomatic patient and the patient with poor LV function. Adv Cardiol.
13. Ford LE, Feldman T, Chiu YC, Carroll JD. Hemodynamic resistance as a measure of functional impairment in aortic valvular stenosis. Circ Res 1990;66:1–7.

14. Tardif J, Rodrigues, AG, Hardy J, et al. Simultaneous determination of aortic valve area by the Gorlin formula and by transesophageal echocardiography under different transvalvular flow conditions. Evidence that anatomic aortic valve area does not change with variations in flow in aortic stenosis. J Am Coll Cardiol 1997;29:1296–1302.
15. Gorlin R, Gorlin SG. Hydraulic formula for calculation of the area of the stenotic mitral valve, other cardiac valves, and central circulatory shunts: I. Am Heart J 1951;41:1–29.
16. Bermejo J, Garcia-Fernandez MA, Torrecilla EG, et al. Effects of dobutamine on Doppler echocardiographic indexes of aortic stenosis. J Am Coll Cardiol 1996;28: 1206–1213.
17. Shively BK, Charlton GA, Crawford MH, Chaney RK. Flow dependence of valve area in aortic stenosis: relation to valve morphology. J Am Coll Cardiol 1998; 311998:654–660.
18. Monin JL, Monchi M, Gest V, Duval-Moulin AM, Dubois-Rande JL, Gueret P. Aortic stenosis with severe left ventricular dysfunction and low transvalvular pressure gradients. J Am Coll Cardiol 2001;37:2101–2107.
19. Milano AD, De CM, Mecozzi G, et al. Clinical outcome in patients with 19-mm and 21-mm St. Jude aortic prostheses: comparison at long-term follow-up. Ann Thorac Surg 2002;73:37–43.
20. Arom KV, Goldenberg IF, Emery RW. Long-term clinical outcome with small size standard St. Jude medical valves implanted in the aortic position. J Heart Valve Dis 1994;3:531–536.

4 Mitral Valve Surgery With Severe Left Ventricular Dysfunction

Vinay Badhwar, MD
and Steven F. Bolling, MD

CONTENTS

INTRODUCTION

The management of patients with congestive heart failure (CHF) has become an international health care problem. In the ever-aging population, advances in basic cardiac care that have extended the average life expectancy have also left more people living with chronic cardiac disease than ever before. In the United States alone, nearly 4.9 million suffer from heart failure, yet of the 500,000 new patients diagnosed annually, fewer than 3000 are offered transplantation because of limitations of age, comorbid conditions, and donor availability.

From: *Contemporary Cardiology: Surgical Management of Congestive Heart Failure*
Edited by: J. C. Fang and G. S. Couper © Humana Press Inc., Totowa, NJ

Therapeutic limitations have left a significant number of these patients and their physicians searching for alternate options. Despite improvements in the medical management of CHF, more than 50% of patients continue to die within 3 years of presentation *(1,2)*. Furthermore, when patients with heart failure develop mitral regurgitation (MR), their 1-year survival has been reported as low as 30%.

This has prompted a renewed interest in the surgical management of MR in cardiomyopathy. Interventions that restore mitral competency in these patients can now be performed with low mortality and provide significant improvements in symptomatology and long-term survival. The following briefly reviews the pathological alterations of the mitral valve in the failing ventricle, outlines essentials of preoperative preparation, and discusses the principles of effective mitral replacement and repair surgery with severe left ventricular (LV) dysfunction.

MITRAL VALVE ALTERATIONS IN HEART FAILURE

Fundamental to the management of MR in heart failure is a firm understanding of the functional anatomy of the mitral valve. The mitral valve apparatus is the physiological union of the annulus, leaflets, chordae tendinae, papillary muscles, and the entire left ventricle. Accordingly, the integrity of this union plays a vital role in the maintenance of normal mitral and ventricular geometry.

MR can be classified into anatomic MR or geometric MR (Table 1). Etiologies of anatomic MR are limited to primary valvular abnormalities. These include infectious, rheumatic, and degenerative changes that alter the structural integrity of the leaflets or apparatus and manifest as perforation, prolapse, stenosis, or a combination. These valvular-based alterations result in valvular-based MR.

Geometric MR, however, results from a structural distortion of the left ventricle, leading to leaflet distraction and a disruption of the zone of coaptation. Whether ischemic or nonischemic, the geometric distortion of the annular–ventricular complex alters the physiological coordination of the mitral apparatus. These ventricular-based alterations result in ventricular-based MR.

Geometric MR is a significant and common complication of cardiomyopathy. It may affect all patients with heart failure as a preterminal or terminal event. Its presence is associated with escalations in CHF symptoms, progressive ventricular dilatation, and significant reductions in long-term survival *(3)*. As the ventricle fails, the geometric dilatation of the left ventricle gives rise to progressive dilatation of the mitral

Table 1
Classification of Mitral Regurgitation

Anatomic MR	
Cause	Primary defect of leaflet or annulus
Etiology	Rheumatic
	Degenerative
	Infectious
Geometric MR	
Cause	Distortion of the annular–ventricular apparatus
Etiology	Ischemia (acute, chronic)
	Dilated cardiomyopathy

annulus, and regurgitation ensues as a consequence of incomplete leaflet coaptation. In ischemic cardiomyopathy, the functional MR from annular dilatation is compounded by ischemic changes to the subvalvular structures of the left ventricle. The phrase *papillary muscle dysfunction* does not simply refer to an isolated disorder of the papillary muscle, but to a disturbance in the coordination between the lateral ventricular walls and the mitral valve apparatus. Thus, the combination of annular dilatation and subvalvular ischemic changes furthers the distortion of ventricular geometry and the perturbation of mitral valve function (Fig. 1).

Regardless of etiology, the progression to heart failure is accompanied by a loss of the normal ellipsoid architecture of the ventricle. Over time, the geometric alterations of the failing left ventricle are guided by the law of Laplace, and thus all patients, ischemic and nonischemic alike, remodel in a similar manner. The left ventricle attains a more spherical configuration, the interpapillary distance widens, and the anterior and posterior papillary muscles become distracted in opposing directions (Fig. 2). The resulting chordal tension leads to apical displacement of the zone of coaptation, increases in leaflet tethering forces, and incomplete mitral closure during systole *(4,5)*. These structural ventricular changes may also lead to limited diastolic leaflet excursion because of reduced anterior motion relative to the posteriorly displaced papillary muscles. This occurs independent to inflow volume and without varying mitral orifice area *(6)*.

The preoperative adaptations to severe MR in cardiomyopathy include increases in ventricular preload, wall tension, and stroke volume. With nearly half of the stroke volume ejected into the left atrium during presystole, the contractile efficiency of the ventricle is

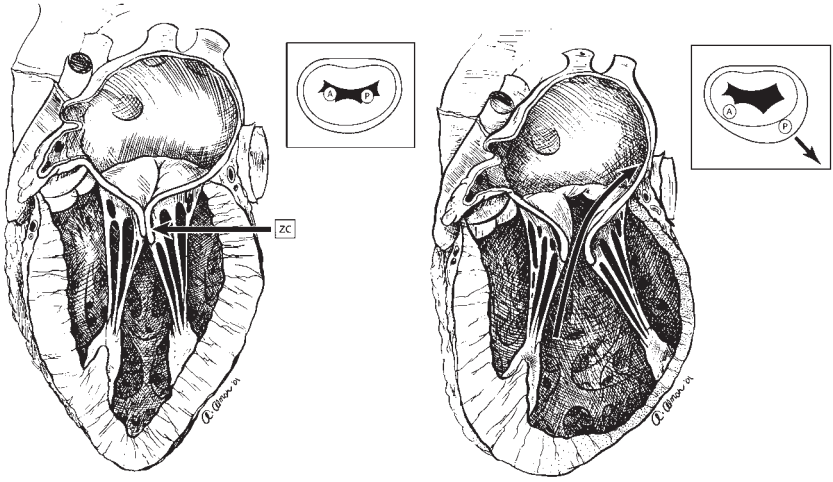


Fig. 1. Note the structural changes that occur from the normal to the ischemic left ventricle. With ischemic damage and thinning of the ventricular wall, there is lateral tethering and displacement of the papillary muscle, resulting in an eccentric jet of mitral regurgitation. This illustrates the concept that ischemic mitral regurgitation results from "lateral wall dysfunction," which if left untreated, may progress to global left ventricular dysfunction and heart failure.

limited even further. The reduction in effective cardiac output combined with increases in left ventricle wall stress serves to restrict coronary flow reserve further. Thus, regardless of the preoperative ejection fraction (EF), surgical elimination of the regurgitant flow results in augmented effective cardiac output, reduced ventricular volume and wall stress, and improved coronary flow reserve.

The firm understanding of the precise mechanism of MR allows effective preoperative and operative management.

PREOPERATIVE PREPARATION

Prior to surgical intervention, myopathic patients with MR require careful evaluation and preoperative management. The process of preoperative investigation should coincide with optimizing the patient's medical management. This should entail an aggressive regimen of diuretic and vasodilator therapy to minimize ventricular afterload and normalize circulating volume. For patients with severe heart failure, a brief period of inotropic therapy for ventricular resuscitation may be

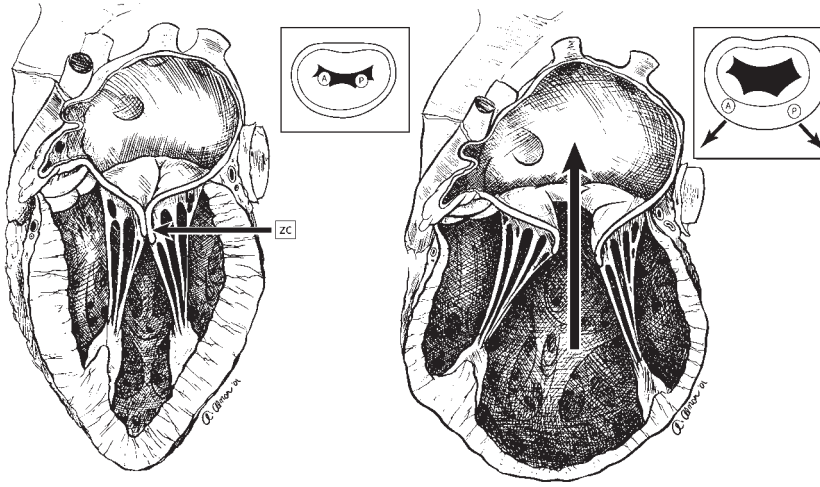


Fig. 2. Note the geometric changes that occur from the normal to the failing left ventricle. With the ventricular and annular dilation of heart failure, the mitral leaflets cannot adequately cover the enlarged mitral orifice. Geometric mitral regurgitation results from a combination of annular dilatation, papillary muscle displacement, increased leaflet tethering forces, and weakened leaflet-closing forces.

necessary for preoperative optimization. Inability to be weaned from this support is often indicative of severe myocardial injury and poor overall prognosis with any surgical therapy other than mechanical ventricular assistance or transplantation. Moreover, markedly elevated pulmonary artery pressures, right ventricular failure, or debilitating ascites should be considered relative contraindications for mitral surgery to avoid unremitting postcardiotomy right ventricle failure.

Physical examination of MR in cardiomyopathy typically reveals a hyperdynamic cardiac impulse and a characteristic blowing holosystolic murmur that may radiate from the apex to the axilla, back, or neck. However, with severely depressed ventricular function, these clinical findings may be inconspicuous. Radiographically, patients usually have an enlarged cardiac silhouette indicative of LV or atrial enlargement. Typical electrocardiogram findings include left atrial enlargement and ventricular hypertrophy.

If ischemia is suspected, coronary angiography should be performed prior to mitral surgery to identify the extent of native coronary disease or to assess the patency of grafts in those patients who have had prior revascularization. Should occlusions be detected, a study to assess

myocardial viability in the distribution of the occluded vessel is advocated to determine if a preoperative percutaneous or a concomitant surgical revascularization procedure is warranted. In this situation, perhaps the most important correlate of successful surgical recovery is the quantification of myocardial viability. Prior to subjecting hearts with limited ventricular function to the temporary stunning of cardiopulmonary bypass, a determination of myocardial contractile reserve is essential. Not only is this useful to ensure the patient can be safely separated from bypass, but also this information is predictive of recovery of ventricular function and long-term survival following operation *(7)*.

Although thallium 201 perfusion scans may distinguish myocytes with membrane integrity from scar, dynamic contrast magnetic resonance imaging (MRI), positron emission tomographic (PET) scanning, and dobutamine stress echocardiography (DSE) have emerged as reliable methods to identify preoperative myocardial viability and predict postoperative function. With the use of systemically administered ^{18}F-deoxyglucose (FDG) to identify aerobic cellular activity, PET scanning detects mismatches between myocardial blood flow and myocyte function to identify hypoperfused FDG-positive areas of the myocardium as viable or hibernating. Despite the high specificity of PET scanning, its cost and relative lack of availability have limited its widespread use. DSE involves the administration of incremental doses of dobutamine and observing for changes in segmental wall thickness and recruitment of segmental ventricular function. A biphasic response to the introduction and withdrawal of inotropy can be highly predictive of contractile reserve and an indicator of the patient's functional recovery following cardiopulmonary bypass. Although this is less expensive and more widely available than a PET scan or dynamic MRI, it requires the expertise of a trained cardiologist and may be observer dependent. Therefore, the optimal test for myocardial viability remains dependent on the facilities available at a particular institution *(7–9)*.

A transthoracic echocardiogram is often the most helpful preliminary investigation to assess ventricular function and estimate the severity of MR. Left ventricular performance is best inferred from the diameter of the left ventricle at end systole. Measurements of end-systolic dimension are less dependent on preload than EF and thus provide a more accurate assessment of contractile function.

Once MR is documented, it is essential to define clearly the mitral pathoanatomy by transesophageal echocardiography. A detailed understanding of leaflet and chordal excursion, including the character of the regurgitant jet, is helpful to plan the correct operative approach

effectively. In the majority of these patients, geometric left ventricle distortion results in a symmetric central jet from mitral annular dilation. Restoring geometry with reduction annuloplasty can readily repair this defect. In cases of anatomic distortion of the valve anatomy, the regurgitant jet may be eccentrically located. These patients often require a partial resection and reconstruction to correct leaflet prolapse or chordal rupture.

Although routine echo color Doppler may provide a semiquantitative analysis of MR, this method is often sensitive to load conditions, driving pressure, jet eccentricity, and left atrial size and thus may lead to incorrect estimations of the true degree of MR. Proximal flow convergence analysis, which calculates the regurgitant volume by measuring the flow proximal to the mitral valve orifice, may be a preferable method to quantify the extent of regurgitation accurately in patients with heart failure *(10–13)*.

The optimal choice of operative technique is dependent on the type of MR, the quality of available leaflet tissue, and the anatomy of the subvalvular structures. With effective management and workup, the operative strategy should be formulated preoperatively, with final confirmation made only after intraoperative inspection of the mitral apparatus.

Regardless of the etiology of MR, the resultant volume overload of the already failing left ventricle begets more MR and further ventricular dilatation, commencing a downward spiral of ventricular function. This may explain why surgical geometric restoration that preserves the annular–subvalvular continuity serves not only to reestablish valvular competency, but also to improve ventricular function.

MITRAL VALVE REPLACEMENT IN HEART FAILURE

Historically, the surgical approach to MR was prosthetic mitral valve replacement (MVR), yet little was understood of the interdependence of ventricular function and annulus–papillary muscle continuity. As a result, patients with low EFs who underwent a classical MVR with removal of the subvalvular apparatus had prohibitively high mortality rates *(14–16)*.

In an attempt to explain these outcomes, the concept of a beneficial "pop off" effect of MR was conceived. This idea erroneously proposed that mitral incompetence provided a low-pressure relief during systolic ejection from the failing ventricle, and that removal of this effect through MVR was responsible for the deterioration in ventricular function. Consequently, MVR in patients with LV dysfunction went into disfavor.

Once it began to be understood that the mitral apparatus was anatomically and functionally contiguous with the ventricle, techniques of mitral surgery were developed to preserve subvalvular integrity. Mounting laboratory and clinical evidence supporting these concepts led surgeons to embrace valve-sparing techniques *(17–19)*. The significant improvements in short- and long-term survival that accompanied these adaptations ushered in the modern era of mitral surgery.

There has been much interest in comparisons between MVR with and without chordal preservation (CP) to elucidate the role subvalvular structures play in mitral and ventricular function. It has been learned that excision or exclusion of the subvalvular structures at the time of MVR results in a series of mechanical and geometric perturbations. This involves changes in myocardial wall thickness at the transsection sites that are accompanied by inhomogeneous local shortening, loss of normal systolic torsional deformation, and increased regional wall stress *(20,21)*. Following chordal transsection, the depression of ventricular function at the defunct papillary muscle base also results in slowed relaxation that may contribute to diastolic dysfunction *(22)*.

Conversely, CP at the time of MVR renders significant hemodynamic benefits, especially in the setting of depressed LV function. The improved ventricular geometry with CP results in a reduction of ventricular wall stress, enhancements in regional wall motion, and diminutions of end-systolic and end-diastolic volumes compared to MVR without CP *(23–25)*. Patients with intact subvalvular continuity have increased EFs and superior LV performance, and perhaps most important, patients with CP have improved long-term survival over those without CP *(19,26)*. These findings have paved the way for effective mitral surgery in patients with severe LV dysfunction.

The techniques used to maintain subvalvular continuity remain dependent, however, on the etiology of MR and the valvular anatomy. Destruction or scarring of the subvalvular apparatus by endocarditis or severe rheumatic disease may make repair impossible and the preservation of native structures difficult. Although these are less common in heart failure than with other etiologies, the preservation of subvalvular continuity is equally important to maintain ventricular geometry and function *(27)*. Thus, techniques have evolved to adapt to the pathology encountered intraoperatively.

The majority of techniques involve keeping the posterior leaflet and chordae intact and resuspending the anterior chordae to the debrided annulus. These preserved chordae can be transfixed to the anterior annulus *(28)* or to both trigones *(29)* or transposed to the posterior annulus *(30)*. When extensive calcification requires debridement and removal of

the posterior leaflet, the anterior leaflet may be transposed to reinforce the posterior annulus prior to prosthesis implantation *(31)*. Alternatively, reconstruction of the subvalvular apparatus at the time of MVR can be readily performed with Gore-Tex or polytetrafluoroethylene (PTFE). These sutures permit resuspension of the papillary muscles in anatomic continuity with the debrided annulus. This material becomes readily incorporated with endothelial coverage and has excellent long-term durability *(32–34)*. Replacement sutures equal to or slightly longer than the excised chordae effectively lower wall stress and preserve global LV function and geometry *(35)*.

Concerns have been raised with total CP MVR regarding obstruction of the left ventricular outflow tract (LVOT) as well as prosthesis impingement because of retained subvalvular structures. These significant complications have directed some to advocate partial CP, usually of only the posterior leaflet *(36,37)*. However, subsequent laboratory and clinical evidence has revealed that much of the geometric and functional benefit of subvalvular integrity is lost with only partial CP. Total preservation results in improved ejection performance, less systolic wall stress, less left ventricle strain, and lower mortality when compared to MVR with partial CP *(38–40)*.

It has also been noted that all prostheses implanted with intact subvalvular structures have an element of flow restriction. When CP is utilized, stented bioprostheses have lower restrictive properties than mechanical prostheses. Frustration with impingement and obstruction have led some surgeons to implant mechanical bileaflet valves in the antianatomic position with PTFE chordal reconstruction, and some even to abandon regressively CP altogether *(41)*.

Much of these mechanical concerns pertain to MVR in patients with normal ventricular volumes. Those with severe LV dysfunction who require prosthetic valve replacement may avoid the issues of LV outflow obstruction because of the widening of the aorto–mitral angle associated with ventricular dilatation. Furthermore, if the mitral valve must be replaced in the setting of severe LV dysfunction, attempts at native or PTFE CP should be utilized because of its clear geometric advantage and long-term benefit in this group. The limited life span of patients with severe LV dysfunction, combined with the improved durability of most third-generation porcine and pericardial valves, make the bioprosthesis the valve of choice when necessary for managing MR in end-stage heart failure.

Despite the noted benefits of MVR with CP, the possibility of prosthesis-related complications, the increased morbidity of anticoagulation therapy, and the 7–15% mortality associated with MVR have

made mitral repair the treatment of choice for MR in cardiomyopathy whenever possible.

GEOMETRIC MITRAL RECONSTRUCTION IN HEART FAILURE

The resurgence of interest in mitral repair surgery over the past decade has provided long-term outcome data supporting its superiority to MVR for the treatment of MR *(42–45)*.

Repaired valves have clear benefits over prostheses in terms of endocarditis risk, need for anticoagulation, stroke incidence, and operative mortality. With the valve-related advantages aside, mitral repair has demonstrated improvements over MVR in terms of cardiac function as well as long-term survival *(26)*. Decreased left ventricle volumes, improved left ventricle performance, and stable or enhanced EFs have all been reported following repair. Patients with repairs also have better systolic and diastolic function compared to those with MVR with subvalvular preservation *(44)*. The superior conservation of ventricular geometry may explain why immediate intraoperative left ventricle function is preserved after repair, but is depressed after MVR *(42)*. Beyond these recognized benefits over MVR, the resulting lower length of stay following repair has also made it a cost-effective treatment for MR *(46,47)*.

One explanation for the inferiority of MVR is the rigid fixation of the mitral annulus. The normal annulus is a dynamic structure that undergoes dorsiflexion and contraction. Thus, the insertion of a rigid prosthesis impairs its normal three-dimensional function. Furthermore, as the left ventricle base consists of the mitral annulus and the LVOT orifice, when the ventricle contracts against an immobile prosthesis, the valve occupies more of the LV in systole, and a relative narrowing of the LVOT results. This antiphysiological fixation of the mitral annulus following MVR may explain why left ventricle function is better served with mitral reconstruction *(48–50)*.

In patients with cardiomyopathy, the etiology of MR is most often caused by mitral annular dilatation and geometric distortion of the mitral apparatus. Accordingly, the most significant determinant of leaflet coaptation and MR is the diameter of the annulus *(51,52)*. The LV dimension is less important because the lengths of the chordae and papillary muscles are similar in myopathic hearts regardless whether MR is present. This may explain why mitral reconstruction can be applied to patients with reduced EFs. Therefore, the primary goal of effective repair in these patients must be to reestablish the zone of coaptation by flexible mitral annular remodeling.

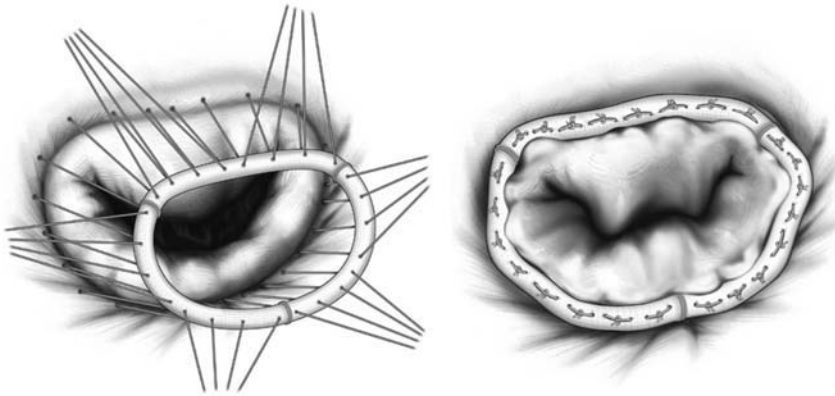


Fig. 3. Successful augmentation of the zone of coaptation and prevention of recurrent MR can be achieved by implanting an undersize circumferential annuloplasty ring.

At the University of Michigan, 145 patients with end-stage cardiomyopathy and refractory severe MR have undergone geometric mitral reconstruction with an undersize flexible annuloplasty ring (Fig. 3). All patients were in New York Heart Association (NYHA) class III or IV heart failure despite receiving maximal medical therapy. Patients had severe LV systolic dysfunction as defined by an EF of less than 25%, with a mean of 14%. On immediate postoperative echocardiograms, the mean transmitral gradient has been only 3 ± 1 mmHg (range 2–6 mmHg). The overall operative mortality has been 3.5%. There were five 30-day mortalities: one intraoperative death because of right ventricular failure, one from a cerebrovascular accident, one from CHF, and two from multisystem organ failure. Only five patients have required intra-aortic balloon counterpulsation (3.5%), and no patient has required mechanical LV assistance. The duration of follow-up of these patients has been between 1 and 75 months, with a mean of 38 months. There have been 27 late deaths: 12 from sudden ventricular arrhythmias, 9 from progression of CHF but without MR, 3 related to complications from other operative procedures, 2 that progressed to transplantation, and 1 suicide. The 1-, 2-, and 5-year actuarial survival is 82, 71, and 57%, respectively.

At 24-month assessment, all patients were in NYHA class I or II. Their mean EF had increased from 14% preoperatively to 26%. NYHA symptoms were reduced from a preoperative mean of 3.2 ± 0.2 to 1.8 ± 0.4 postoperatively. These improvements paralleled subjective

Table 2
Matched Preoperative and Postoperative Echocardiographic Data at 24 Months Following Mitral Reconstruction for Heart Failure

ECHO parameter	*Preoperative*	*Postoperative (24 mo)*	*p*
End diastolic volume (mL)	281 ± 86	206 ± 88	<0.001
Ejection fraction (%)	16 ± 5	26 ± 8	0.008
Regurgitant fraction (%)	70 ± 12	13 ± 10	<0.001
Cardiac output (L/min)	3.1 ± 1.0	5.2 ± 0.8	0.001
Sphericity index (D/L)	0.82 ± 0.10	0.74 ± 0.07	0.005

functional improvements reported by all patients. Echocardiographically, there were marked improvements in regurgitant fraction, end-diastolic volume, cardiac output, and sphericity index (Table 2). Although significant undersizing of the mitral annulus was employed to overcorrect for the zone of coaptation, no systolic anterior motion of the anterior leaflet or mitral stenosis was noted in these patients.

The technique of undersizing in mitral reconstruction avoids systolic anterior motion in these myopathic patients likely because of widening of the aorto–mitral angle in these hearts with increased left ventricle size. Furthermore, acute remodeling of the base of the heart with this reparative technique may also reestablish the somewhat normal geometry and ellipsoid shape the left ventricle. As evidenced by the decreased sphericity index and left ventricle volumes seen in these patients, the geometric restoration of mitral reconstruction not only effectively corrects MR, but also achieves surgical unloading of the ventricle *(53–55)*.

In our study, patients with MR and severe refractory heart failure were selected to undergo geometric mitral reconstruction regardless of etiology. No patients required coronary revascularization. There were no differences in operative mortality, immediate postoperative recovery, or 1-year survival between patients with ischemic or nonischemic cardiomyopathy. However, it has been observed that those with ischemic etiologies do have a comparative decrease in long-term survival despite negative preoperative viability studies. This may represent the relative inability of the myocardium to reverse remodel in these patients. There were also slightly more late sudden deaths observed in this subpopulation, which may suggest a potential role for automatic implantable cardioverter defibrillator therapy in patients with ischemic cardiomyopathy who are not suitable for revascularization.

Mitral reconstruction can now be performed with reproducible long-term results and minimal operative mortality *(56–60)*. The physiological

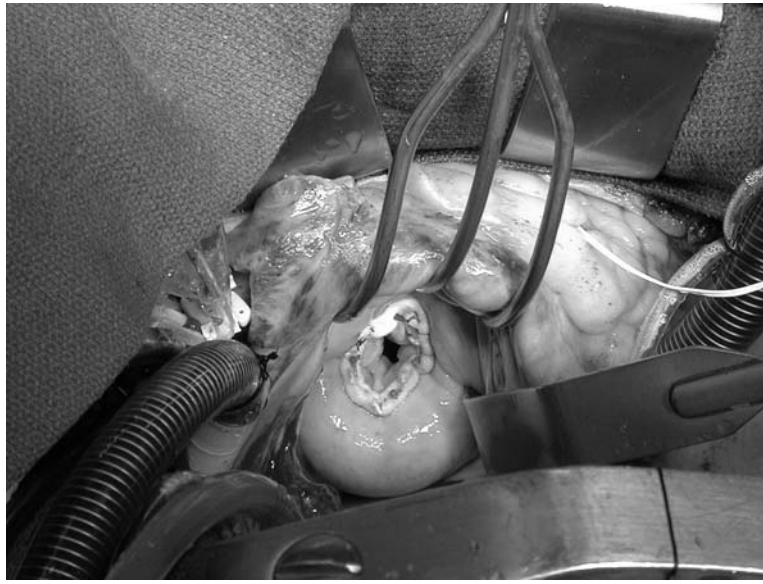


Fig. 4. Technique of geometric mitral reconstruction: bicaval cannulation, approaching the mitral valve through the interatrial groove, and the use of a self-retaining retractor greatly enhances exposure. Multiple circumferential annular sutures are placed, followed by the implantation of an undersize flexible ring. Note the reduced size of the annulus after successful reconstruction.

improvement in contractile efficiency and cardiac output affords patients significant improvements in functional status and quality of life. The straightforward technique of this geometric remodeling operation (Fig. 4) has resulted in some surgeons accepting a policy of "no EF is too low" for mitral reconstruction. Intermediate-term outcomes have attained the level of those obtained from transplantation, but without the need for immunosuppression.

Other groups have corroborated these encouraging results. The following studies illustrate that mitral surgery can be readily performed in the presence of dilated or ischemic cardiomyopathy. Each of these studies indicated that mitral surgery can be performed safely in the setting of severe LV dysfunction.

Chen et al. reported a series of 81 patients in Boston with MR and dilated cardiomyopathy managed with mitral repair *(56)*. In this series, 77% underwent concomitant coronary revascularization, and at follow-up, LVEF improved from 24 to 32%, with an improvement in the mean NYHA class from 3.3 to 1.6. Survival in their study was 73, 58, and 38 at 1, 3, and 5 years, respectively.

Bishay et al. examined 35 patients in Cleveland who underwent mitral repair and 9 who underwent MVR in the setting of severe LV dysfunction *(57)*. They reported LVEF improvements from 28 to 36% and mean NYHA class reductions from 2.9 to 1.2 at follow-up. Survival was 89, 86, and 67% at 1, 2, and 5 years, respectively.

In Chieti, Italy, Calafiore et al. reported a series of 49 patients with dilated cardiomyopathy; 29 underwent mitral repair, and 20 had MVR, with a mortality of 4.2% and comparable long-term survival *(58)*. Bitran et al. from Jerusalem, Israel, reported on 21 patients with ischemic cardiomyopathy and EF below 25% who underwent mitral repair with concomitant coronary revascularization with no early mortality *(59)*. At 3-year follow-up, 67% of the patients were in NYHA class I–II, with a late mortality of 14%.

SUMMARY

Mitral reconstruction in conjunction with medical management may now be offered to all patients with MR and cardiomyopathy as a first-line therapy for heart failure, and it should now be included in the armamentarium of every heart failure surgeon.

Advances in diagnostic and surgical techniques for the management of MR have resulted in improved long-term outcomes and survival rates. Although renewed approaches to mitral surgery in severe LV dysfunction have been successful, more effort is needed to encourage the early referral of patients with MR before ventricular deterioration occurs. With knowledge of the natural history of regurgitation and its negative impact on ventricular remodeling and long-term survival, it behooves us to withhold surgical therapy until heart failure appears *(61–64)*. With this renewed multidisciplinary approach to MR, repairs may be made earlier and impact the survival of heart failure with a modicum of prevention.

REFERENCES

1. Tavazzi L. Epidemiology of dilated cardiomyopathy: a still undetermined entity. Eur Heart J 1997;18:4–6.
2. Hunt SA. Current status of cardiac transplantation. JAMA 1998;280:1692–1698.
3. Blondheim DS, Jacobs LE, Kotler MN, Costacurta GA, Parry WR. Dilated cardiomyopathy with mitral regurgitation: decreased survival despite a low frequency of left ventricular thrombus. Am Heart J 1991;122(3 part 1):763–771.
4. Hashim SR, Fontaine A, He S, et al. A three-component force vector cell for in vitro quantification of the force exerted by the papillary muscle on the left ventricular wall. J Biomech 1997;30:1071–1075.
5. Dagum P, Timek TA, Green GR, et al. Coordinate-free analysis of mitral valve dynamics in normal and ischemic hearts. Circulation 2000;102(19 suppl 3): III62–III69.

6. Otsuji Y, Gilon D, Jiang L, et al. Restricted diastolic opening of the mitral leaflets in patients with left ventricular dysfunction: evidence for increased valve tethering. J Am Coll Cardiol 1998;32:398–404.
7. Marwick TH, Zuchowski C, Lauer MS, et al. Functional status and quality of life in patients with heart failure undergoing coronary bypass surgery after assessment of myocardial viability. J Am Coll Cardiol 1999;33:750–758.
8. DiCarli MF, Maddahi J, Roshsar S, et al. Long-term survival of patients with coronary artery disease and left ventricular dysfunction: implications for the role of myocardial viability assessment in management decisions. J Thorac Cardiovasc Surg 1998;116:997–1004.
9. Senior R, Kaul S, Lahiri A. Myocardial viability on echocardiography predicts long-term survival after revascularization in patients with ischemic congestive heart failure. J Am Coll Cardiol 1999;33:1848–1854.
10. Spain MG, Smith MD, Grayburn PA, et al. Quantitative assessment of mitral regurgitation by Doppler color flow imaging: angiographic and hemodynamic correlations. J Am Coll Cardiol 1989;13:585–590.
11. Cape EG, Yoganathan AP, Weyman AE, et al. Adjacent solid boundaries alter the size of regurgitant jets on Doppler color flow maps. J Am Coll Cardiol 1991;17: 1094–1102.
12. Boltwood CM, Tei C, Wong M, et al. Quantitative echocardiography of the mitral complex in dilated cardiomyopathy: the mechanism of functional mitral regurgitation. Circulation 1983;68:498–508.
13. Hansen A, Haass M, Zugck C, et al. Prognostic value of Doppler echocardiographic mitral inflow patterns: implications for risk stratification in patients with chronic congestive heart failure. J Am Coll Cardiol 2001;37:1049–1055.
14. Pitarys CJ II, Forman MB, Panayiotou H, et al. Long-term effects of excision of the mitral apparatus on global and regional ventricular function in humans. J Am Coll Cardiol 1990;15:557–563.
15. Phillips HR, Levine FH, Carter JE, et al. Mitral valve replacement for isolated mitral regurgitation: analysis of clinical course and late postoperative left ventricular ejection fraction. Am J Cardiol 1981;48:647–654.
16. David TE, Uden DE, Strauss HD. The importance of the mitral apparatus in left ventriuclar function after correction of mitral regurgitation. Circulation 1983;68 (3 part 2):II76–II82.
17. Sarris GE, Cahill PD, Hansen DE, et al. Restoration of left ventricular systolic performance after reattachment of the mitral chordae tendineae. The importance of valvular–ventricular interaction. J Thorac Cardiovasc Surg 1988;95:969–979.
18. Miki S, Ueda Y, Tahata T, et al. 1988: Mitral valve replacement with preservation of chordae tendinae and papillary muscles. Updated in 1995. Ann Thorac Surg 1995;60:225–226.
19. Okita Y, Miki S, Ueda Y, et al. Left ventricular function after mitral valve replacement with or without chordal preservation. J Heart Valve Dis 1995;4(suppl 2): S181–S192.
20. DeAnda A Jr, Komeda M, Nikolic SD, et al. Left ventricular function, twist, and recoil after mitral valve replacement. Circulation 1995;92(9 suppl):II458–II466.
21. Moon MR, DeAnda A Jr, Daughters GT II, et al. Effects of chordal disruption on regional left ventricular torsional deformation. Circulation 1996;94(9 suppl): II143–II51.
22. Takayama Y, Holmes JW, LeGrice I, et al. Enhanced regional deformation at the anterior papillary muscle insertion site after chordal transsection. Circulation 1996;93:585–593.

23. Straub U, Feindt P, Huwer H, et al. Postoperative assessment of chordal preservation and changes in cardiac geometry following mitral valve replacement. Eur J Cardiothorac Surg 1996;10:734–740.
24. Straub U, Huwer H, Kalweit G, et al. Improved regional left ventricular performance in mitral valve replacement with orthotopic refixation of the anterior mitral leaflet. J Heart Valve Dis 1997;6:395–403.
25. Natsuaki M, Itoh T, Tomita S, et al. Importance of preserving the mitral subvalvular apparatus in mitral valve replacement. Ann Thorac Surg 1996;61:585–590.
26. David TE, Armstrong S, Sun Z. Left ventricular function after mitral surgery. J Heart Valve Dis 1995;4(suppl 2):S175–S180.
27. Essop MR, Kontozis L, Sareli P. Preoperative left ventricular systolic dysfunction correlates with the adverse postoperative consequences of annular–papillary disconnection in the course of mitral valve replacement for stenosis. J Heart Valve Dis 1998;7:431–437.
28. Rose EA, Oz MC. Preservation of anterior leaflet chordae tendinae during mitral valve replacement. Ann Thorac Surg 1994;57:768–769.
29. Miki S, Kusuhara K, Ueda Y, et al. Mitral valve replacement with preservation of the chordae tendinae and papillary muscles. Ann Thorac Surg 1988;45:28–34.
30. Feikes HL, Daugharthy JB, Perry JE, et al. Preservation of all chordae tendinae and papillary muscle during mitral valve replacement with a tilting disc valve. J Card Surg 1990;5(2):81-5.
31. Casselman FP, Gillinov AM, McDonald ML, et al. Use of the anterior mitral leaflet to reinforce the posterior mitral annulus after debridement of calcium. Ann Thorac Surg 1999;68:261–262.
32. Minatoya H, Okabayashi H, Shimada I, et al. Pathologic aspects of polytetrafluoroethylene sutures in human heart. Ann Thorac Surg 1996;61:883–887.
33. Kobayashi J, Sasako J, Bando K, et al. Ten-year experience of chordal replacement with expanded polytetrafluoroethylene in mitral valve repair. Circulation 2000;102(19 suppl 3):III30–III34.
34. Sintek CF, Khonsari S. Use of extended polytetrafluoroethylene (ePTFE) chordae to re-establish annular–papillary connection after mitral valve excision. J Heart Valve Dis 1996;5:362–364.
35. Reimink MS, Kunzelman KS, Cochran RP. The effect of chordal replacement suture length on function and stresses in repaired mitral valves: a finite element study. J Heart Valve Dis 1996;5:365–375.
36. Esper E, Ferdinand FD, Aronson S, et al. Prosthetic mitral valve replacement: late complications after native valve preservation. Ann Thorac Surg 1997;63: 541–543.
37. Greenwood JP, Nolan J, Mackintosh AF. Late, intermittent obstruction of a mitral prosthesis by chordal remnants. Eur J Cardiothorac Surg 1997;12:804–806.
38. Moon MR, DeAnda A Jr, Daughters GT II, et al. Effects of mitral valve replacement on regional left ventricular systolic strain. Ann Thorac Surg 1999;68: 894–902.
39. Yun KL, Sintek CF, Miller DC, et al. Randomized trial of partial vs complete chordal preservation methods of mitral valve replacement. A preliminary report. Circulation 1999;100(19 suppl):II90–II94.
40. Yu Y, Gao C, Li G, et al. Mitral valve replacement with complete mitral leaflet retention: operative techniques. J Heart Valve Dis 1999;8:44–46.
41. Fontaine AA, He S, Stadter R, et al. In vitro assessment of prosthetic valve function in mitral valve replacement with chordal preservation techniques. J Heart Valve Dis 1996;5:186–198.

42. Ren JF, Aksut S, Lightly GW Jr, et al. Mitral valve repair is superior to valve replacement for the early preservation of cardiac function: relation of ventricular geometry to function. Am Heart J 1996;131:974–981.
43. Lawrie GM. Mitral valve repair vs replacement. Current recommendations and long-term results. Cardiol Clin 1998;16:437–448.
44. Corin WJ, Sutsch G, Mukakami T, et al. Left ventricular function in chronic mitral regurgitation: preoperative and postoperative comparison. J Am Coll Cardiol 1995;25:113–121.
45. Lee EM, Shapiro LM, Wells FC. Importance of subvalvular preservation and early operation in mitral valve surgery. Circulation 1996;94:II117–II123.
46. Pagani FD, Benedict MB, Marshall BL, et al. The economics of uncomplicated mitral valve surgery. J Heart Valve Dis 1997;6:466–469.
47. Barlow CW, Imber CJ, Sharples LD, et al. Cost implications of mitral valve replacement vs repair in mitral regurgitation. Circulation 1997;96(9 suppl): II90–II93.
48. Komoda T, Hertzer R, Oellinger J, et al. Mitral annular flexibility. J Card Surg 1997;12:102–109.
49. Komeda M, Glasson JR, Bolger AF, et al. Three-dimensional dynamic geometry of the normal canine mitral annulus and papillary muscles. Circulation 1996;94 (9 suppl):II159–II163.
50. Komoda T, Hertzer R, Sinlawaski H, et al. Effects of prosthetic valve replacement on mitral annular dynamics and the left ventricular base. ASAIO J 2001;47: 60–65.
51. Rosario LB, Stevenson LW, Solomon SD, et al. The mechanism of decrease in dynamic mitral regurgitation during heart failure treatment: importance of reduction in the regurgitant orifice size. J Am Coll Cardiol 1998;32:1819–1824.
52. Kono T, Sabbah HN, Rosman H, et al. Left ventricular shape is the primary determinant of functional mitral regurgitation in heart failure. J Am Coll Cardiol 1992;20:1594–1598.
53. Bolling SF, Deeb GM, Brunsting LA, et al. Early outcome of mitral valve reconstruction in patients with end-stage cardiomyopathy. J Thorac Cardiovasc Surg 1995;109:676–683.
54. Bach DS, Bolling SF. Improvement following correction of secondary mitral regurgitation in end-stage cardiomyopathy with mitral annuloplasty. Am J Cardiol 1996;78:966–969.
55. Bolling SF, Pagani FD, Deeb GM, et al. Intermediate-term outcome of mitral reconstruction in cardiomyopathy. J Thorac Cardiovasc Surg 1998;115:381–388.
56. Chen FY, Adams DH, Aranki SF, et al. Mitral valve repair in cardiomyopathy. Circulation 1998;98:II-124–II-127.
57. Bishay ES, McCarthy PM, Cosgrove DM, et al. Mitral valve surgery in patients with severe left ventricular dysfunction. Eur J Cardiothorac Surg 2000;17: 213–221.
58. Calafiore AM, Gallina S, DiMauro M, et al. Mitral valve procedure in dilated cardiomyopathy: repair or replacement? Ann Thorac Surg 2001;71:1146–1152.
59. Bitran D, Merrin O, Klutstein MW, et al. Mitral valve repair in severe ischemic cardiomyopathy. J Card Surg 2001;16:79–82.
60. deVarennes B, Haichin R. Impact of preoperative left ventricular ejection fraction on postoperative left ventricular remodeling after mitral valve repair for degenerative disease. J Heart Valve Dis 2000;9:313–318.
61. Ling LH, Enriquez-Sarano M, Seward JB, et al. Clinical outcome of mitral regurgitation due to flail leaflet. N Engl J Med 1996;335:1417–1423.

62. Ofili E, Oduwole A, Lapa-Bula R. Surgical timing for mitral valve regurgitation. Echocardiography 2000;17:285–292.
63. Carabello BA. The pathophysiology of mitral regurgitation. J Heart Valve Dis 2000;9:600–608.
64. Smolens IA, Pagani FD, Deeb GM, et al. Prophylactic mitral reconstruction for asymptomatic mitral regurgitation. Ann Thorac Surg 2001;72:1210–1215.

5 Tricuspid Valve Surgery in Right Heart Failure

James P. Greelish, MD,
Bradley J. Phillips, MD,
James C. Fang, MD,
and John G. Byrne, MD

CONTENTS

INTRODUCTION

Tricuspid valve disease is often found in combination with other valvular pathology. Tricuspid regurgitation (TR), the most common tricuspid valvular condition, is commonly asymptomatic, although progressive, in nature. With time, it may lead to right ventricular (RV) enlargement, annular dilatation, and systolic dysfunction. Clinical symptoms and the degree of RV impairment usually determine whether

From: *Contemporary Cardiology: Surgical Management of Congestive Heart Failure*
Edited by: J. C. Fang and G. S. Couper © Humana Press Inc., Totowa, NJ

medical or surgical therapy is most appropriate. However, operative intervention should be carefully considered; there is an unusually high mortality rate associated with tricuspid valve surgery, ranging from 19 to 25% *(1–3)*. In this chapter, we review the pathophysiology and surgical therapy of the tricuspid valve for the management of RV failure.

ANATOMY OF THE RIGHT HEART AND TRICUSPID VALVE

The right heart serves as a collection chamber. The right atrium can be divided into three sections: the atrial appendage, the vestibule, and the tricuspid valve. The appendage is a triangular-shape structure that is frequently used for venous cannulation during cardiac surgery and marks the location of the sinus node. The atrioventricular node lies within the triangle of Koch, defined by the septal annulus posteriorly, the ostium of the coronary sinus on the right, and the tendon of Todaro on the left (Fig. 1). The bundle of His travels through the central fibrous body and into the membranous part of the interventricular septum. Misplaced sutures in this region can result in various degrees of heart block. Temporary atrial and ventricular pacing wires are routinely placed at the conclusion of most tricuspid operations for this reason.

The vestibule of the right atrium has two embryologically distinct areas: (1) a smooth-walled posterior part, called the sinus venarium, that receives blood from the venae cavae/coronary sinus and (2) a rough-walled anterior region that has internal muscular ridges (musculi pectinati). These two parts of the atrial vestibule are separated externally by the sulcus terminalis (i.e., terminal groove) and internally by the crista terminalis. A prominent feature of this area is the fossa ovalis. This fetal remnant of the foramen ovale is a thumbprint-size translucent depression facing the inferior vena cava.

The three leaflets of the tricuspid valve reflect their anatomical location: septal, anterior, and posterior. All three leaflets are folds of endocardium strengthened by fibrous tissue. The leaflets are continuous with the tricuspid ring and join at their zones of apposition or commissures; they are tethered by fan-shaped chords arising from prominent papillary muscles (Fig. 2) *(4)*. The individual leaflets are ill defined from a surgical standpoint, and their exact papillary relationships can vary. However, a trifoliate relationship almost always exists despite the various fibrous interconnections.

Classically, the largest anterior leaflet extends from the subpulmonary conus; the septal leaflet attaches to the membranous and muscular septum. The posterior leaflet bridges the space between the

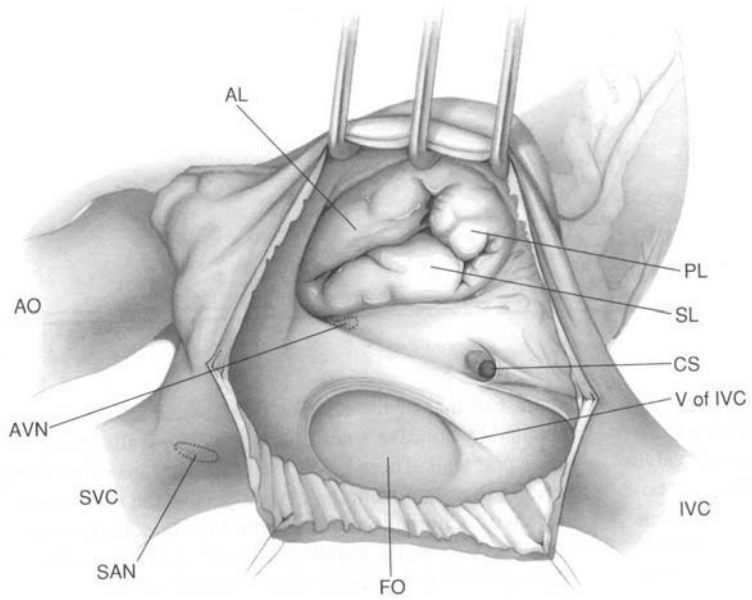


Fig. 1. The right heart. AL, anterior leaflet; PL, posterior leaflet, AO, aorta, SL, septal leaflet, AVN, atrioventricular node; SVC, superior vena cava; FO, fossa ovalis; CS, coronary sinus; V of IVC, valve of inferior vena cava; SAN, sinoatrial node; IVC, inferior vena cava. (Reproduced with permission from ref. *4*.)

intraventricular septum and the anterolateral wall. These leaflets are anchored at their periphery to a fibrous "annulus" and centrally by chordae tendinae. Although chordae of the anterior leaflet generally attach to a dominant papillary muscle, the chordae of the septal and posterior leaflets attach directly to the ventricular myocardium. These direct ventricular attachments are unique in valvular anatomy and help to define the true identity of this valve in congenital anomalies.

It is also important to realize that a well-formed tricuspid annulus does not exist. Instead of having a distinct, collagenous band surrounding the valve orifice (as seen in other valves), the tricuspid valve lies within an atrioventricular groove, a fibrofatty tissue plane separating the right atrium from its ventricle, that folds in on itself to form the base of the tricuspid valve leaflets. The orifice of this annulus is larger than that of the mitral valve (approx 3.1–4.0 cm in diameter). In general, annular dilatation is the most common mechanism of TR.

The right ventricle is a thin-wall structure with its free wall normally measuring less than 5 mm thick. The outlet portion of the right

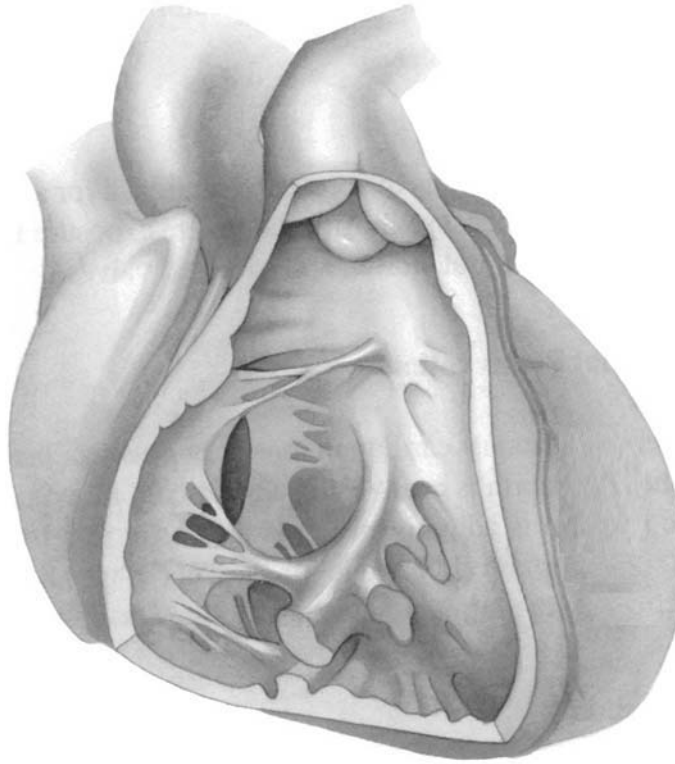


Fig. 2. The right ventricle. (Reproduced with permission from ref. *4*.)

ventricle is composed of the muscular infundibulum, which supports the leaflets of the pulmonary valve. The geometry of the RV chamber is difficult to characterize, but some have likened it to a triangular bellows with the apex at the pulmonic valve and the base formed by the diaphragmatic surface of the heart. The right ventricle has a smaller mass than the left, but is much more compliant and therefore able to accommodate large diastolic volumes.

The coronary anatomy of this region also has significance in right-sided heart failure. RV dysfunction from coronary artery disease is usually a result of extension of an inferoposterior transmural infarction. Given that the blood supply to the right ventricle is most commonly derived from the right coronary artery and acute marginal branches (i.e., "right-sided dominance"), an inferior myocardial infarction (MI) from proximal right coronary occlusion usually leads to RV dilatation *(5,6)*. TR can also occur with an inferoseptal infarction because, as described above, some tricuspid chordae are septophilic (i.e., directly

attached to the ventricular septum). This "ischemic TR" is usually responsive to coronary revascularization. Only in isolated cases has tricuspid valve surgery been attempted for intractable regurgitation after an inferior MI *(7)*. Although RV infarction commonly accompanies inferior MI, the right ventricle is generally resistant to permanent dysfunction and usually recovers.

PATHOPHYSIOLOGY OF RIGHT-SIDED FAILURE

The right ventricle normally propels blood toward a low-resistance pulmonary bed. When an elevated pulmonary vascular resistance (PVR) challenges the ventricle, systolic failure may ensue. This inability to overcome additional afterload stress differentiates the right ventricle from its left-sided counterpart and is an important consideration when planning a surgical procedure that results in the right ventricle pumping against near-systemic pressures (i.e., the Fontan operation for hypoplastic left ventricular [LV] syndromes).

The most common cause of RV dysfunction, and subsequent TR, is LV failure. Elevation of the LV end-diastolic pressure (LVEDP) passively creates secondary pulmonary hypertension. If severe enough, the right ventricle will fail, manifested by ventricular enlargement and tricuspid annular dilatation. Secondary TR in this situation will further exacerbate RV failure by decreasing the forward cardiac output.

The geometric relationship of the cardiac chambers to one another, the shared ventricular septum, and pericardial constraint produce ventricular interdependence. RV shape is unlike that of the left: Both the RV free wall and the interventricular septum are concave. On the right side of the heart, the free wall moves toward the septum in a near-parallel fashion, which is commonly referred to as a *bellows effect*. Classically, the septum normally moves to the left during systole and to the right during diastole. However, in the presence of RV volume overload (i.e., TR), an abnormal "paradoxical" motion occurs. The septum moves to the left during both systole and diastole, which reduces systolic shortening in the dimension of the septum to the LV free wall and decreases the LV stroke volume and ejection fraction (EF). Louie et al. *(8)* demonstrated this concept in a study of volume- and pressure-loaded right ventricles. They studied 10 patients with severe TR following tricuspid valve resection to elucidate the impact of pure volume overload on LV function. They found that the LVEF was significantly less compared to age-matched controls (51 ± 4% vs 60 ± 4%, $p < 0.001$); LV end-diastolic volumes were similar between groups (84 ± 26 vs 77 ± 20 mL, p not significant). In contrast, pressure-loaded right

ventricles (in patients with pulmonary hypertension) had normal resting LVEFs because of augmented systolic shortening despite relative ventricular underfilling. These investigators have also demonstrated that severe TR results in marked right atrial distension, reversal of the normal interatrial curvature, and compression of the left atrium (left atrium cross-sectional area: 5.9 ± 2.2 vs 8.6 ± 1.2 cm^2/m^2, $p < 0.005$). In this manner, the volume-overloaded right ventricle also decreases left atrial preload and consequently LV stroke volume *(9)*.

Because the left and right ventricles share a common, space-limiting envelope (i.e., the pericardium), there are other consequences of RV dilatation. When the pericardium is intact, expansion of one ventricle will have an impact on the diastolic function of the other. In this way, RV dilatation can mimic tamponade, leading to an increased RV end-diastolic pressure and decreased LV diastolic volume. In this manner, right-sided failure can mimic pericardial heart disease. In fact, classic findings of pericardial constraint such as diastolic pressure equalization, a "dip-and-plateau" or "square-root" sign, pulsus paradoxus, and Kussmaul's sign have all been documented in patients with RV failure. In fact, sporadic cases of misdiagnosis have led to pericardial surgery *(10)*.

When the right atrial and RV end-diastolic pressure exceed the pulmonary capillary wedge and LVEDP, advanced RV failure is present. The presence of a noncompliant right atrial waveform (i.e., an M or W wave) with a Y descent deeper than the X descent is also highly specific *(11)*. In the absence of pericardial or valvular disease, these findings are rather specific for RV failure.

The neurohormonal profile of right-sided heart failure has also been characterized *(12,13)*. In a group of patients with advanced right heart failure from carcinoid heart disease (right atrial pressure 16 mmHg, cardiac index 1.9 $L/min/m^2$), preoperative atrial natriuretic peptide levels were markedly elevated and paralleled the clinical signs of right heart failure. All patients demonstrated significant and dramatic reductions of atrial natriuretic peptide levels following tricuspid valve replacement (Fig. 3).

SURGICAL APPROACHES TO THE TRICUSPID VALVE

When severe TR is early in its course, medical therapy (diuresis, digoxin, and salt restriction) can usually control symptoms and maintain compensated hemodynamics. However, in the advanced stages of TR, the right ventricle begins to fail from chronic volume overload (and pressure overload when pulmonary hypertension is present). At

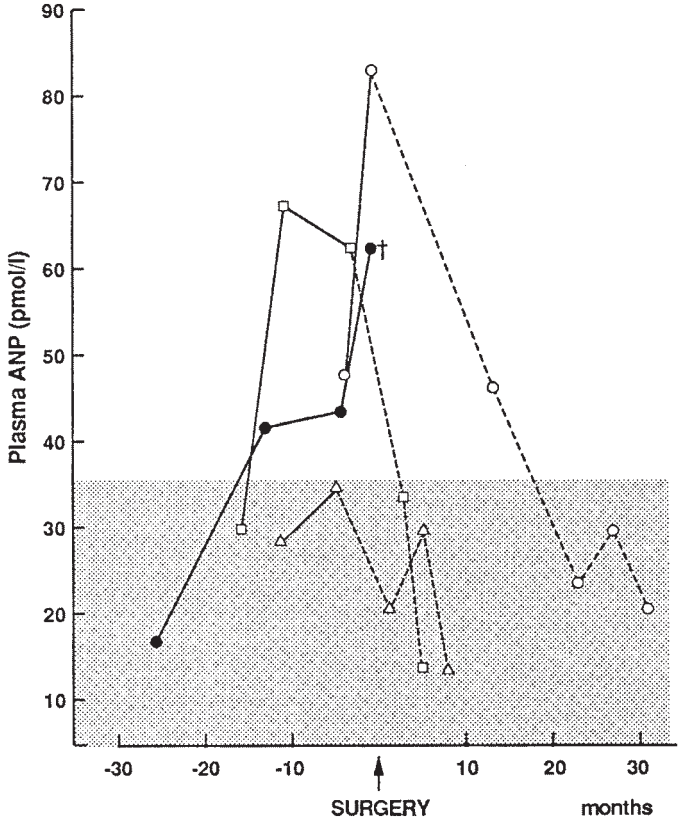


Fig. 3. Plasma atrial natriuretic peptide (ANP) levels in TR. Solid line, preoperative; dashed line, postoperative; open circles, case 1; closed circles, case 2; open triangle, case 3; open square, case 4, †, death postoperatively. (Reproduced with permission from ref. *12*.)

this point, the right heart becomes a passive conduit, and the circulation becomes univentricular. Fluid administration and elevated central venous pressures (to increase RV end-diastolic volume) may be necessary to support the cardiac output *(14)*. In the presence of severe pulmonary hypertension, an atrial septostomy may be required simply to maintain left ventricular preload. Maintaining A-V synchrony and avoiding agents that reduce preload, such as nitroglycerin and morphine, are also useful *(15)*. Inotropic support (e.g., milrinone, dobutamine, isoproterenol) may be required.

When right heart dysfunction is secondary to left-sided failure, treatment of the left-sided disease should take precedent. In this setting, surgical therapy of secondary TR may serve as an adjuvant to surgical

therapy of the left ventricle (i.e., coronary bypass or mitral valve repair). Rarely is it indicated to operate solely on the tricuspid valve when the regurgitation is secondary to left heart disease. In contrast, when TR is primary (i.e., endocarditis), valve repair or replacement is warranted when medical therapy cannot control symptoms.

The tricuspid valve is usually approached through a median sternotomy. A right anterolateral thoracotomy may alternatively be performed in reoperative cases. Minimally invasive approaches have also been described, but may require femoral cannulation. Most patients requiring surgery for tricuspid disease have enlarged right atriums, making visualization of the tricuspid valve easier. Bicaval venous cannulation is performed in the standard manner, and arterial cannulation is obtained via the aorta. After initiation of bypass, the patient is cooled, and the aorta is cross-clamped. All other procedures are performed prior to addressing the tricuspid valve (e.g., coronary artery bypass graft, aortic valve, mitral valve, etc.).

The mitral valve can be reached through a transseptal incision, thereby avoiding a second atriotomy. Generally, we perform tricuspid procedures during rewarming after the aortic cross-clamp has been removed. Prior to this, snares are secured around the superior vena cava and inferior vena cava venous cannulae to avoid inadvertent blood flow. This technique creates a relatively dry field, with the exception of blood draining from the coronary sinus. Although previously considered the standard method of diagnosis, we have not found it helpful to assess the degree of regurgitation by finger palpation through the right atrium; we rely primarily on preoperative and intraoperative echocardiography.

Once the anatomy of this region has been identified, the valve itself is inspected. Asymmetric dilatation in the posterior region is commonly present and is a consequence of the septal leaflet's annular structure fixation to the fibrous skeleton of the heart. Therefore, Cohn *(16)* and others *(17–20)* have suggested techniques to reduce the clinical role of this region. In Cohn's technique, a partial annuloplasty is performed in the region of the posterior annulus using a sizing obturator to avoid unnecessary constriction (Fig. 4). This method is a variation of the classic annuloplasty technique initially proposed by De Vega *(21)*. De Vega's method utilizes a double continuous suture placed from the anteroseptal commissure to the posteroseptal commissure in a clockwise fashion. This suture is nearly circumferential and ends in the region of the conduction bundle, placing the atrioventricular node in jeopardy (Fig. 5). The Kay-Wooler repair also tries to reduce the tricuspid annulus in the posterior region. This technique approximates and opposes the annulus at the posterior leaflet, thus "bicuspidizing" the tricuspid valve (Fig. 6) *(19)*.

Fig. 4. Modified De Vega annuloplasty. (Reproduced with permission from ref. *16*.)

When 3 to 4+ TR exists, some surgeons elect to repair the valve with a ring annuloplasty. This repair utilizes a structured band to reduce annular dimension. The ring is sized to the septal leaflet and secured carefully to avoid the bundle of His. Ring types most commonly used are those described by Carpentier-Edwards and colleagues *(22)*, Duran and Ubago *(23)*, and McCarthy and Cosgrove *(24)* (Fig. 7).

Ring annuloplasty and commisurotomy may be indicated for rheumatic-induced tricuspid stenosis (TS). The fused commissures, which can be identified by their fan chordae, are incised with a scalpel, taking care not to enter the annulus proper. To avoid iatrogenically induced regurgitation, commissurotomy should be limited to one or two commissures; we usually do not incise the anteroseptal commissure because this area is most likely to develop insufficiency. When performed, commisurotomy should be combined with a ring to ensure durability.

If the tricuspid valve has to be replaced, we excise or imbricate the anterior and posterior leaflets. Imbrication has the distinct advantage of allowing the surgeon to retain the subvalvular apparatus, an important principle of mitral valve surgery. Sutures are placed in the septal leaflet proper to avoid the specialized conductive tissue (Fig. 8). Valve competency is tested by infusing saline into the right ventricle and

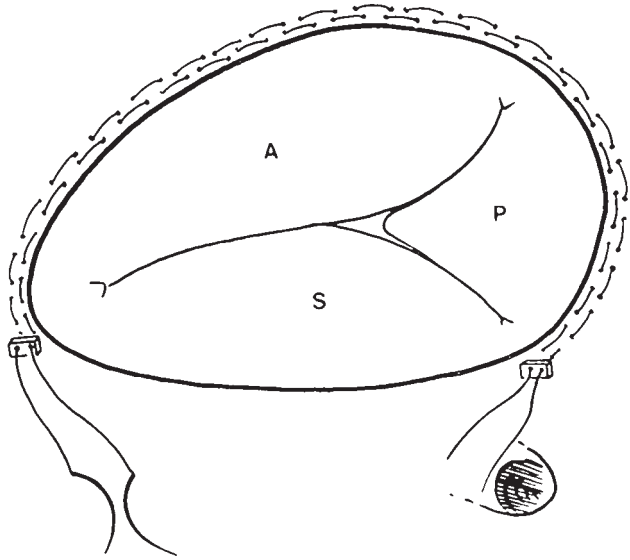


Fig. 5. De Vega annuolplasty. A, anterior leaflet; P, posterior leaflet; S, septal leaflet. (Reproduced with permission from ref. *81*.)

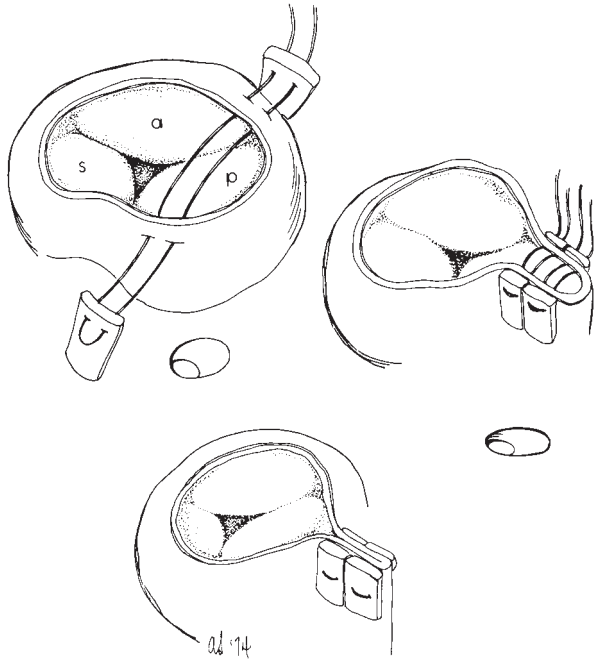


Fig. 6. Kay or Wooler annuloplasty. a, anterior leaflet; p, posterior leaflet; s, septal leaflet. (Reproduced with permission from ref. *82*.)

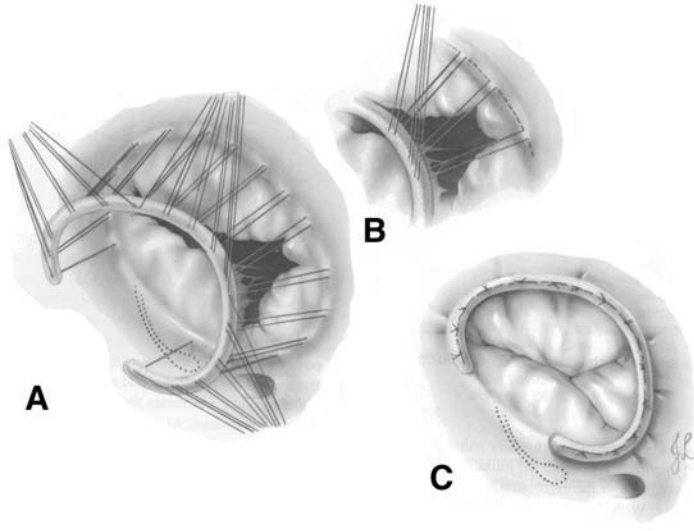


Fig. 7. Carpentier ring annuloplasty. A, anchoring mattress sutured; B, reducing the size of the annulus; C, restoring the valve to its normal configuration. (Reproduced with permission from ref. *4*.)

assessing leaflet coaptation. If this proves satisfactory, the atrium is closed, and the patient is weaned from bypass with transesophageal echocardiographic confirmation prior to decannulation. In 88 patients treated by reparative techniques at the Brigham and Women's Hospital, 72 patients had suture annuloplasty (69 De Vega, 3 Kay-Wooler); 16 had ring annuloplasty (all 16 had 4+ TR; 15 Carpentier-Edwards, 1 Duran). There were 79 patients in New York Heart Association class III or IV, and 82 patients underwent concomitant mitral valve replacement. The operative mortality was 11.5%. A 2-year follow-up was available for 53 patients: TR was absent in 7, "trace TR" was present in 28, and "mild TR" was identified in 18 *(16)*.

In general, many of the left ventricular hemodynamic benefits derived from mitral valve repair can also be seen in the right ventricle with tricuspid repair *(25)*. Although the tricuspid valve is more forgiving of surgical technique, valve repair has been associated with a higher incidence of residual insufficiency compared to replacement. The decision of repair vs replacement is typically based on the degree of regurgitation. In general, we follow the American College of Cardiology/American Heart Association guidelines: Mild TR is treated conservatively; moderate TR is treated with annuloplasty; and severe TR is treated with replacement *(26)*. When a valve is required, a bioprosthesis theoretically can avoid the

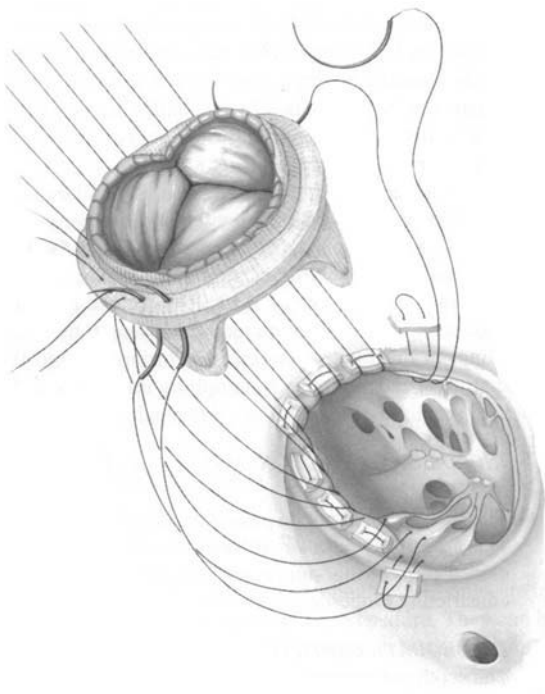


Fig. 8. Tricuspid valve replacement. (Reproduced with permission from ref. *4*.)

risk of mechanical thrombosis *(27)*. Valve durability is also much greater in the tricuspid position than it is in the aortic or mitral positions *(28–30)*. Also, mechanical valve replacement requires placement of permanent epicardial pacing wires because percutaneous leads cannot be placed through the mechanical valve. We favor the use of long-term anticoagulation for mechanical and biologic tricuspid valves. In our opinion, the relatively low flow rate through the valve orifice increases the likelihood of valvular thrombi. Others, however, limit anticoagulation to only those patients with mechanical valves *(31)*.

RIGHT HEART FAILURE CAUSED BY SPECIFIC CLINICAL CONDITIONS

The surgical approach to right heart failure generally involves the treatment of tricuspid valve disease (Table 1). Pulmonic valve disease is rarely severe enough to produce right heart failure, and a discussion of its surgical treatment is not reviewed here. TR is the most common form of tricuspid valve disease associated with right heart failure. TS is much more rare, as are mixed stenosis and regurgitation (Tables 2 and 3).

Table 1
Relative Indications for Tricuspid Surgery

1. Medically refractory right-sided heart failure secondary to severe TR
   - Postcardiac transplant
   - Endocarditis
   - Trauma
   - Carcinoid heart disease
   - Rheumatic
2. Moderate-to-severe TR at time of left heart surgery (i.e., mitral valve or coronary)
3. TS with a valve gradient ≥5 mmHg

Table 2
Primary Causes of Tricuspid Valve Disease

Tricuspid regurgitation
Endocarditis
Ebstein's anomaly
Atrioventricular canal deformity
Myxomatous degeneration
Carcinoid heart disease
Trauma
Biopsy induced
Tricuspid stenosis
Congenital tricuspid atresia

Tricuspid Regurgitation

TR is relatively common and can arise from a variety of causes. Primary TR is usually seen with congenital anomalies of the tricuspid valve or acquired leaflet deformities. Secondary TR typically develops in the setting of pressure overload (i.e., primary or secondary pulmonary hypertension) or RV cardiomyopathies (i.e., RV infarction, arrythmogenic RV dysplasia). Functional TR generally becomes evident when the RV systolic pressure becomes greater than 55 mmHg *(26)*. As the degree of regurgitation worsens, the progressive volume overload distends the ventricle and the tricuspid annulus, producing more TR. The right atrial hemodynamic tracing becomes ventricularized with increasing degrees of insufficiency, producing larger and larger V waves (Fig. 9). Eventually, clinical signs of right-sided failure appear: jugular venous distension, hepatic congestion, ascites, and peripheral edema.

Table 3
Secondary Causes of Tricuspid Valve Disease

Tricuspid regurgitation
Aortic valve disease (stenosis or insuffiency)
Mitral valve disease (stenosis or regurgitation)
Congestive heart failure
Primary pulmonary hypertension
Pulmonary stenosis
Right-sided ventricular infarction
Dilated cardiomyopathy
Pulmonary embolism
Marfan syndrome
Rheumatic heart disease
Diet drugs: fenfluramine/phentermine
Arrhythmogenic right ventricular dysplasia
Tricuspid stenosis
Rheumatic heart disease
Constrictive pericarditis
Carcinoid syndrome
Fibroelastosis
Endomyocardial fibrosis
Lupus erythematosus
Right atrial myxoma

Tricuspid Stensosis

TS produces mechanical obstruction to RV filling *(32,33)*. TS is almost exclusively caused by rheumatic inflammation and accompanies rheumatic mitral stenosis in up to 30% of patients. Rheumatic TS is usually associated with some degree of TR as well. TS may also be secondary to the carcinoid syndrome, endocarditis, and intracardiac tumors. Clinically, TS is not well tolerated. Impairment to RV filling (with mean diastolic gradients as low as 5 mmHg) may produce impressive symptoms of right-sided failure, and the importance of coexisting mitral disease therefore may be overestimated *(32,33)*.

Although medical management of TS (sodium restriction and diuresis) suffices early in its course, the disease is progressive, and surgical therapy is usually required. Operative strategies include open and closed commissurotomy *(33)*. Balloon valvuloplasty has been performed, but with variable success *(34)*. Unfortunately, these techniques are associated with poor long-term outcomes, primarily because of sur-

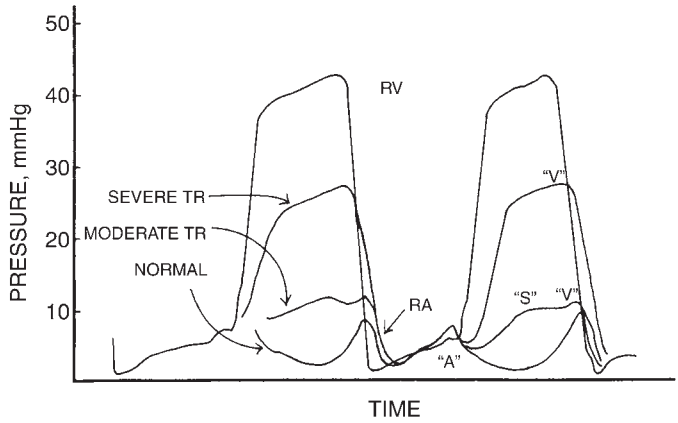


Fig. 9. Pressure tracing of tricuspid regurgitation. RA, right atrium; RV, right ventricle. (Reproduced with permission from ref. *83*.)

gically induced regurgitation. To achieve long-term success, valve replacement is commonly required.

Tricuspid Valve Endocarditis

Tricuspid valve endocarditis results from seeding of the valve leaflets during sustained bacteremia. Surgical indications in tricuspid valve endocarditis include continued sepsis despite appropriate antibiotic coverage, heart failure caused by tricuspid insufficiency, and recurrent multiple pulmonary emboli. Arbulu et al. *(35)* were the first to advocate complete excision of the tricuspid valve (without subsequent replacement). From an infectious disease standpoint, this approach has the distinct advantage of complete extirpation of infected tissue and avoids placement of prosthetic material. Although initially tolerated, this procedure unfortunately produces late-onset right-sided failure in the majority of patients *(35–37)*. In a 20-year follow-up of the originally reported series of 55 patients with intractable right-sided endocarditis who underwent tricuspid valvulectomy without replacement, 2 patients (4%) died in the postoperative period because of right-sided failure. Six patients (11%) required prosthetic valve insertion 2 days to 13 years later for medically refractory right-sided heart failure. Of the 6 who underwent reoperation, 4 (66%) died. Therefore, severe hepatic congestion and the need for reoperative valve replacement have made this approach untenable to some authors *(38)*. An alternative treatment option is to delay valve replacement for 3–9 months. Reparative strategies at time of the original

operation have also been successful in treating this challenging group of patients *(4,39)*.

TR After Heart Transplantation

The reported incidence of TR in the heart transplant population varies widely, occurring in 20–83% of patients *(40,41)*. Regardless of the actual incidence, TR after transplantation is generally not severe (either asymptomatic or easily controlled with diuretics). Occasionally, the degree of regurgitation may be severe enough to warrant tricuspid valve surgery *(42,43)*. The etiology of TR in this select population has been attributed to a number of mechanisms: anastomotic technique, ischemic reperfusion injury, iatrogenic damage from endomyocardial biopsies, size mismatch between donor and recipient hearts, and chronic rejection.

The technique of orthotopic heart transplantation commonly performed until the 1990s was that of Lower and Shumway *(44,45)* using a biatrial anastomosis. Although this technique preserved a portion of the recipient's right atrium, the final geometry of the atria were often dilated and distorted and complicated by asynchronous atrial contraction. Before long, reports of TR and mitral regurgitation surfaced (in the context of a normal valve apparatus) *(46,47)*.

The now-contemporary bicaval anastomosis, popularized by Sievers et al. *(48)*, appears to alleviate some of these issues. In their original report, when tested in a prospective randomized trial, the bicaval anastomosis was associated with less TR and smaller right atria during exercise. Sarsam et al. *(49)* found a lower incidence of postoperative right heart failure and right atrial pressure (4.9 mmHg vs 9.6 mmHg, $p < 0.01$) in those transplanted with bicaval anastomoses despite a lack of difference in pulmonary artery pressures.

Percutaneous transvenous endomyocardial biopsy of the transplanted heart is the conventional method to detect allograft rejection *(50)*. It is a generally safe procedure, and major complications, such as cardiac perforation and tamponade, are unusual (<0.4% of cases) *(51)*. However, TR may result from the inadvertent injury of tricuspid valve by the bioptome and may be as frequent as 6% *(52)*. Fortunately, it is generally well tolerated and of modest severity. The need for surgical correction for medically refractory iatrogenic TR is rare *(53)*.

In addition to the aforementioned etiologies, some authors have also attributed the higher incidence of TR in the transplant population to preoperative pulmonary hypertension. Lewen et al. *(54)* found that preoperative pulmonary hypertension (>55 mmHg) was a predictor of late postoperative moderate-to-severe TR (mean 17 months) and was asso-

ciated with postoperative elevation in the PVR. Other investigators have confirmed these observations *(41)*. When TR does occur in the transplant patient, medical management is usually effective. When medical therapy fails to control symptoms, valve replacement is usually favored over repair to avoid the potential need for repeated operative intervention in an immunocompromised patient.

Rheumatic TR

The most common cause of organic tricuspid disease worldwide is rheumatic fever, typically in association with mitral and/or aortic involvement. Commonly, rheumatic tricuspid disease is both stenotic and with regurgitant. Functional TR reported in these patients is a misnomer; the rheumatic tricuspid annulus is actually structurally weakened by the rheumatic inflammation rather than dilated from RV enlargement. This type of annular pathology may be suspected when normal valve leaflets accompany the regurgitation in a patient with a history of rheumatic fever, a markedly dilated annulus, and severe TR. The regurgitant jet in these cases is frequently large in volume and low in velocity. Rheumatic TR may be exacerbated by rheumatic mitral disease and concomitant pulmonary hypertension.

Distinguishing whether the dilated tricuspid annulus is caused by secondary causes or primary rheumatic weakening may be difficult, but this distinction can influence the surgical approach. A number of authors have recognized the significance of rheumatic weakening of the tricuspid annulus in the absence of rheumatic leaflet damage and have noted that it may manifest well after rheumatic mitral valve surgery *(2,55)* (*see* section on Tricuspid Valve Disease Following Mitral Valve Surgery). Thus, some have advocated tricuspid annuloplasty at the time of rheumatic mitral surgery even if there is no overt tricuspid pathology.

Rheumatic valvular surgery may also be complicated by the restriction–dilation syndrome, described originally by Barlow *(56,57)* (Fig. 10). The pressure and volume overload of the right heart from left-sided heart disease sets into motion a vicious cycle of ventricular dilatation, but pericardial constraint. As the right heart dilates, there is an exaggerated diastolic septal shift to the left, further increases in LVEDP/left atrium pressures, greater pulmonary hypertension, worsening TR, more right heart volume overload, and again more RV dilation. Although LV systolic function may be intrinsically normal under these conditions, the LVEDP will be elevated. Postoperative adhesions will further exacerbate this cycle by precluding compensatory ventricular expansion and exaggerating the septal shift. This

Fig. 10. The restriction–dilation syndrome. LV, left ventricle; RV, right ventricle; TR, tricuspid regurgitation; RVEDP, right ventricular end-diastolic pressure; PAHT, pulmonary artery hypertension; LVEDP, left ventricular end-diastolic pressure; AR, aortic regurgitation; MR, mitral regurgitation; PVHT, pulmonary vein hypertension; MS, mitral stenosis; LA, left atrial; PTED, pulmonary thromboembolic disease; COAD, coronary occlusive arterial disease. (Reproduced with permission from ref. *56*.)

syndrome is possible after any left-sided surgery, but is most commonly seen in rheumatic heart disease *(55–58)*. Correction of TR at the time of operative therapy for hemodynamically important left-sided valvular disease will interrupt this cycle.

Tricuspid Valve Disease Following Mitral Valve Surgery

Although early-onset TR following mitral valve surgery may reflect a variety of underlying causes (persistent pulmonary hypertension, mitral prosthetic dysfunction, progressive aortic valve disease, or LV failure), late-onset TR usually reflects intrinsic RV dysfunction and/or tricuspid annular abnormalities *(59–61)*. Functional tricuspid insufficiency has been reported in up to 67% of those undergoing left heart surgery and is thought to be from the effects of transmitted afterload from left heart disease *(62–64)*. Therefore, conservative management of TR was initially advocated *(65)* because of expected improvements in functional regurgitation after left-sided surgery. However, it is now generally accepted that symptoms of right heart failure and exercise intolerance will persist in a significant number of patients with this approach *(3)*. Furthermore, tricuspid valve annuloplasty (or valve

replacement) for functional TR at the time of the initial aortic/mitral valve surgery does appear to improve outcomes *(66–68)*.

It is difficult to discern whether TR after mitral valve repair is a primary disorder of the tricuspid apparatus or is secondary to the mitral surgery. Groves et al. *(59)* compared the clinical and echocardiographic characteristics of 26 patients with and without late-onset TR after mitral valve surgery. Both groups had similar pulmonary artery pressures and no evidence of prosthetic valve dysfunction, significant aortic valve disease, or intrinsic tricuspid pathology. Only tricuspid annular diameter and RV size were greater in those patients that developed severe late-onset TR. Similarly, Porter et al. *(64)* reviewed late-onset TR in patients who had previously undergone mitral valve replacement without tricuspid valve surgery for rheumatic heart disease. Again, it was difficult to predict who would go on to develop late-onset TR: The pre- and postoperative pulmonary artery pressures, the predominance of mitral lesions, the prosthetic valve gradients, and the degree of regurgitation were similar in patients with and without late-onset TR.

The decision to operate on patients with late-onset TR following remote left-sided valve surgery is a difficult one. Staab et al. *(69)* reviewed 34 patients who underwent isolated tricuspid valve operations for severe TR following prior left-sided valve surgery. Although 85% of survivors improved symptomatically, the early mortality rate was 8.8%, and the 5-year event-free actuarial survival was only 41.6%. Predictors of poor outcome were increased age and previous cardiac surgery. Outcome did not vary depending on the degree of pulmonary hypertension, LV function, RV size/function, annular diameter, or the use of valve replacement vs repair.

King et al. *(2)* reviewed their series of 16 tricuspid annuloplasties and 16 tricuspid valve replacements 4 months to 14 years after mitral valve surgery. Of patients, 53% required concomitant mitral or aortic valve surgery at the time of reoperation. The in-hospital mortality was 25%, and the 5-year actuarial survival was 44%. Moreover, nearly 54% of those surviving longer than 30 days had little or no improvement in tricuspid valve function following the procedure. They concluded that late-onset TR occurring after left-sided surgery was a signal of RV failure, and restoring valve competence was merely palliative: Patient outcome was primarily determined by RV function.

Given the high incidence of late mortality and poor long-term results, the timing of reoperative tricuspid surgery is crucial and probably should not be considered in advanced degrees of RV dysfunction. This approach reemphasizes the need for early diagnosis and treatment

of TR when present at the initial operation *(3,55,60,64)*. Our general policy is to treat moderate or severe TR during the initial aortic or mitral valve operation. We share the opinion that reoperation for late-onset TR following left-sided valvular surgery should be approached with caution.

Traumatic TR

The pathophysiology of traumatic TR is thought to involve a severe and sudden elevation in RV intracavitary pressure, leading to disruption of the valve apparatus. This acute-onset regurgitation, if not diagnosed promptly, leads to volume loading of the right ventricle, ventricular enlargement, and subsequent annular dilatation. In a review of 13 patients with nonpenetrating traumatic tricuspid insufficiency, Miller et al. *(70)* found that the primary mechanism of regurgitation was a flail anterior leaflet. In more than 90% of patients, this was caused by ruptured chords, an avulsed anterior papillary muscle, or a tear in the leaflet proper. Severity of the valvular disease and associated injuries will then dictate the appropriateness of surgical repair. A thorough echocardiographic evaluation should also be undertaken at the time of surgery *(70–72)*.

When feasible, tricuspid valve damage should be repaired electively unless tamponade or heart failure mandates immediate intervention *(72)*. It should be noted that delayed presentation is common; in Miller et al.'s series, the average time to presentation was 9 years. Although valve replacement has traditionally been performed, traumatic lesions are frequently amenable to repair, thereby avoiding a mechanical prosthesis and systemic anticoagulation *(70)*.

Carcinoid Tricuspid Valve Disease

The carcinoid syndrome results from midgut carcinoid tumors metastatic to the liver and/or lung. Once these organs are involved, serotonin and other vasoactive amines are released directly into the systemic venous system, thus bypassing the detoxification that would have normally occurred when delivered via the portal vein. These substances produce vasomotor changes, bronchospasm, diarrhea, and telangiectasias. The mural and valvular endothelium of the right heart are directly exposed to these vasoactive products, resulting in endomyocardial fibrosis, diastolic dysfunction, and tricuspid/pulmonic stenosis/insufficiency. Characteristically, the tricuspid and pulmonic valve leaflets are thickened and restricted in motion or even fixed. TR is almost universal. Right heart failure in the absence of left-sided heart disease is common *(73)*.

The natural history of carcinoid heart disease is ominous *(73,74)*. However, the recent development of somatostatin analogs (serotonin antagonists), catheter-based hepatic embolization, and chemotherapy have dramatically improved symptoms and survival, approaching 50% at 5 years *(74–76)*. Unfortunately, right heart failure from tricuspid or pulmonic valve involvement is a common cause of the high mortality in this disease. Approximately one-third of patients with metastatic disease will suffer from right-sided failure *(12)*.

The primary disease should be controlled prior to operative intervention. Patients with rapid deterioration or multisystem organ failure should be excluded from surgery. At the other end of the spectrum, asymptomatic patients should not undergo surgery purely on the basis of echocardiographic evidence of carcinoid heart disease. Generally, one-third of patients with carcinoid heart disease will eventually present to cardiac surgery *(12)*. Preoperatively, somatostatin should be administered prophylactically to prevent the potential intraoperative complications of hypotension, bronchospasm, and tachycardia that can result from tumor release of vasoactive substances *(77,78)*.

The ability to repair valves affected by carcinoid disease is rare, and patients almost always require valve replacement. Involvement of the pulmonary valve may require combined valve replacement or pulmonary valvotomy/valvectomy to avoid right ventricle outflow obstruction. These last procedures should not be used in the setting of advanced right-sided failure. The type of tricuspid replacement, mechanical or bioprosthetic, remains controversial, but this decision does not appear to affect survival significantly. Reports of carcinoid involvement of bioprosthetic tissue leaflets have been reported *(75,79)* and led some to advocate the use of mechanical valves. In such settings, the risk of anticoagulation must be weighed against the potential risk of serotonin-induced damage to bioprosthetic leaflets *(77)*.

The largest surgical series of patients with carcinoid heart disease was reported by Connolly et al. *(78)*. Of 26 patients with tricuspid surgery (who were compared to historical controls), one-third died within 30 days, and half of these deaths were attributed to cardiovascular causes. Of those who survived, another one-third died late from primarily hepatic failure (up to 1.5 years). One-third survived 2 or more years, compared to an 8% survival in historical controls. Those who survived had an improvement of one to two New York Heart Association functional classes. Predictors of late survival included a lower preoperative somatostatin requirement and a lower preoperative 5-hydroxyindoleacetic acid level. However, those with cardiac involvement generally have more symptoms, higher serotonin

levels, and increased urine 5-hydroxyindoleacetic acid levels compared to those without cardiac involvement *(80)*. Therefore, patients with carcinoid heart disease have to be selected carefully for operative intervention.

CONCLUSION

The surgical management of right heart failure is primarily directed at the operative strategies for tricuspid valve regurgitation. Timing of operative intervention for TR should take into account the symptomatic status of the patient, a functional assessment of RV function, and consideration of left heart disease. Because tricuspid disease is generally found in combination with valvular or myocardial disease of the left heart, operative management of tricuspid valve disease should be considered at the time of left heart surgery. Early and aggressive surgical attention to the tricuspid valve combined with appropriate patient selection can lead to an improvement in right heart failure.

REFERENCES

1. Jamieson WR, Edwards FH, Schwartz M, Bero JW, Clark RE, Grover FL. Risk stratification for cardiac valve replacement. National Cardiac Surgery Database. Database Committee of the Society of Thoracic Surgeons. Ann Thorac Surg 1999;67:943–951.
2. King RM, Schaff HV, Danielson GK, et al. Surgery for tricuspid regurgitation late after mitral valve replacement. Circulation 1984;70(3 part 2):I193–I197.
3. Kaul TK, Ramsdale DR, Mercer JL. Functional tricuspid regurgitation following replacement of the mitral valve. Int J Cardiol 1991;33:305–313.
4. Khonsari S. Surgery of the Tricuspid Valve. Cardiac Surgery: Safeguards and Pitfalls in Operative Technique. Lippincott-Raven, Philadelphia, PA: 1997, pp. 105–112.
5. Isner JM, Roberts WC. Right ventricular infarction complicating left ventricular infarction secondary to coronary heart disease. Frequency, location, associated findings and significance from analysis of 236 necropsy patients with acute or healed myocardial infarction. Am J Cardiol 1978;42:885–894.
6. D'Arcy B, Nanda NC. Two-dimensional echocardiographic features of right ventricular infarction. Circulation 1982;65:167–173.
7. Korr KS, Levinson H, Bough EW, et al. Tricuspid valve replacement for cardiogenic shock after acute right ventricular infarction. JAMA 1980;244:1958–1960.
8. Louie EK, Lin SS, Reynertson SI, Brundage BH, Levitsky S, Rich S. Pressure and volume loading of the right ventricle have opposite effects on left ventricular ejection fraction. Circulation 1995;92:819–824.
9. Louie EK, Bieniarz T, Moore AM, Levitsky S. Reduced atrial contribution to left ventricular filling in patients with severe tricuspid regurgitation after tricuspid valvulectomy: a Doppler echocardiographic study. J Am Coll Cardiol 1990;16: 1617–1624.
10. Lorell B, Leinbach RC, Pohost GM, et al. Right ventricular infarction. Clinical diagnosis and differentiation from cardiac tamponade and pericardial constriction. Am J Cardiol 1979;43:465–471.

11. Lopez-Sendon J, Coma-Canella I, Gamallo C. Sensitivity and specificity of hemodynamic criteria in the diagnosis of acute right ventricular infarction. Circulation 1981;64:515–525.
12. Lundin L, Hansson HE, Landelius J, Oberg K. Surgical treatment of carcinoid heart disease. J ThoracCardiovasc Surg 1990;100:552–561.
13. Lundin L, Landelius J. Echocardiography for carcinoid heart disease. Ann NY Acad Sci 1994;733:437–445.
14. Goldstein JA, Vlahakes GJ, Verrier ED, et al. Volume loading improves low cardiac output in experimental right ventricular infarction. J Am Coll Cardiol 1983;2:270–278.
15. Topol EJ, Goldschlager N, Ports TA, et al. Hemodynamic benefit of atrial pacing in right ventricular myocardial infarction. Ann Intern Med 1982;96: 594–597.
16. Cohn LH. Tricuspid regurgitation secondary to mitral valve disease: when and how to repair. J Card Surg 1994;9(2 suppl):237–241.
17. Reed GE, Boyd AD, Spencer FC, Engelman RM, Isom OW, Cunningham JN. Operative management of tricuspid regurgitation. Circulation 1976;54(6 suppl): III96–III98.
18. Bex JP, Lecompte Y. Tricuspid valve repair using a flexible linear reducer. J Card Surg 1986;1:151–159.
19. Kay JH. Surgical treatment of tricuspid regurgitation. Ann Thorac Surg 1992;53: 1132–1133.
20. Minale C, Lambertz H, Messmer BJ. New developments for reconstruction of the tricuspid valve. J Thorac Cardiovasc Surg 1987;94:626–631.
21. De Vega NG. [Selective, adjustable and permanent annuloplasty. An original technic for the treatment of tricuspid insufficiency]. Rev Esp Cardiol 1972;25: 555–556.
22. Carpentier A, Deloche A, Hanania G, et al. Surgical management of acquired tricuspid valve disease. J ThoracCardiovasc Surg 1974;67:53–65.
23. Duran CG, Ubago JL. Clinical and hemodynamic performance of a totally flexible prosthetic ring for atrioventricular valve reconstruction. Ann Thorac Surg 1976; 22:458–463.
24. McCarthy JF, Cosgrove DM. Tricuspid valve repair with the Cosgrove-Edwards annuloplasty system. Ann Thorac Surg 1997;64:267–268.
25. Rabago G, Fraile J, Martinell J, Artiz V. Technique and results of tricuspid annuloplasty. J Card Surg 1986;1:247–253.
26. Bonow RO, Carabello B, de Leon AC Jr, et al. Guidelines for the management of patients with valvular heart disease: executive summary. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Management of Patients With Valvular Heart Disease). Circulation 1998;98:1949–1984.
27. Boskovic D, Elezovic I, Simin N, Rolovic Z, Josipovic V. Late thrombosis of the Björk-Shiley tilting disc valve in the tricuspid position. Thrombolytic treatment with streptokinase. J Thorac Cardiovasc Surg 1986;91:1–8.
28. Jegaden O, Perinetti M, Barthelet M, et al. Long-term results of porcine bioprostheses in the tricuspid position. Eur J Cardiothorac Surg 1992;6:256–260.
29. McGrath LB, Chen C, Bailey BM, Fernandez J, Laub GW, Adkins MS. Early and late phase events following bioprosthetic tricuspid valve replacement. J Card Surg 1992;7:245–253.
30. Treasure T. Which prosthetic valve should we choose? Curr Opin Cardiol 1995; 10:144–149.

31. Braunwald E. Valvular heart disease: tricuspid, pulmonic, and multivalvular disease: tricuspid stenosis. In: Braunwald E., Zipes DP, Libby P. eds. Heart Disease. A Textbook of Cardiovascular Medicine, 6th ed. WB Saunders, Philadelphia, PA, 2001, pp. 1643–1722.
32. Gibson R, Wood P. The diagnosis of tricuspid stenosis. Br Heart J 1955; 17:552–562.
33. Kitchen A, Turner R. Diagnosis and treatment of tricuspid stenosis. Br Heart J 1964;26:354–379.
34. Ribeiro PA, Al Zaibag M, Al Kasab S, et al. Percutaneous double balloon valvotomy for rheumatic tricuspid stenosis. Am J Cardiol 1988;61:660–662.
35. Arbulu A, Thoms NW, Wilson RF. Valvulectomy without prosthetic replacement. A lifesaving operation for tricuspid pseudomonas endocarditis. J Thorac Cardiovasc Surg 1972;64:103–107.
36. Arbulu A, Asfaw I. Tricuspid valvulectomy without prosthetic replacement. Ten years of clinical experience. J Thorac Cardiovasc Surg 1981;82:684–691.
37. Arbulu A, Holmes RJ, Asfaw I. Surgical treatment of intractable right-sided infective endocarditis in drug addicts: 25 years experience. J Heart Valve Dis 1993;2: 129–37; discussion 138–139.
38. Karp RB. Acquired disease of the Tricupid Valve. In: Sabiston DC and Spencer FC, eds. Surgery of the Chest, 5th ed. W. B. Saunders, Philadelphia, PA, pp. 1667–1672.
39. Yee ES, Ullyot DJ. Reparative approach for right-sided endocarditis. Operative considerations and results of valvuloplasty. J Thorac Cardiovasc Surg 1988;96: 133–140.
40. Yankah AC, Musci M, Weng Y, et al. Tricuspid valve dysfunction and surgery after orthotopic cardiac transplantation. Eur J Cardiothorac Surg 2000;17: 343–348.
41. Rees AP, Milani RV, Lavie CJ, Smart FW, Ventura HO. Valvular regurgitation and right-sided cardiac pressures in heart transplant recipients by complete Doppler and color flow evaluation. Chest 1993;104:82–87.
42. Votapka TV, Appleton RS, Pennington DG. Tricuspid valve replacement after orthotopic heart transplantation. Ann Thorac Surg 1994;57:752–754.
43. Stahl RD, Karwande SV, Olsen SL, Taylor DO, Hawkins JA, Renlund DG. Tricuspid valve dysfunction in the transplanted heart. Ann Thorac Surg 1995;59: 477–480.
44. Lower RR, Shumway NE. Studies of the orthotopic homotransplantation of the canine heart. Ann Thorac Surg 1960;11:18–23.
45. Shumway NE, Lower RR, Stofer RC. Transplantation of the heart. Adv Surg 1966;2:265–284.
46. Stevenson LW, Dadourian BJ, Kobashigawa J, Child JS, Clark SH, Laks H. Mitral regurgitation after cardiac transplantation. Am J Cardiol 1987;60:119–122.
47. Angermann CE, Spes CH, Tammen A, et al. Anatomic characteristics and valvular function of the transplanted heart: transthoracic vs transesophageal echocardiographic findings. J Heart Transplant 1990;9:331–338.
48. Sievers HH, Weyand M, Kraatz EG, Bernhard A. An alternative technique for orthotopic cardiac transplantation, with preservation of the normal anatomy of the right atrium. Thorac Cardiovasc Surg 1991;39:70–72.
49. Sarsam MA, Campbell CS, Yonan NA, Deiraniya AK, Rahman AN. An alternative surgical technique in orthotopic cardiac transplantation. J Card Surg 1993;8: 344–349.

50. Caves PK, Stinson EB, Billingham ME, Rider AK, Shumway NE. Diagnosis of human cardiac allograft rejection by serial cardiac biopsy. J Thorac Cardiovasc Surg 1973;66:461–466.
51. Fowles RE, Mason JW. Endomyocardial biopsy. Ann Intern Med 1982;97: 885–894.
52. Braverman AC, Coplen SE, Mudge GH, Lee RT. Ruptured chordae tendineae of the tricuspid valve as a complication of endomyocardial biopsy in heart transplant patients. Am J Cardiol 1990;66:111–113.
53. Huddleston CB, Rosenbloom M, Goldstein JA, Pasque MK. Biopsy-induced tricuspid regurgitation after cardiac transplantation. Ann Thorac Surg 1994;57: 832–836; discussion 836–837.
54. Lewen MK, Bryg RJ, Miller LW, Williams GA, Labovitz AJ. Tricuspid regurgitation by Doppler echocardiography after orthotopic cardiac transplantation. Am J Cardiol 1987;59:1371–1374.
55. Barlow JB. Mitral valve disease: a cardiologic-surgical interaction. Isr J Med Sci 1996;32:831–842, 843–844.
56. Popcock, WA, Antunes MJ, Sareli P, Meyer TE. Late postoperative course and complicatons: emphasis on the "restriction-dilation" syndrome. In: Barlow JB, ed. Perspectives on the Mitral Valve. FA Davis, Philadelphia, PA, 1987, pp. 270–288.
57. Barlow JB. Aspects of tricuspid valve disease, heart failure and the "restriction-dilatation syndrome." Rev Port Cardiol 1995;14:991–1004.
58. Barlow JB. Aspects of mitral and tricuspid regurgitation. J Cardiol Suppl 1991; 25:3–33.
59. Groves PH, Lewis NP, Ikram S, Maire R, Hall RJ. Reduced exercise capacity in patients with tricuspid regurgitation after successful mitral valve replacement for rheumatic mitral valve disease. Br Heart J 1991;66:295–301.
60. Groves PH, Hall RJ. Late tricuspid regurgitation following mitral valve surgery. J Heart Valve Dis 1992;1:80–86.
61. Groves PH, Ikram S, Ingold U, Hall RJ. Tricuspid regurgitation following mitral valve replacement: an echocardiographic study. J Heart Valve Dis 1993;2:273–278.
62. Cohen SR, Sell JE, McIntosh CL, Clark RE. Tricuspid regurgitation in patients with acquired, chronic, pure mitral regurgitation. II. Nonoperative management, tricuspid valve annuloplasty, and tricuspid valve replacement. J Thorac Cardiovasc Surg 1987;94:488–497.
63. Goldman ME, Guarino T, Fuster V, Mindich B. The necessity for tricuspid valve repair can be determined intraoperatively by two-dimensional echocardiography. J Thorac Cardiovasc Surg 1987;94:542–550.
64. Porter A, Shapira Y, Wurzel M, et al. Tricuspid regurgitation late after mitral valve replacement: clinical and echocardiographic evaluation. J Heart Valve Dis 1999;8: 57–62.
65. Braunwald NS, Ross J, Morrow AG. Conservative management of tricuspid regurgitation in patients undergoing mitral valve replacement. Circulation 1967;35 (4 suppl):I63–I69.
66. Brilla C, Hammen M, Jaksch R, Unterberg R, Seboldt H, Karsch KR. [Effect of tricuspid annuloplasty in mitral/aortic valve replacement on the clinical aspects and global function of the right heart chamber]. Thorac Cardiovasc Surg 1988;36: 122–126.
67. Breyer RH, McClenathan JH, Michaelis LL, McIntosh CL, Morrow AG. Tricuspid regurgitation. A comparison of nonoperative management, tricuspid annuloplasty, and tricuspid valve replacement. J Thorac Cardiovasc Surg 1976;72:867–874.

68. Duran CM, Pomar JL, Colman T, Figueroa A, Revuelta JM, Ubago JL. Is tricuspid valve repair necessary? J Thorac Cardiovasc Surg 1980;80:849–860.
69. Staab ME, Nishimura RA, Dearani JA. Isolated tricuspid valve surgery for severe tricuspid regurgitation following prior left heart valve surgery: analysis of outcome in 34 patients. J Heart Valve Dis 1999;8:567–574.
70. Miller FA, Seward JB, Gersh BJ, Tajik AJ, Mucha P. Two-dimensional echocardiographic findings in cardiac trauma. Am J Cardiol 1982;50:1022–1027.
71. Chirillo F, Totis O, Cavarzerani A, et al. Usefulness of transthoracic and transoesophageal echocardiography in recognition and management of cardiovascular injuries after blunt chest trauma. Heart 1996;75:301–306.
72. Doty JR, Cameron DE, Elmaci T, Salomon NW. Penetrating trauma to the tricuspid valve and ventricular septum: delayed repair. Ann Thorac Surg 1999;67: 252–253.
73. Soga J, Yakuwa Y, Osaka M. Carcinoid syndrome: a statistical evaluation of 748 reported cases. J Exp Clin Cancer Res 1999;18:133–141.
74. Moertel CG. Karnofsky memorial lecture. An odyssey in the land of small tumors. J Clin Oncol 1987;5:1502–1522.
75. Knott-Craig CJ, Schaff HV, Mullany CJ, et al. Carcinoid disease of the heart. Surgical management of 10 patients. J Thorac Cardiovasc Surg 1992;104: 475–481.
76. Oberg K, Persson U, Alm G, Eriksson B. Long-term treatment with alpha interferons of patients with malignant carcinoid tumors: the 6 year experience. In: Stewart WE, Schellekens H, eds. The Biology of the Interferon System. Elsevier, Amsterdam, The Netherlands: 1989, pp. 361–384.
77. DiSesa VJ, Mills RM, Collins JJ. Surgical management of carcinoid heart disease. Chest 1985;88:789–791.
78. Connolly HM, Nishimura RA, Smith HC, Pellikka PA, Mullany CJ, Kvols LK. Outcome of cardiac surgery for carcinoid heart disease. J Am Coll Cardiol 1995; 25:410–416.
79. Schoen FJ, Hausner RJ, Howell JF, Beazley HL, Titus JL. Porcine heterograft valve replacement in carcinoid heart disease. J Thorac Cardiovasc Surg 1981;81: 100–105.
80. Robiolio PA, Rigolin VH, Wilson JS, et al. Carcinoid heart disease. Correlation of high serotonin levels with valvular abnormalities detected by cardiac catheterization and echocardiography. Circulation 1995;92:790–795.
81. deRibrolles C. Techniques de correction de L'insuffisance trcuspidienne. In: Bex JP, ed. Pathologie de la valve tricuspide. Masson, Paris: 1981 pp. 24–34.
82. Boyd A, Engleman R, Isom OW, et al. Tricuspid annuloplasty, five and one-half years' experience with 78 patients. J Thorac Cardiovasc Surg 1974;68:344.
83. Grossman W, ed. Cardiac Catheterization and Angiography, 5th ed. Lea and Febiger, Philadelphia, PA: 1996.

6 Pacing in Heart Failure

Uday N. Kumar, MD,
Teresa De Marco, MD,
and Leslie A. Saxon, MD

CONTENTS

INTRODUCTION

Background

Heart failure is a disease of immense burden and cost to individuals and society. It is estimated that more than 4.5 million people in the United States currently suffer from heart failure, and more than 400,000 cases are newly diagnosed each year *(1)*. The prevalence of the disease increases with age such that nearly 10% of the population will be affected in the ninth decade of life *(2)*. Furthermore, heart failure is the leading cause of hospitalizations of individuals older than 65 years, and it was estimated that there would be more than 1 million hospitalizations for heart failure in 2004, with an economic cost exceeding

From: *Contemporary Cardiology: Surgical Management of Congestive Heart Failure*
Edited by: J. C. Fang and G. S. Couper © Humana Press Inc., Totowa, NJ

$40 billion *(3)*. Given the tremendous scope of heart failure, a great deal of research has gone into finding therapies that can reduce its morbidity and mortality.

Numerous trials have resulted in guidelines that currently recommend the use of β-blockers, angiotensin-converting enzyme (ACE) inhibitors, diuretics, aldosterone antagonists, and digoxin for the treatment of patients with heart failure at various stages of the disease *(4)*. Despite these advances in the pharmacological management of patients with heart failure, it is clear that there still remain a significant number of patients with persistent symptoms who are on maximal medical therapy. More important, heart failure continues to be one of the most progressive and lethal diseases and still directly and indirectly contributes to 250,000 deaths annually *(4)*. It is expected that the personal, societal, and economic burden of heart failure will only grow as the number of individuals over the age of 65 increases in the next few decades. Given this background, device therapies represent a promising new modality in the treatment of patients with heart failure, especially as advances in these device technologies allow them to be studied in a very safe and controlled manner.

Ventricular Dyssynchrony

An important characteristic of heart failure is the presence of dysrhythmias and conduction system abnormalities. Some have estimated that up to 53% of patients with heart failure have an intraventricular conduction delay (IVCD) that can lead to abnormal electrical depolarization and subsequent dyssynchrony between the right and left ventricles *(5)*. Although many efforts have focused on other aspects of heart failure, such as optimization of preload, afterload, and contractility, technological breakthroughs have now made addressing the correction of ventricular dyssynchrony a possibility. This is significant because the consequences of ventricular dyssynchrony, including abnormal interventricular septal wall motion, reduction in stroke volume, reduction in the rate of rise of left ventricular (LV) pressure, diminished diastolic filling times, and prolongation of mitral regurgitation, all contribute to worsening heart failure and can cause symptomatic deterioration *(6–8)*.

To identify patients for whom ventricular dyssynchrony may be a problem, the presence of a bundle branch block (BBB) or IVCD on a standard electrocardiogram (ECG) has been used because these findings are the manifestation of ventricular dyssynchrony. In fact, the presence of a wide QRS complex has been shown to be an independent or

contributing risk factor in patients with heart failure, with the degree of conduction delay possibly serving as a marker of disease severity *(5,9–12)*.

Thus, it was hypothesized that, because ventricular dyssynchrony is primarily an aberrance of normal conduction, perhaps pacemakers, which are primarily designed to treat atrioventricular (AV) and sinus node conduction defects, could be modified to help correct ventricular dyssynchrony and its deleterious consequences.

Role of Pacemakers

Numerous pacing strategies using traditional right-sided pacemakers, which have right atrial (RA) and right ventricular (RV) leads, have been attempted to resynchronize electrical depolarization. Attempts to manipulate parameters, such as the AV delay, have yielded inconsistent results and in certain cases have worsened ventricular dyssynchrony *(6–8,13–20)*.

These results subsequently led to investigations of various stimulation sites within the right ventricle, including the apex, septum, and outflow tract, as well as studies looking at LV and biventricular (BV) stimulation using epicardial leads placed through a thoracotomy. Except for a small subset of patients with dilated cardiomyopathy (DCM) for whom traditional right-sided pacing may have a role, results have convincingly demonstrated that LV and BV strategies are far superior in achieving a hemodynamic improvement, in part thought to be because of improvement of ventricular dyssynchrony *(21–26)*.

Figure 1 demonstrates the ECG from a patient enrolled in a resynchronization trial at baseline and after BV stimulation; note the narrowing of the QRS complex with BV stimulation. In terms of specific parameters, improved LV contractility, increased pulse pressure, decreased myocardial oxygen utilization, decreased LV end-diastolic and end-systolic volumes, and improved myocardial performance index have all been seen *(23,25–31)*. Furthermore, improvement in 6-minute walk distances, oxygen uptake at peak exercise, quality-of-life (QoL) scores, and New York Heart Association (NYHA) class has been seen *(31–33)*. Finally, preliminary results from currently ongoing randomized trials have shown that BV resynchronization in patients with heart failure significantly improves myocardial performance and numerous clinical parameters. Perhaps most important, recently reported data comparing resynchronization therapy to medical therapy demonstrated significant improvements in the composite end points of all-cause hospitalization and mortality *(34–37)*.

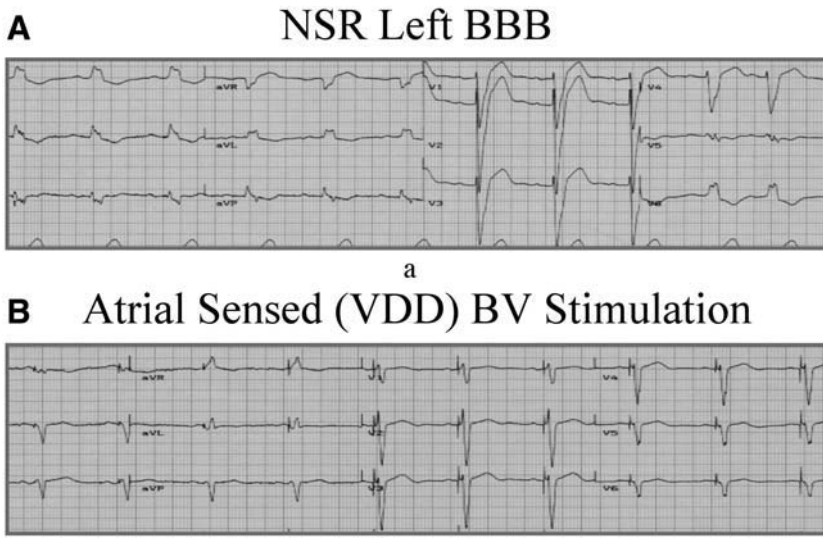


Fig. 1. (A) Baseline electrocardiogram from a patient enrolled in a resynchronization trial demonstrating normal sinus rhythm (NSR) and a left bundle branch block (BBB). (B) Electrocardiogram in the same patient during atrial-sensed (VDD mode) biventricular stimulation showing narrowing of the QRS complex.

An important aspect of recent trials has been the replacement of LV epicardial leads placed via a thoracotomy by coronary venous leads placed percutaneously; initial experience with these leads has been very good in terms of their functioning and in terms of reduced implantation morbidity *(38,39)*. Based on this technological advancement, current investigational systems now incorporate entirely percutaneously placed leads and support various programmable resynchronization therapies.

This chapter reviews the established and emerging indications for pacing devices in the setting of heart failure. The discussion briefly considers the use of standard dual-chamber pacing in DCM and the role of pacing in patients with atrial fibrillation (AF), but mainly focuses on the use of resynchronization therapies in patients with heart failure. Current trials of resynchronization therapies also are reviewed.

STANDARD DUAL-CHAMBER PACING IN DILATED CARDIOMYOPATHY

Rationale

The effect of standard dual-chamber pacing in DCM is not clearly understood. A potential benefit was suggested in an uncontrolled study of 17 patients with DCM who had medically refractory heart failure and

severe symptoms *(15,16)*. Pacing was in the dual mode, dual pacing, dual sensing mode with an AV interval of 100 ms, and patients were followed for up to 5 years. All patients had significant improvements in functional capacity, which was maintained throughout the follow-up period, and in left ventricular ejection fraction (LVEF; 16 vs 26%), which tended to decrease with time. No patient required hospitalization for an exacerbation of heart failure. During the first few months after implantation, cessation of pacing for 2 to 4 hours led to a marked reduction in LVEF; in comparison, pacing withdrawal in later months had a progressively less-deleterious effect *(16)*. The median survival was 22 months, with no patient dying from progressive heart failure. Although much enthusiasm resulted from these data, a well-controlled trial of chronic short AV delay pacing did not find a consistent benefit *(17)*.

Potential Mechanisms

Despite the possible benefit of dual-chamber pacing in DCM, the mechanisms responsible for the improvements seen in some trials are still poorly understood. Possible mechanisms include increased filling time, optimization of left heart mechanical AV delay, and normalization of intraventricular activation, which result in a more coordinated ventricular contraction pattern and an improvement in LVEF *(40)*. When ventricular contraction occurs shortly after atrial contraction, valve closure is optimized, and the time for diastolic mitral regurgitation is minimized. In addition, atrial pacing is less effective than atrial sensing and ventricular pacing (ventricular sensing dual mode, dual pacing [VDD] mode), possibly because of an increase in interatrial conduction delay.

Current and Future Indications

Although the data on dual-chamber pacing in the patient with DCM are limited, it seems likely that a subset of patients will benefit. However, there is no clear method to predict which patients will respond, and thus there are currently no established criteria to identify the patient who will benefit from dual-chamber pacing or to determine when it should be used.

The future in this area may lie with multisite ventricular pacing, including transvenous BV stimulation with standard RA pacing, or through the development of techniques and technologies, which will allow for pacing leads to be placed in the optimal atrial and ventricular sites to minimize conduction delays *(41)*. Data about these types of pacing strategies also remain limited, and there is as yet no consensus on how to optimize the parameters of these systems. However, it is

hoped numerous ongoing trials of various pacing strategies in heart failure, described below, will lead to the establishment of guidelines defining when and how a particular pacing strategy should be used in DCM.

PACING IN ATRIAL FIBRILLATION

Background

Paroxysmal or persistent AF occurs in up to 30% of patients with heart failure *(42)*. Low-dose amiodarone is the safest and most efficacious therapy for maintenance of normal sinus rhythm (NSR) and ventricular rate control *(43)*. However, up to 30 to 40% of patients with heart failure will have recurrent AF on low-dose amiodarone or have a side effect or contraindication to amiodarone therapy *(42,43)*.

Drugs with AV nodal blocking properties traditionally used to control the rate response to AF, such as calcium channel blockers or β-blockers, may be contraindicated in some patients with heart failure or not be well tolerated at the doses needed to achieve rate control during activity. In addition, a small percentage of patients with a rapid ventricular response to AF may actually have a tachycardia-mediated cardiomyopathy and will experience improvement in LVEF with control of the ventricular response *(44)*.

Role for Pacemakers

Both rate control *(45,46)* and rate regularity *(46–48)* appear to be important to optimize symptom status in patients with AF, particularly in the presence of depressed ventricular function. Both of these objectives can be achieved with radiofrequency ablation of the AV node and pacemaker therapy with traditional RV-based pacemakers. As an example, a controlled trial evaluated the efficacy of this approach in 66 patients with clinical heart failure, AF, and a resting ventricular rate greater than 90 beats per minute; the patients were randomly assigned to pharmacological AV nodal blockade or AV nodal ablation and implantation of a ventricular rate-responsive pacemaker *(48)*. After a 12-month follow-up, patients undergoing AV nodal ablation and a pacemaker had significant reductions in palpitations (78%) and dyspnea with exertion (22%) compared to those receiving pharmacological therapy. There was, however, no difference in overall QoL, NYHA functional class, or objective measures of cardiac function; cardiac performance remained stable over time in both groups. In addition, another long-term observational study found that AV nodal ablation and pacing had no adverse effects on survival *(49)*.

To avoid the need for a pacemaker, AV nodal modification rather than ablation has been proposed. One study addressed this issue by randomly assigning 44 patients with heart failure and uncontrolled AF to AV nodal ablation or modification *(50)*. Nodal modification was associated with a small improvement in exercise tolerance, but no change in LVEF or QoL scores. It also resulted in a substantial risk of late complete heart block. In contrast, nodal ablation was associated with a significant improvement in all of these parameters.

Pacing using an LV lead to achieve cardiac resynchronization could potentially extend the benefit of radio-frequency AV nodal ablation followed by standard pacing in AF and thus merits further clinical study *(51)*.

His Bundle Pacing in Atrial Fibrillation

A still-investigational approach for patients with DCM who have chronic AF and normal ventricular activation (QRS ≤ 120 ms) is direct His bundle pacing. Compared to apical pacing, His bundle pacing produces synchronous ventricular depolarization and improved cardiac function. This was illustrated in a series of 18 patients in whom the ventricular rate during AF was controlled pharmacologically or with ablation; chronic His bundle pacing was accomplished using a single-chamber rate-responsive pacemaker and a screw-in lead *(52)*. After a 23-month follow-up, there was a reduction in LV end-diastolic and end-systolic dimensions, an increase in LVEF from 20 to 31%, and a decrease in the cardiothoracic ratio. However, given the high incidence of an IVCD in these patients, this approach may be limited to only a subset of patients with intact intraventricular conduction who are not pacemaker dependent.

RESYNCHRONIZATION THERAPY

Definition

Pacing modalities that utilize BV or LV stimulation to optimize cardiac pump function through synchronization of ventricular contraction are referred to as *resynchronization* or *ventricular resynchronization* therapy *(53)*. Resynchronization therapies can be present in a single device or in a device equipped with bradycardia pacing support or incorporated into an implantable cardioverter defibrillator (ICD).

Rationale

As briefly outlined in the introduction, the rationale for resynchronization therapy is based on several observational studies that showed

that the presence of an IVCD, as manifested by a prolonged QRS, in patients with heart failure caused by systolic dysfunction was associated with a worsening of symptom class status and poorer overall outcome when compared to matched patients with normal intraventricular conduction *(6,9)*. Data from the PATH-CHF trial suggested that a QRS duration of 155 ms had the best positive and negative predictive accuracy for predicting hemodynamic improvement with BV pacing *(54)*. Other studies have shown that the longer the QRS delay at baseline, the greater the response to resynchronization therapy; however, it is unclear if the extent of QRS narrowing because of resynchronization can predict the extent of the response to therapy *(24)*.

Resynchronization therapy is currently approved in Europe for symptomatic heart failure that occurs in the setting of IVCD or BBB. This approval was granted on the basis of several studies of acute resynchronization therapy and data compiled for approx 150 patients receiving BV or LV stimulation for 3 months as part of two nonrandomized studies, InSync and PATH-CHF *(31,32,36)*. Because it is estimated that 20 to 30% of patients with symptomatic heart failure have an IVCD and resultant discordant ventricular contraction, there are many patients who may qualify for resynchronization therapy *(34)*. In fact, it has been estimated that approx 10%% of an unselected group of patients with heart failure would be appropriate candidates for resynchronization therapy *(55)*.

There is also another setting in which resynchronization might be important. It is estimated that approx 8 to 15% of patients with advanced heart failure have pacemakers implanted for symptomatic bradycardia; an additional group of patients with heart failure have an ICD and use the bradycardia feature of the device to pace the right ventricle. Such patients have an increased risk of mortality or urgent transplantation because of progressive pump dysfunction; in one series, the risk at 1 year was 49 vs 15% in patients without a pacemaker *(56)*. This difference may be in part be caused by the dyssynchronous contraction caused by right ventricle-based pacing. Whether such patients would benefit from "upgrading" these devices to resynchronization therapies by the addition of an LV lead is not known.

Results of the DAVID Trial suggested that there may be deleterious effects of chronic right ventricle pacing in patients with impaired LV function *(57)*. The observation that the risk of heart failure hospitalization is higher in patients receiving ventricular pacing challenges us to reconsider whether a more physiological way of pacing can be achieved in bradycardia-indicated patients with depressed LV function. Furthermore, uncontrolled data, reported in patients with AF who were

receiving chronic right ventricle pacing, suggested that improvement in symptoms and a reduction in heart failure hospitalizations can be achieved *(58)*.

Data from animal models of heart failure with and without dyssynchrony indicated that dyssynchrony can result in alterations in myocardial protein expression *(59)*. These are the first data to demonstrate evidence of molecular remodeling associated with chronic dyssynchrony.

Potential Mechanisms

Effect on Contractile Function

Hemodynamic data acquired in patients with heart failure and BBB during acute BV or LV stimulation have consistently shown improvements in measures of contractile response, such as force of contraction, cardiac output, LVEF, and pulmonary artery pressure, when compared to NSR or right ventricle pacing *(21,23–26,60–62)*. Interestingly, in contrast to other therapies that increase myocardial contractility, BV and LV stimulation appear to reduce myocardial energy demands and myocardial oxygen consumption modestly *(28)*.

In one study of 18 patients with DCM and an IVCD, aortic and LV pressures, dp/dt, and pressure–volume measurements were obtained during acute stimulation at single RV endocardial or single LV epicardial sites or during BV pacing *(25)*. The following observations were made:

- There was an improvement in systolic pressures with LV free wall or BV stimulation, primarily because of an improvement in systolic function; there was no benefit on diastolic filling pressure or relaxation.
- RV apical or septal stimulation did not produce any hemodynamic changes.
- Patients who had the greatest hemodynamic improvement had the longest QRS duration (i.e., the greatest IVCD); however, the QRS duration did not consistently shorten with stimulation. In addition, the conduction delay pattern generally predicted the pacing sites of greatest benefit.

Another study evaluated the effects of acute resynchronization therapy on the coordination of global contraction in 13 patients with DCM and an IVCD, using the novel method of phase analysis applied to equilibrium-gated blood pool scintigraphy *(61)*. During sinus rhythm, ventricular contraction was markedly abnormal, and the degree of interventricular dyssynchrony correlated with the LVEF; the more marked the conduction system delay, the more inhomogeneous was the ventricular contraction. Resynchronization therapy using BV

pacing improved measures of ventricular coordination that correlated with acute improvements in LVEF; the degree of interventricular dyssynchrony present in sinus rhythm correlated with the magnitude of improvement in synchrony during BV pacing *(61)*.

Interestingly, although markers of sympathetic activation, such as serum norepinephrine and heart rate variability, often vary directly with the severity of heart failure, these markers have not predictably changed in patients for whom resynchronization therapy appears to improve contractile function *(63–65)*.

Reverse Remodeling

Based on echocardiographic data, preliminary results from the Multicenter InSync Randomized Clinical Investigation (MIRACLE) trial suggested that BV pacing is associated with reverse remodeling in patients with heart failure *(66,67)*. BV pacing produced very significant reduction in mitral regurgitation jet area and a significant reduction in LV mass, both signs of reverse remodeling. Reverse remodeling, particularly by LV dimension measures, was also seen in the CONTAK CD, VIGOR-CHF, and PATH-CHF trials, in which there were significant reductions in both LV end-systolic and end-diastolic dimensions among patients receiving BV pacing *(66–68)*.

Figure 2 demonstrates improvements in LV systolic volume, diastolic volume, and internal dimension indices observed in the VIGOR-CHF trial after 12 weeks of continuous BV pacing in 34 patients. Figure 3 illustrates changes in LV dimension indices observed in more than 400 patients followed for 6 months in the CONTAK CD trial who were randomly assigned to resynchronization therapy or to no resynchronization therapy. Echocardiograms were analyzed at a single core laboratory in both studies and had excellent intra- and interobserver variability *(67,68)*.

Similar improvements in LV size and thickness have been reported from the MIRACLE trial *(69)*.

Surgical Issues Regarding Implantation of Resynchronization Devices

History of Implantation of BV Systems

In the first clinical trials, PATH-CHF and VIGOR-CHF, LV stimulation was achieved using a limited thoracotomy, and an active fixation epicardial lead was placed on the LV. The LV lead body was then tunneled to the pectoral space. The right-sided atrial and ventricular leads were implanted using a transvenous approach. This procedure was associated with additional operative risk because of the underlying

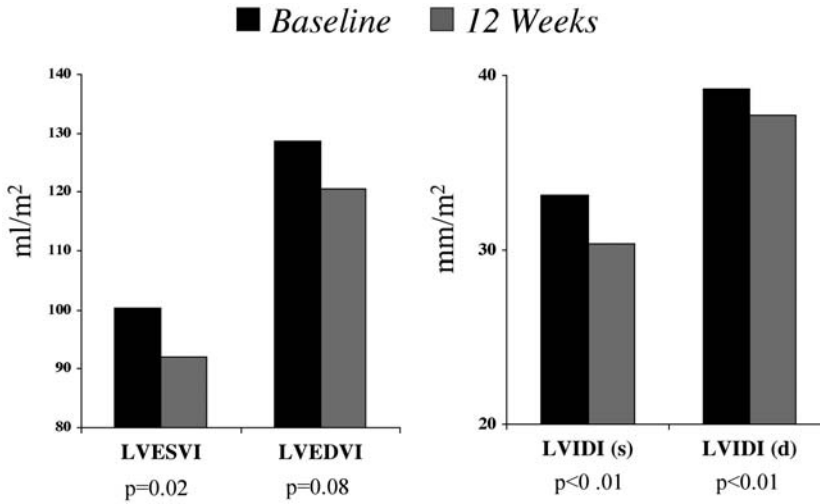


Fig. 2. Improvements in left ventricular systolic and diastolic volume indices and internal dimensions at baseline and after 12 weeks of biventricular (BV) stimulation in the VIGOR-CHF trial. LVESVI, left ventricular end-systolic volume index; LVEDVI, LV end-diastolic volume index; LVIDI, LV internal dimension index during systole (s) or diastole (d).

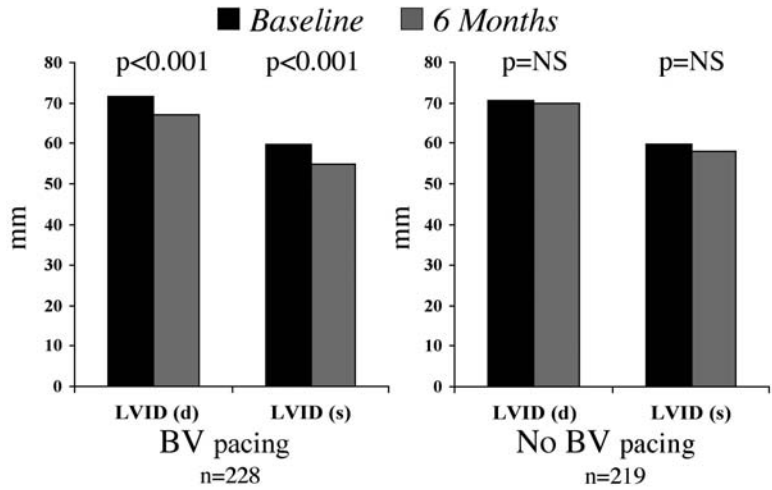


Fig. 3. Changes observed in left ventricular (LV) internal dimension at baseline and after 6 months in the CONTAK CD trial. Improvements in LV internal dimensions were only seen with biventricular (BV) pacing. LVID, LV internal dimension during diastole (d) or systole (s); NS, not significant.

severity of heart failure in the patients undergoing implantation coupled with the need for general anesthesia *(70)*. The expected complications, such as pneumonia and pleural effusions, occurred because of the need for a thoracotomy. In addition, exacerbations of underlying heart failure were observed. The epicardial LV leads were less reliable than endocardial RV or subsequent epicardial coronary sinus leads and had a greater than 10% risk of chronic elevation of capture thresholds *(34–36)*. There were additional concerns about LV epicardial lead placement using a thoracotomy because this approach provides limited epicardial exposure and risks compromise to a bypass conduit in patients with a prior history of coronary artery bypass grafting. Despite these concerns, patients enrolled in these early trials had improvement in the clinical measures of therapy efficacy *(31,36,43,53)*. Yet, the need for a thoracotomy and suboptimal performance of the epicardial lead limited applicability of the therapy to the more advanced heart failure group.

Evolution of Pacing Technology

The coronary sinus provides for the venous drainage from the heart and can be accessed from its os in the inferior septal RA at the tricuspid annulus. The vein then continues as the great cardiac vein along the AV groove, eventually becoming the anterior interventricular vein. There are several other major branch vein tributaries, in some cases extending toward the apex of the LV. These include the posterior, middle cardiac, or lateral veins and the anterior interventricular vein.

Figure 4 demonstrates the normal anatomy of the coronary sinus and branch veins in the right anterior oblique (RAO) and left anterior oblique (LAO) radiographic views, obtained by occlusive venography. There is also marked patient variability in the location of the coronary os, the course of the great cardiac vein, and the extent and course of the major tributaries. This is particularly true in subjects with heart failure with both ischemic and nonischemic etiologies of heart failure. Figure 5A illustrates the coronary sinus anatomy, obtained by occlusive venography, in a patient with ischemic cardiomyopathy. The major branch veins are atretic, tortuous, and narrowed. Figure 5B shows an over-the-wire coronary sinus lead successfully placed in the anterolateral branch of the lateral vein. The types of variabilities seen in these vessels require novel lead designs beyond those used for standard transvenous pacing of the endocardial RA and RV surfaces.

Electrogram recordings from temporary pacing and recording catheters placed in the great cardiac vein, along the AV groove, are frequently used in electrophysiology studies. Recordings of electrical activity along the inferior tricuspid and mitral annulus help target sites

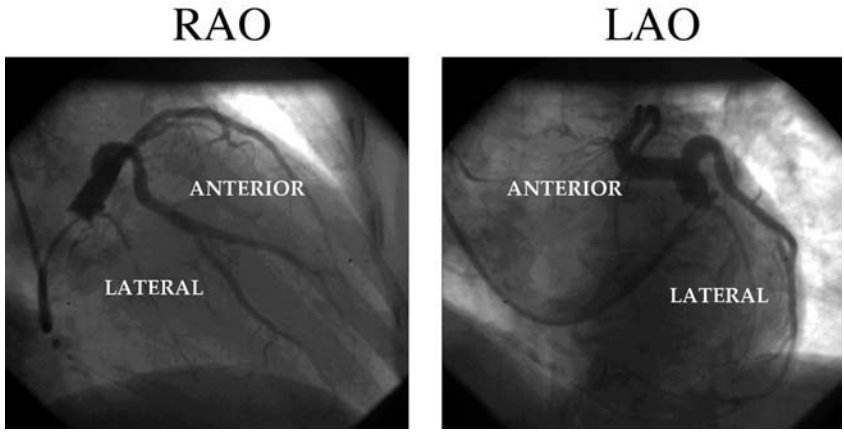


Fig. 4. Fluoroscopic views obtained in the right anterior oblique (RAO) and left anterior oblique (LAO) projections illustrating the coronary sinus branch vein anatomy. In this example, the anterior and lateral cardiac branch veins are seen; the posterior vein is not visualized.

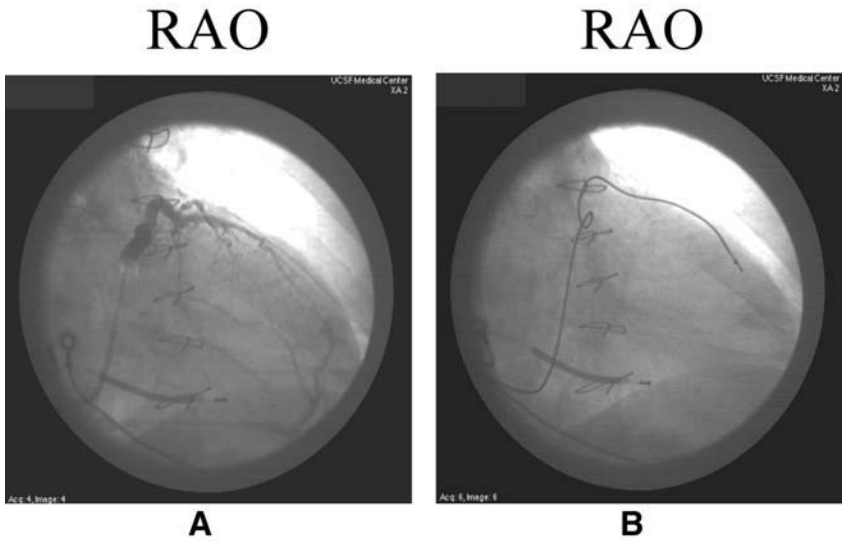


Fig. 5. (A) Fluoroscopic right anterior oblique (RAO) occlusive venogram of the coronary sinus showing atretic coronary sinus branch veins. Note the collateral flow to the posterior vein from the anterior interventricular vein. This patient had a prior left anterior descending artery infarction. **(B)** Successful placement of an over-the-wire chronic left ventricular lead in the mid- to apical portion of the anterolateral vein despite the small caliber of the veins. A defibrillation lead is seen in the right ventricular apex.

for ablation of AV nodal reentrant tachycardia accessory pathways *(71)*. Cannulation of one of the branch vein tributaries allows for pacing and recording of the LV. Historically, chronic pacing leads placed in the great cardiac vein or a branch vein have been used to achieve left atrial (LA) pacing in patients with congenital heart disease or other anatomic limitations to placement of RA leads. The coronary sinus leads were more difficult to place and subject to dislodgment *(72)*. Chronic leads placed in the great cardiac vein were also used in the early transvenous defibrillators as a component of the shocking lead defibrillation circuit *(72)*.

In 1997 and 1998, chronic transvenous coronary sinus pacing leads were incorporated into clinical trials for pacing the LV to achieve LV stimulation for use in BV or LV resynchronization devices. The earliest transvenous lead, employed in the initial phases of the European InSync trial, was designed and approved for atrial pacing from the coronary sinus (Medtronic Inc., Attain™ model 2188). This lead was placed in a coronary sinus tributary to achieve LV pacing, mostly at the base of the heart. The lead is a traditional pacing lead maneuvered using shaped stylets placed through the lumen of the lead. LV pacing could be achieved in more than 70% of patients using this lead *(31,32)*. Subsequent modifications to this stylet-driven coronary sinus lead (Attain™ model 2187) have improved the ability to place leads in several venous tributaries and to advance the lead further toward the apex of the LV. This has improved lead placement success rates to 90% as well as resulting in excellent long-term patient thresholds *(66,73)*.

A major breakthrough in lead technology was the development of an over-the-wire lead designed specifically for coronary sinus branch vein LV pacing (Guidant Corp., EASYTRAK™), which was incorporated into clinical trials in 1998. This lead, unlike stylet-driven leads, has an open lumen that permits atraumatic steerability. The lead is tracked over a standard 0.014 guide wire to allow access to multiple sites within the branch veins. In addition, it is small caliber (4 French size), allowing it to be placed in a more tapered, distal vein location. The distal section of the lead is flexible with an atraumatic silicone rubber tip. Unlike the newer stylet-driven leads, this lead has a tined tip, which allows for passive fixation, stabilizing the lead in a terminal vein *(39)*. Acute and chronic pacing thresholds are excellent, and the implant success rates exceed 95% in centers with implant experience *(73)*. Figure 6 shows RAO and LAO radiographic images of an over-the-wire lead placed in a basal LV location in a patient with ischemic cardiomyopathy; Figure 7 shows an over-the-wire lead in an apical-lateral LV location in a patient with nonischemic cardiomyopathy.

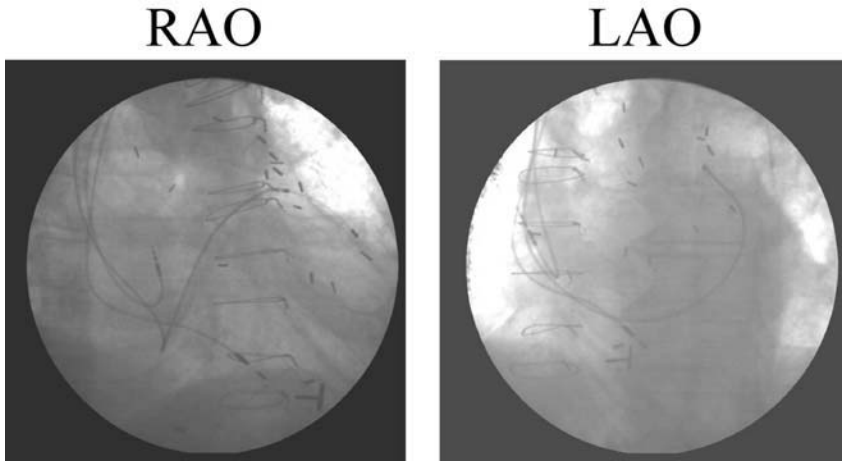


Fig. 6. Fluoroscopic right anterior oblique (RAO) and left anterior oblique (LAO) views of a coronary sinus lead placed in the anterolateral vein of the coronary sinus in a patient with ischemic cardiomyopathy. Despite the fact that the lead could only be advanced to the midbasal left ventricle because of prior bypass surgery, excellent left ventricular sensing and capture thresholds were obtained, and the patient symptomatically improved.

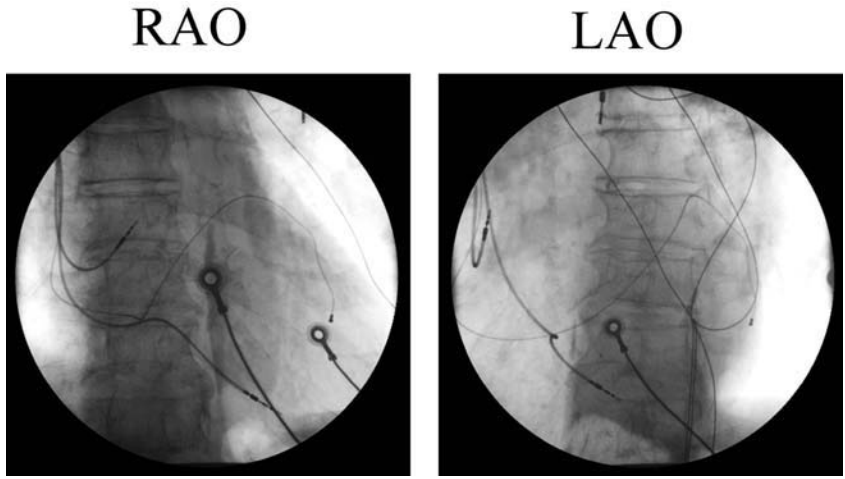


Fig. 7. Fluoroscopic right anterior oblique (RAO) and left anterior oblique (LAO) views of a coronary sinus lead placed in an apical-lateral left ventricular location in a patient with nonischemic cardiomyopathy. The large branch vein caliber allowed advancement of the lead deep into the branch vein. Endocardial right atrial appendage and right ventricular apical leads are also seen.

Implantation of the Coronary Sinus Branch Vein LV Lead

Significant care and thoughtful planning need to be taken to implant resynchronization devices successfully with minimal operative morbidity and mortality. The patient population with advanced systolic dysfunction and left BBB are particularly vulnerable to operative complications resulting from excessive procedure times. General anesthesia with endotracheal intubation, excessive contrast use, and fluid administration are all poorly tolerated (investigating officers of COMPANION Steering Committee Implant Guidelines, personal communication, March 12, 2001).

There are several important considerations in the successful placement of a coronary sinus LV lead that extend beyond the need to obtain a stable branch vein lead position with an acceptable pacing threshold. A delivery system must also be used to access the coronary sinus os and provide stability and support in the RA and in the great cardiac vein to permit lead placement in a branch vein. In addition, the coronary sinus branch vein anatomy needs to be at least partially visualized.

After cannulation of a right- or left-sided subclavian or cephalic vein (the left-sided approach is favored in the United States; the right-sided approach is favored in Europe), a flexible guide catheter is placed over an electrophysiology electrode catheter or guide wire into the great cardiac vein. The electrophysiology electrode catheter is advantageous because it allows for both anatomical and electrical documentation of the guide catheter in its proper location in the great cardiac vein. Preformed tip shapes are currently available to accommodate anatomic variations. These guiding sheaths have flexible tips to minimize the risk of vascular trauma and should not be placed without a guiding wire or catheter.

Coronary sinus venography can then be performed with a gentle injection of contrast, either directly through the end of the guiding catheter or with the addition of an occluding balloon to visualize the branch veins and provide a "road map" to facilitate lead placement. Because of retrograde flow from the coronary sinus, a balloon inflation during injection of contrast usually allows more complete visualization of the branch veins, but may be associated with a higher incidence of coronary sinus trauma *(39)*. It is imperative to have a fluoroscopy system capable of both RAO and LAO projections to identify lead position correctly. The lead is then deployed to the branch vein through the guide and placed in a stable position.

Of note, the majority of coronary sinus leads have been placed in the midportion of the ventricle midway between the apex and base, most

often in a lateral or anterior-lateral branch vein. It is critically important not only to document acceptable LV lead pacing and sensing thresholds, but also to test for phrenic nerve stimulation, which can occur when pacing from an epicardial LV site. If phrenic nerve stimulation is present, the lead must be maneuvered to an alternative location.

Once an acceptable lead position within a branch vein is achieved, the guide catheter must be removed without dislodgment of the lead. This procedure must be performed under continuous fluoroscopic guidance and with care. A stylet or other stiff wire can be placed partially through the lead to aid in lead stability during guide catheter removal, or the lumenal wire can be left in place. The guide is removed primarily or may be cut and peeled away, depending on guide design. After lead removal, the lead is fixed at the venotomy site and to the fascia using standard practices incorporating lead sleeves.

Most physicians who are experienced in LV lead implants prefer to implant the RA and RV pacing leads prior to coronary sinus lead placement. The rationale for this practice is that it helps to identify the right-sided anatomy as well as provides the capability of RV pacing support in the event that transient heart block is observed during LV lead placement.

The technical difficulties encountered during implants are most commonly related to two issues: (1) difficulty in engaging the coronary sinus os and branch vein to permit advancement of a guiding sheath and (2) difficulty in obtaining a stable branch vein position to allow for acceptable sensing and pacing thresholds without phrenic nerve stimulation (investigating officers of COMPANION Steering Committee Implant Guidelines, personal communication, March 12, 2001). In addition, the variations in coronary sinus anatomy may render identification and cannulation of the os and great cardiac vein difficult. The presence of semilunar valves at the os and in the course of the great cardiac vein may further impede lead placement *(74)*.

The incidence of trauma to the coronary sinus is 2–5%, occurring during some part of the LV lead delivery procedure (investigating officers of COMPANION Steering Committee Implant Guidelines, personal communication, March 12, 2001). The majority of these events involve staining of the coronary sinus intima and do not result in clinical sequelae such as cardiac tamponade. The incidence of coronary sinus perforation resulting in tamponade is less than 1% *(66)*.

Long-Term Issues

Technology continues to evolve, and improvements in both the LV leads and the delivery tools occur constantly. Thus far, 1-year follow-up data in more than 3000 patients enrolled in US clinical trials indicated

•Symptomatic heart failure on stable medical therapy (90% ACE inhibitors, 30-60% beta-blockers, 90% diuretics, 25-30% amiodarone)	•LVEF < 0.3-.35 •QRS duration > 120 msec •No indications for bradycardia pacing •In some trials, indications for ICD
•NYHA Class II-IV	

Fig. 8. Usual inclusion criteria for enrollment in current trials of resynchronization therapy. The percentages given for the various medications represent the percentage of patients enrolled in resynchronization trials who were on these medications.

that the LV leads and resynchronization devices have an excellent track record in terms of system safety and chronic thresholds *(66,73)*.

The issues of the ease and risk of lead extraction have not yet become significant. Leads that acutely dislodge can be replaced successfully, and infected leads generally are removed without difficulty *(66,73)*. There have not yet been a significant number of events to consider this a real, as opposed to theoretical, hazard.

Clinical Trials

General Overview

There are a number of trials evaluating the role of resynchronization therapy in patients with heart failure caused by systolic dysfunction. As demonstrated in Fig. 8, the usual inclusion criteria include symptomatic heart failure that is stable on medical therapy, NYHA class II to IV, LVEF below 35%, QRS duration longer than 120 to 140 ms, and in some trials, an indication for an ICD. Most exclude patients with AF and patients with standard indications for bradycardia rate support. Thus far, the majority of patients enrolled in clinical trials of resynchronization therapies have been on optimal medical therapies for heart failure *(67,73,75)*. The treated patients usually receive LV or BV stimulation in the VDD mode. Figure 9 illustrates the chronological progression of clinical trials of resynchronization therapy using LV or simultaneous BV stimulation.

The identification of appropriate end points for cardiac resynchronization therapy devices and the duration of follow-up required to detect an improvement in heart failure status have been difficult to

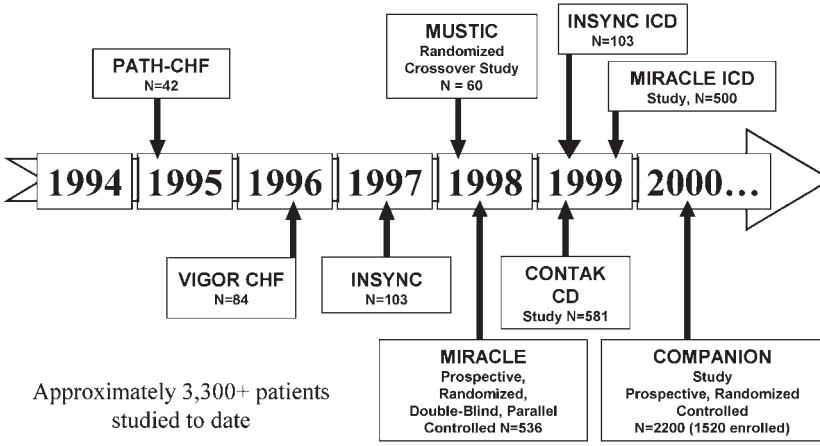


Fig. 9. Chronological progression of clinical trails of resynchronization therapy. See text for the details of specific trails.

determine. The Food and Drug Administration (FDA) initially approved studies having a duration of therapy of 12 weeks to assess the efficacy and safety of cardiac resynchronization therapy. However, as the trials progressed, the FDA considered 6 months a more appropriate duration of therapy and determined that the most appropriate end points should be total mortality and hospitalization. Figure 10 lists the end points of the US trials of chronic resynchronization therapy.

The initial clinical trials of resynchronization therapy utilized an epicardial lead for LV pacing or a transvenous lead that was not specifically designed and tested for long-term LV pacing *(31,34)*. As described in the discussion of pacing technology, the development of a completely transvenous coronary sinus lead designed for long-term LV pacing has simplified the implant procedure and markedly reduced operative risk; it is now used in clinical trials.

Some initial trials have reported results, and many trials are still ongoing. Preliminary data suggested that the improvement in LV function and hemodynamics results in an improvement in functional status in many patients.

Current Trials With Released Data

VIGOR-CHF. VIGOR-CHF, a trial now closed to enrollment, included patients with heart failure primarily caused by nonischemic cardiomyopathy and with a left BBB but no indication for conventional

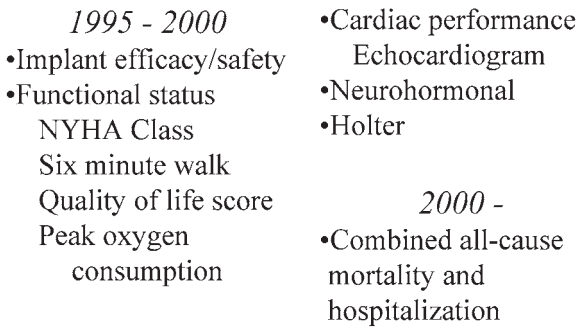


Fig. 10. Clinical end points for US trials of chronic resynchronization therapy.

bradycardia pacemaker therapy *(34)*. The patients were randomly assigned to receive either BV pacing or no pacing for 6x weeks, after which both groups received BV pacing therapy. This was the first US trial of resynchronization therapy, initiated in 1995 when transvenous leads were not yet available. After the introduction of the transvenous lead, this trial failed to complete enrollment and was closed after enrolling only 58 patients. However, all patients had serial echocardiograms at all study points, performed at a single core laboratory. As mentioned in the section on reverse remodeling, there was evidence of reverse remodeling, as shown by significant decreases in LV systolic and diastolic parameters (Fig. 2) *(34)*.

MUSTIC Study. The Multisite Stimulation in Cardiomyopathies (MUSTIC) study is a single-blind, randomized, controlled crossover study involving 131 patients, who were divided into two groups based on their underlying rhythm *(76)*.

Group 1 included 67 patients with NYHA class III heart failure, a QRS duration longer than 150 ms, stable sinus rhythm, and no conventional indications for pacemaker therapy; they were randomly assigned to BV pacing or no BV pacing for 3 months, after which the pacing modes were switched. Forty-eight patients completed both phases of the study. Exercise tolerance, as measured by the 6-minute walk distance, increased by 23% after BV pacing (399 vs 326 m, $p < 0.001$). Other significant improvements included a 32% increase in QoL score, an 8% increase in peak oxygen consumption, and a 66% reduction in hospitalizations. Furthermore, active BV pacing was preferred by 85% of patients.

Group 2 included 64 patients with chronic AF who required a permanent pacemaker because of a slow ventricular rate; the patients were

randomly assigned to either single-site RV pacing or BV pacing in the same fashion as in group 1 *(77)*. BV pacing was associated with improvements in exercise tolerance and peak oxygen consumption, but the changes were not as marked as those seen in patients with NSR; there also were no improvements in QoL scores or hospitalization rates. Not all patients were completely pacemaker dependent, however, and thus may not have had the benefit of continuous BV pacing.

MIRACLE Trial. The MIRACLE trial randomly assigned 510 patients with heart failure to BV or no pacing for 6 months *(66,67)*. Data presented on the first 266 patients showed a significantly greater proportion of patients undergoing BV pacing had an improvement in NYHA functional status by at least one class (69 vs 34% for no pacing, $p < 0.001$) and an increase in 6-minute walk distance by 50 meters or more (50 vs 30%).

InSync Trial. The InSync trial was a nonrandomized study that evaluated atrial-synchronous BV pacing in 103 patients with DCM who met the entry criteria for BV pacing *(31,32)*. After a 1-month follow-up, 70% of patients responded with an improvement in NYHA class (≥1), an improvement in QoL score, and an increase in 6-minute walk distance (≥100 meters); there was further improvement in these parameters at 1 year. Responders to resynchronization had a consistent shortening of QRS duration, an increase in LVEF, and a reduction in LV end-diastolic diameter.

VENTAK CHF/CONTAK CD. VENTAK CHF/CONTAK CD included patients with heart failure who also had an indication for an ICD; it utilized an ICD system designed to provide BV pacing *(34)*. In contrast to VIGOR-CHF, most patients primarily had ischemic cardiomyopathy, reflecting the large percentage of postinfarction ventricular tachycardia (VT) observed in ICD recipients *(78,79)*. Of the more than 500 patients followed, the majority were male, had NYHA class II–IV heart failure, a QRS duration longer than 120 ms, and an indication for an ICD. The patients all had an ICD and were programmed to receive BV pacing or no pacing for 6 months.

Preliminary results from this trial showed that 25% of patients had at least one episode of a life-threatening arrhythmia requiring device discharge. At 1 year, the composite end point (death, heart failure hospitalizations, worsening heart failure requiring other interventions, and VT or ventricular fibrillation [VF] events) was reduced by 21% with BV pacing; the incidence of death was reduced by 23%, worsening heart failure requiring other interventions by 26%, heart failure hospitalizations by 13%, and VT/VF events by 9% *(73)*. BV pacing also improved 6-minute

walk distance by an average of 35 meters, peak oxygen consumption by 0.9 mL/kg per minute, and QoL score by 16% compared to baseline. For all three of these measures, patients with the most advanced heart failure showed the most improvement. As mentioned in the section on remodeling, favorable effects on remodeling were observed at 6 months *(66)*.

Figure 11A–D summarizes the results of the major studies of chronic resynchronization therapy, demonstrating the improvements in the clinical end points of QoL score, NYHA functional class, 6-minute walk distance, and peak oxygen consumption *(36,53,67,73,76)*.

COMPANION. The Comparison of Medical Therapy, Pacing, and Defibrillation in Chronic Heart Failure (COMPANION) trial is a recently completed, open-label prospective, multicenter, randomized study that evaluated cardiac resynchronization therapy with and without an ICD compared to standard drug therapies for heart failure *(75)*. The COMPANION trial results were presented at the American College of Cardiology Annual Scientific Sessions in March 2003. The goal of the study was to determine whether optimal drug therapy combined with ventricular resynchronization alone or with an ICD would decrease a combined end point of mortality and all-cause hospitalization when compared to optimal drug therapy alone.

After optimal heart failure therapy was initiated, patients were randomly assigned in a 1:2:2 scheme to drug therapy (control arm) vs drug therapy and cardiac resynchronization therapy vs drug therapy plus cardiac resynchronization therapy coupled with an ICD (Fig. 12). COMPANION was the first study to evaluate cardiac resynchronization therapy with and without an ICD in patients with no history of a significant ventricular arrhythmia. It was also the first completed trial using the heart end points of all-cause hospitalization and mortality as primary end points.

COMPANION enrolled 1520 patients and was halted November 20, 2003, when the prespecified boundaries had been crossed for efficacy. A 19% reduction in time to death or any hospitalization was achieved with resynchronization therapy compared to medical therapy. In addition, more than a 35% reduction was observed in the incidence of heart failure hospitalization. The secondary end point of mortality alone was reduced only in the group receiving a resynchronization defibrillator. As prespecified, the use of heart failure medications was excellent in the COMPANION trial. In addition to ACE inhibitor therapy, more than 65% of COMPANION patients were receiving β-receptor blocker therapy, and more than 50% were taking spironolactone.

The results of COMPANION suggested that the majority of patients eligible for resynchronization therapy should be considered for a resyn-

chronization ICD. It also needs to be emphasized that COMPANION patients were required to have a hospitalization for heart failure worsening in the year prior to enrollment. Patients enrolled in COMPANION therefore had severe symptom class heart failure, and the results of this trial should not be extrapolated to a less-symptomatic group of patients.

Ongoing Trials

A number of ongoing trials should provide additional information about the efficacy of resynchronization therapy. The following is a summary of the basic designs of some of these trials.

CARE-HF. The Cardiac Resynchronization for Heart Failure (CARE-HF) trial is a double-blind, controlled study of 800 patients comparing medical therapy to BV pacing (Medtronics Inc., 2003). The end points to be considered include total mortality, peak oxygen consumption, and 6-minute walk distance. The results of CARE-HF will be of great interest when compared to the COMPANION trial results. This will be especially important in assessing the relative risk–cost–benefit analysis of the resynchronization device alone compared to inclusion of ICD capability.

RE-LE-VENT. The Remodeling of Cardiac Cavities by Long-Term Left Ventricular-Based Pacing in Patients With Severe Heart Failure (RE-LE-VeNT) trial will randomly assign 240 patients to medical therapy, LV pacing alone, or BV pacing (St. Jude Medical, 2003). The end points of the RE-LE-VeNT trial are total mortality, quality of life, and various echocardiographic indices.

PACMAN. The Pacing for Cardiomyopathies, a European Study (PACMAN) is a European trial that will compare resynchronization delivered with BV or LV stimulation and outcomes when resynchronization is coupled to an ICD.

Efficacy in AF

The effects of resynchronization therapy may be more apparent in patients with heart failure who have established AF. This was illustrated in a report of 37 patients with DCM; the improvements in exercise capacity and LVEF with BV pacing were greater in patients with AF compared to those in sinus rhythm *(51)*. This may have resulted from the combined effects of resynchronization and better heart rate control because of AV nodal ablation.

The Effects of Ventricular Pacing Site Variation on Cardiac Function and Chronic Status in Patients With Chronic Atrial Fibrillation and Ventricular-Based Pacing (PAVE) trial is the first controlled study in

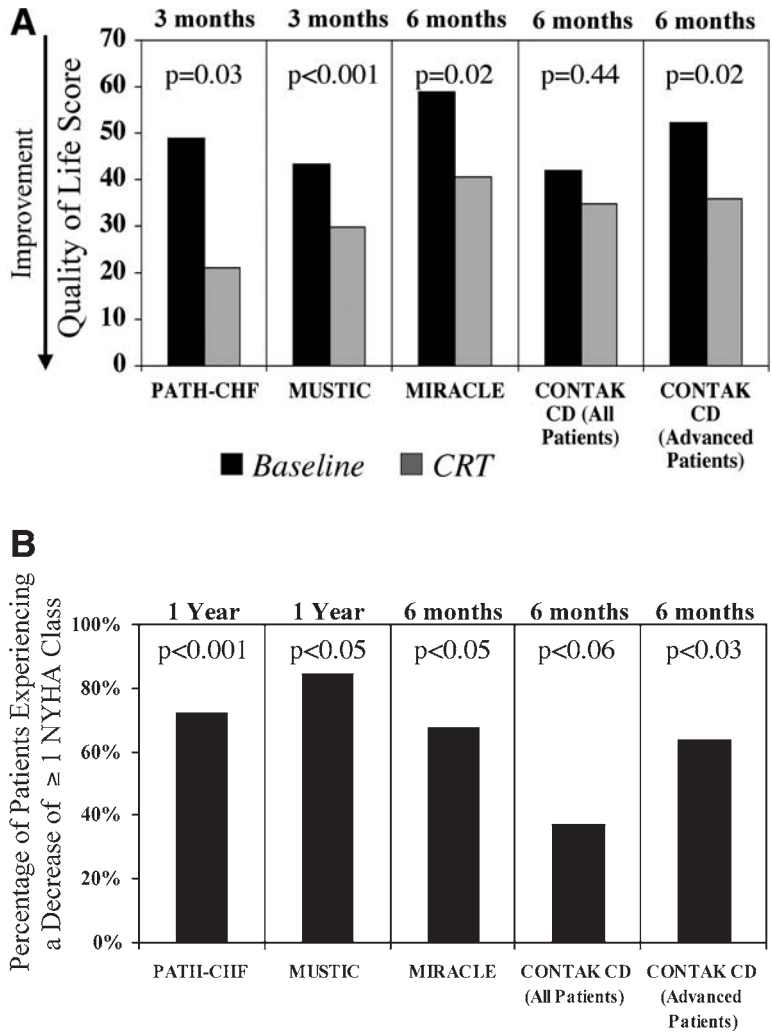


Fig. 11. (A) Improvement in the average quality-of-life score seen in different trials of chronic resynchronization therapy (CRT). Quality-of-life scores were determined using the Minnesota Living With Heart Failure Questionnaire. The advanced patients in the CONTAK CD trial were classified as having NYHA class III heart failure at baseline. **(B)** Improvements in NYHA class seen in different trials of CRT. The advanced patients in the CONTAK CD trial were classified as having NYHA class III heart failure at baseline.

the United States that will evaluate the role of resynchronization therapy in patients with heart failure who have established AF (St. Jude Medical, 2003). The objective is to evaluate exercise capacity and

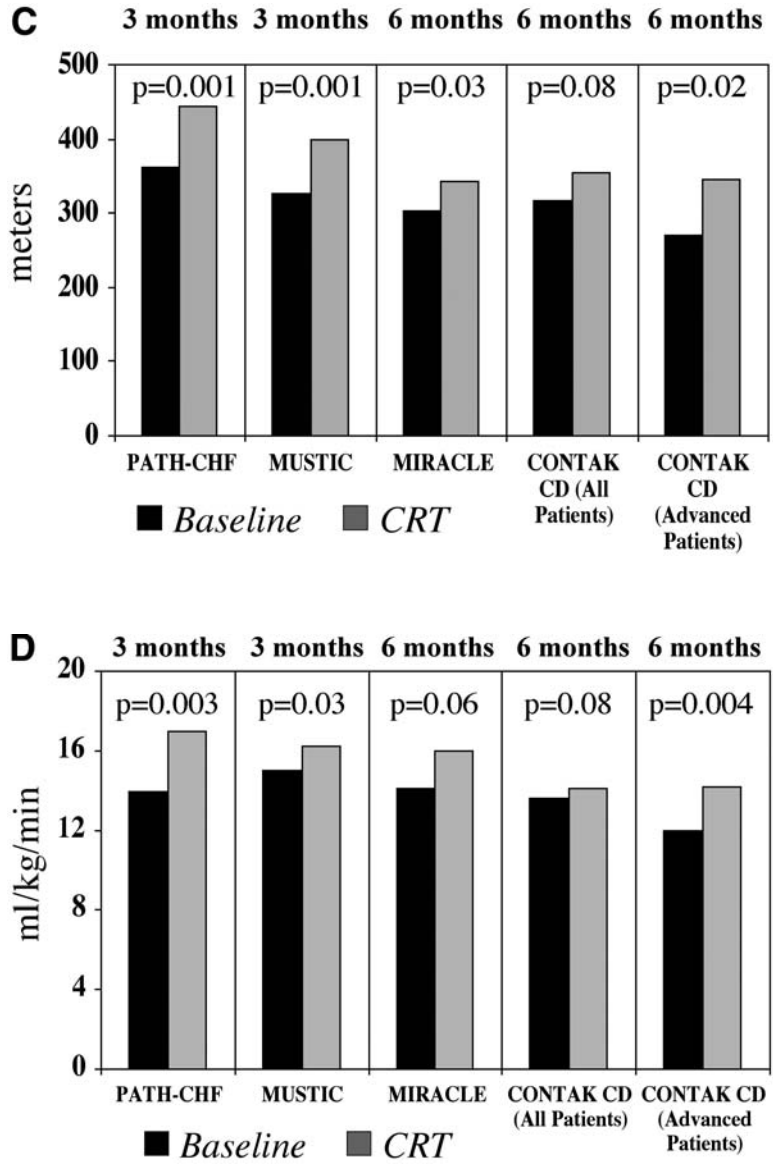


Fig. 11. *(continued)* **(C)** Improvements in the average 6-minute walk distance seen in different trials of CRT. The advanced patients in the CONTAK CD trial were classified as having NYHA class III heart failure at baseline. **(D)** Improvements in the average peak oxygen consumption seen in different trials of CRT. The advanced patients in the CONTAK CD trial were classified as having NYHA class III heart failure at baseline.

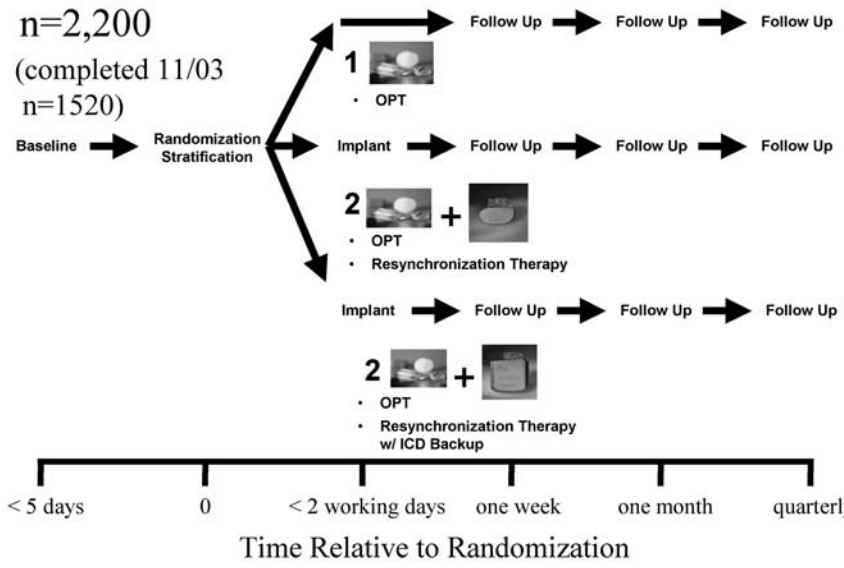


Fig. 12. Overview of the study design, enrollment parameters, and randomization scheme for the COMPANION trial. OPT, optimal medical therapy.

global cardiac performance associated with RV vs LV vs BV pacing sites. The trial was closed in October 2003 after enrolling 361 patients and is currently in the follow-up phase. A premarket approval has been submitted to the FDA.

Left Ventricular Pacing

Although BV pacing is extensively studied, there has also been interest in trying to achieve the same benefit using only LV stimulation. Numerous uncontrolled studies demonstrated a benefit equivalent to BV pacing when acute hemodynamic parameters were considered *(23,25,26,28)*. Based on these preliminary data, to assess the clinical follow-up of LV pacing, a prospective observational study was undertaken in which 33 patients with NYHA class III or IV and a left BBB were assigned to LV or BV pacing for 6 months in a nonrandomized way *(80)*. There was no difference between the two groups in numerous parameters, including improvement in NYHA functional class. However, LV end-diastolic dimension was more significantly decreased in the BV group. Of note, other trials mentioned here, including the RE-LE-VeNT, PACMAN, and PAVE trials, have LV pacing as independent arms in their study designs (St. Jude Medical and Guidant Corp., 2003).

Although LV pacing alone appears to result in similar acute hemodynamic benefit to BV stimulation, a study showed that electrical dispersion is increased with LV pacing alone *(81)*. These data point out that achieving mechanical resynchronization can actually worsen electrical synchrony.

SUMMARY AND FUTURE INDICATIONS

BV pacing to achieve cardiac resynchronization is a promising approach to the therapy of patients with heart failure and an IVCD. Studies completed to date demonstrated that BV stimulation can improve exercise tolerance and NYHA functional class and, most important, the combined end point of time to hospitalization and mortality. Given the very debilitating symptoms that patients with heart failure experience, often despite maximal medical therapy, and the cost of repeat hospitalizations for treatment of exacerbations, the need for an adjunctive therapy such as resynchronization therapy is clear *(82)*. The COMPANION data suggested additional mortality benefit can be obtained with the inclusion of an ICD.

One of the more important and overlooked aspects of resynchronization therapy is its potential to allow maximal optimization of the pharmacological treatment of heart failure. This can be achieved by the ability of the resynchronization device to help support blood pressure and heart rate while also treating arrhythmias. However, the use of resynchronization devices, at present, is limited by the technical skill required to implant resynchronization devices and the need for longer term follow-up. Based on the early data presented and the rapid pace of innovation and development in this field, these limitations are sure to be overcome in the next few years.

REFERENCES

1. American Heart Association. 1999 Heart and Stroke Statistical Update. American Heart Association, Dallas, TX: 1998.
2. Ho KK, Pinsky JL, Kannel WB, Levy D. The epidemiology of heart failure: the Framingham Heart Study. J Am Coll Cardiol 1993;22(4 suppl A):6A–13A.
3. O'Connell JB, Bristow MR. Economic impact of heart failure in the United States: time for a different approach. J Heart Lung Transplant 1994;13:S107–S112.
4. Heart Failure Society of America (HFSA) practice guidelines: HFSA guidelines for management of patients with heart failure caused by left ventricular systolic dysfunction—pharmacological approaches. J Card Fail 1999;5(4):357–382.
5. Aaronson KD, Schwartz JS, Chen TM, et al. Development and prospective validation of a clinical index to predict survival in ambulatory patients referred for cardiac transplant evaluation. Circulation 1997;95:2660–2667.

6. Grines CL, Bashore TM, Boudoulas H, et al. Functional abnormalities in isolated left bundle branch block. The effect of interventricular asynchrony. Circulation 1989;79:845–853.
7. Xiao HB, Lee CH, Gibson DG. Effect of left bundle branch block on diastolic function in dilated cardiomyopathy. Br Heart J 1991;66:443–447.
8. Xiao HB, Brecker SJ, Gibson DG. Effects of abnormal activation on the time course of the left ventricular pressure pulse in dilated cardiomyopathy. Br Heart J 1992;68:403–407.
9. Shamim W, Francis DP, Yousufuddin M, et al. Intraventricular conduction delay: a prognostic marker in chronic heart failure. Int J Cardiol 1999;70:171–178.
10. Xiao HB, Roy C, Fujimoto S, Gibson DG. Natural history of abnormal conduction and its relation to prognosis in patients with dilated cardiomyopathy. Int J Cardiol 1996;53:163–170.
11. Schoeller R, Andresen D, Buttner P, et al. First- or second-degree atrioventricular block as a risk factor in idiopathic dilated cardiomyopathy. Am J Cardiol 1993; 71:720–726.
12. Wilensky RL, Yudelman P, Cohen AI, et al. Serial electrocardiographic changes in idiopathic dilated cardiomyopathy confirmed at necropsy. Am J Cardiol 1988; 62:276–283.
13. Nishimura RA, Hayes DL, Holmes DR Jr, Tajik AJ. Mechanism of hemodynamic improvement by dual-chamber pacing for severe left ventricular dysfunction: an acute Doppler and catheterization hemodynamic study. J Am Coll Cardiol 1995; 25:281–288.
14. Shinbane JS, Chu E, DeMarco T, Sobol Y, et al. Evaluation of acute dual-chamber pacing with a wide range of atrioventricular delays on cardiac performance in refractory heart failure. J Am Coll Cardiol 1997;30:1295–1300.
15. Hochleitner M, Hortnagl H, Ng CK, et al. Usefulness of physiologic dual-chamber pacing in drug-resistant idiopathic dilated cardiomyopathy. Am J Cardiol 1990;66: 198–202.
16. Hochleitner M, Hortnagl H, Hortnagl H, et al. Long-term efficacy of physiologic dual-chamber pacing in the treatment of end-stage idiopathic dilated cardiomyopathy. Am J Cardiol 1992;70:1320–1325.
17. Gold MR, Feliciano Z, Gottlieb SS, Fisher ML. Dual-chamber pacing with a short atrioventricular delay in congestive heart failure: a randomized study. J Am Coll Cardiol 1995;26:967–973.
18. Rosenqvist M, Isaaz K, Botvinick EH, et al. Relative importance of activation sequence compared to atrioventricular synchrony in left ventricular function. Am J Cardiol 1991;67:148–156.
19. Betocchi S, Piscione F, Villari B, et al. Effects of induced asynchrony on left ventricular diastolic function in patients with coronary artery disease. J Am Coll Cardiol 1993;21:1124–1131.
20. Leclercq C, Gras D, Le Helloco A, et al. Hemodynamic importance of preserving the normal sequence of ventricular activation in permanent cardiac pacing. Am Heart J 1995;129:1133–1141.
21. Cazeau S, Ritter P, Bakdach S, et al. Four chamber pacing in dilated cardiomyopathy. Pacing Clin Electrophysiol 1994;17(11 part 2):1974–1979.
22. Foster AH, Gold MR, McLaughlin JS. Acute hemodynamic effects of atriobiventricular pacing in humans. Ann Thorac Surg 1995;59:294–300.
23. Blanc JJ, Etienne Y, Gilard M, et al. Evaluation of different ventricular pacing sites in patients with severe heart failure: results of an acute hemodynamic study. Circulation 1997;96:3273–3277.

24. Saxon LA, Kerwin WF, Cahalan MK, et al. Acute effects of intraoperative multisite ventricular pacing on left ventricular function and activation/contraction sequence in patients with depressed ventricular function. J Cardiovasc Electrophysiol 1998;9:13–21.
25. Kass DA, Chen CH, Curry C, et al. Improved left ventricular mechanics from acute VDD pacing in patients with dilated cardiomyopathy and ventricular conduction delay. Circulation 1999;99:1567–1573.
26. Auricchio A, Stellbrink C, Block M, et al. Effect of pacing chamber and atrioventricular delay on acute systolic function of paced patients with congestive heart failure. The Pacing Therapies for Congestive Heart Failure Study Group. The Guidant Congestive Heart Failure Research Group. Circulation 1999;99: 2993–3001.
27. Touissaint JF, Ritter P, Lavergne T, et al. Biventricular resynchronization in end-stage heart failure: an eight-month follow-up by phase map radionuclide angiography. Pacing Clin Electrophysiol 1999;22(4 part 2):840.
28. Nelson GS, Berger RD, Fetics BJ, et al. Left ventricular pre-excitation improves mechanoenergetics of patients with dilated cardiomyopathy and ventricular conduction delay. J Am Coll Cardiol 2000;35(2 suppl A):230A.
29. Breithardt O, Stelbrink C, Diem B, et al. Effect of chronic multisite pacing on left ventricular volumes in patients with congestive heart failure. Pacing Clin Electrophysiol 1999;22(4 part 2):732.
30. Stellbrink C, Breithardt OA, Diem B, et al. Acute effects of multisite pacing with different AV delays on diastolic and systolic function in congestive heart failure. Pacing Clin Electrophysiol 1999;22(4 part 2):829.
31. Gras D, Mabo P, Tang T, et al. Multisite pacing as a supplemental treatment of congestive heart failure: preliminary results of the Medtronic Inc. InSync study. Pacing Clin Electrophysiol 1998;21(4 part 2):2249.
32. Gras D, Mabo P, Bucknall C, et al. Responders and nonresponders to cardiac resynchronization therapy: results from the InSync trial. J Am Coll Cardiol 2000;35(2 suppl A):230A.
33. Krahnfeld O, Vogt J, Tenderich G, et al. Changes in QRS-duration in patients with biventricular pacing system for congestive heart failure treatment and clinical outcome. Pacing Clin Electrophysiol 1999;22(4 part 2):733.
34. Saxon LA, Boehmer JP, Hummel J, et al. Biventricular pacing in patients with congestive heart failure: two prospective randomized trials. The VIGOR CHF and VENTAK CHF Investigators. Am J Cardiol 1999;83(5B):120D–130D.
35. Stellbrink C, Auricchio A, Diem B, et al. Potential benefit of biventricular pacing in patients with congestive heart failure and ventricular tachyarrhythmia. Am J Cardiol 1999;83(5B):143D–150D.
36. Auricchio A, Stellbrink C, Sack S, et al. Chronic benefit as a result of pacing in congestive heart failure: results of the PATH-CHF trial. J Card Fail 1999; 5(3 suppl 1):78.
37. Bristow MR, Saxon LA, Boehmer J, et al. for the COMPANION Investigators. Cardiac resynchronization therapy (CRT) reduces hospitalizations, and CRT plus an implantable defibrillator (CRT-D) reduces mortality in chronic heart failure: results of the COMPANION trial. N Engl J Med 2004;350;2140–2150.
38. Auricchio A, Sack S, Stellbrink C, et al. Transvenous left ventricular pacing using a new over the wire coronary venous lead. Pacing Clin Electrophysiol 1999;22(4 part 2):717.
39. Auricchio A, Klein H, Tockman B, et al. Transvenous biventricular pacing for heart failure: can the obstacles be overcome? Am J Cardiol 1999;83(5B):136D–142D.

40. Auricchio A, Salo RW. Acute hemodynamic improvement by pacing in patients with severe congestive heart failure. Pacing Clin Electrophysiol 1997;20 (2 part 1):313–324.
41. Walker S, Levy TM, Coats AJ, et al. Bi-ventricular pacing in congestive cardiac failure. Current experience and future directions. The Imperial College Cardiac Electrophysiology Group. Eur Heart J 2000;21:884–889.
42. Saxon LA. Atrial fibrillation and dilated cardiomyopathy: therapeutic strategies when sinus rhythm cannot be maintained. Pacing Clin Electrophysiol 1997;20 (3 part 1):720–725.
43. Wood MA, Brown-Mahoney C, Kay GN, Ellenbogen KA. Clinical outcomes after ablation and pacing therapy for atrial fibrillation: a meta-analysis. Circulation 2000;101:1138–1144.
44. Roy D, Talajic M, Dorian P, et al. Amiodarone to prevent recurrence of atrial fibrillation. Canadian Trial of Atrial Fibrillation Investigators. N Engl J Med 2000; 342:913–920.
45. Shinbane JS, Wood MA, Jensen DN, et al. Tachycardia-induced cardiomyopathy: a review of animal models and clinical studies. J Am Coll Cardiol 1997;29: 709–715.
46. Daoud EG, Weiss R, Bahu M, et al. Effect of an irregular rhythm on cardiac output. Am J Cardiol 1996;78:1433–1436.
47. Natale A, Zimerman L, Tomassoni G, et al. Impact on ventricular function and quality of life of transcatheter ablation of the atrioventricular junction in chronic atrial fibrillation with a normal ventricular response. Am J Cardiol 1996;78:1431–1433.
48. Brignole M, Menozzi C, Gianfranchi L, et al. Assessment of atrioventricular junction ablation and VVIR pacemaker vs pharmacological treatment in patients with heart failure and chronic atrial fibrillation: a randomized, controlled study. Circulation 1998;98:953–960.
49. Ozcan C, Jahangir A, Friedman PA, et al. Long-term survival after ablation of the atrioventricular node and implantation of a permanent pacemaker in patients with atrial fibrillation. N Engl J Med 2001;344:1043–1051.
50. Twidale N, McDonald T, Nave K, Seal A. Comparison of the effects of AV nodal ablation vs AV nodal modification in patients with congestive heart failure and uncontrolled atrial fibrillation. Pacing Clin Electrophysiol 1998;21(4 part 1): 641–651.
51. Leclercq C, Victor F, Alonso C, et al. Comparative effects of permanent biventricular pacing for refractory heart failure in patients with stable sinus rhythm or chronic atrial fibrillation. Am J Cardiol 2000;85:1154–1156.
52. Deshmukh P, Casavant DA, Romanyshyn M, Anderson K. Permanent, direct His-bundle pacing: a novel approach to cardiac pacing in patients with normal His-Purkinje activation. Circulation 2000;101:869–877.
53. Saxon LA, Kumar UN, De Marco T. Heart failure and cardiac resynchronization therapies: US experience in the year 2000. Ann Noninvasive Electrocardiol 2000; 5:188–194.
54. Kadhiresan V, Vogt J, Auricchio A, et al. Sensitivity and specificity of QRS duration to predict acute benefit in heart failure patients with cardiac resynchronization. Pacing Clin Electrophysiol 2000;23(4 part 2):555.
55. Farwell D, Patel NR, Hall A, et al. How many people with heart failure are appropriate for biventricular resynchronization? Eur Heart J 2000;21:1246–1250.
56. Saxon LA, Stevenson WG, Middlekauff HR, Stevenson LW. Increased risk of progressive hemodynamic deterioration in advanced heart failure patients requiring permanent pacemakers. Am Heart J 1993;125(5 part 1):1306–1310.

57. The DAVID Trial Investigators. Dual chamber pacing or ventricular backup pacing in patients with an implantable defibrillator. JAMA 2002;288:3115–3123.
58. Leon AR, Greenberg JM, Kanuru N, et al. Cardiac resynchronization in patients with congestive heart failure and chronic atrial fibrillation: effect of upgrading to biventricular pacing after chronic right ventricular pacing. J Am Coll Cardiol 2002;39:1258–1263.
59. Spragg DD, Leclercq C, Loghmani M, et al. Regional alterations in protein expression in the dyssynchronous failing heart. Circulation 2003;108:929–932.
60. Leclercq C, Cazeau S, Le Breton H, et al. Acute hemodynamic effects of biventricular DDD pacing in patients with end-stage heart failure. J Am Coll Cardiol 1998;32:1825–1831.
61. Kerwin WF, Botvinick EH, O'Connell JW, et al. Ventricular contraction abnormalities in dilated cardiomyopathy: effect of biventricular pacing to correct interventricular dyssynchrony. J Am Coll Cardiol 2000;35:1221–1227.
62. Kerwin WF, Foster E, Paccanaro M, et al. Effect of chronic biventricular pacing on Doppler measures of myocardial performance correlate with Doppler measures of systolic function. Pacing Clin Electrophysiol 1999;22(4 part 2):732.
63. Saxon LA, DeMarco T, Chatterjee K, et al. The magnitude of sympathoneural activation in advanced heart failure is altered with chronic biventricular pacing. Pacing Clin Electrophysiol 1998;21(4 part 2):499.
64. Dibs SR, Kerwin WF, Godin G, et al. Chronic biventricular pacing does not worsen autonomic imbalance in heart failure. Pacing Clin Electrophysiol 2000; 23(4 part 2):660.
65. Auricchio A, on behalf of the PATH-CHF Investigators. Optimal cardiac resynchronization decreases heart rate and increases heart rate variability in heart failure patients with conduction delay. Pacing Clin Electrophysiol 2000;23(4 part 2): 602.
66. July 10th Circulatory Systems Device Panel (MIRACLE trial). IDE G980219. Available at: www.FDALive, accessed 2001.
67. Saxon LA, De Marco T, Dibs S, et al. Chronic biventricular pacing improves indices of systolic function and reduces left ventricular volume. Pacing Clin Electrophysiol 2000;23(4 part 2);635.
68. De Marco T, Schafer J, Foster E, Saxon LA. Chronic resynchronization therapy results in reverse remodeling in mild to moderate heart failure. J Card Fail 2001; 7(3 suppl 2):58.
69. St John Sutton MG, Plappert TJ, Abraham WT, et al. Cardiac resynchronization therapy results in improvement in echocardiographic parameters in heart failure patients: Evidence from MIRACLE and MIRACLE ICD trials [abstract]. J Cardiac Fail 2002;8:abstract 034.
70. Saxon LA, De Marco T, Chatterjee K, et al. Operative risk associated with chronic biventricular pacemaker implantation in advanced heart failure. Pacing Clin Electrophysiol 1998; 21(4 part 2):498.
71. Leon A, Langberg J. Energy sources for catheter ablation. In: Zipes D, Jalife J, eds. Cardiac Electrophysiology: From Cell to Bedside, 2nd ed. WB Saunders, Philadelphia, PA: 1995.
72. Reynolds D, Belott P. Permanent pacemaker and implantable cardioverter-defibrillator implantation. In: Ellenbogen K, Kay G, Wilkoff B, eds. Clinical Cardiac Pacing and Defibrillation, 2nd ed. WB Saunders, Philadelphia, PA: 2000.
73. July 10th Circulatory Systems Device Panel (CONTAK CD trial). IDE G970259. Available at: www.FDALive, accessed 2002.

74. Hewitt M, Chen J, Ravon CE, Gallagher JJ. Coronary sinus atrial pacing: radiographic considerations. Am J Roentgenol 1981;136:323–328.
75. Bristow MR, Feldman AM, Saxon LA. Heart failure management using implantable devices for ventricular resynchronization: Comparison of Medical Therapy, Pacing, and Defibrillation in Chronic Heart Failure (COMPANION) trial. COMPANION Steering Committee and COMPANION Clinical Investigators. J Card Fail 2000;6:276–285.
76. Cazeau S, Leclercq C, Lavergne T, et al. Effects of multisite biventricular pacing in patients with heart failure and intraventricular conduction delay. N Engl J Med 2001;344:873–880.
77. Data presented at the European Society of Cardiology Scientific Sessions, Amsterdam, The Netherlands, 2000.
78. Buxton AE, Lee KL, Fisher JD, et al. A randomized study of the prevention of sudden death in patients with coronary artery disease. Multicenter Unsustained Tachycardia Trial Investigators. N Engl J Med 1999;341:1882–1890.
79. Moss AJ, Hall WJ, Cannom DS, et al. Improved survival with an implanted defibrillator in patients with coronary disease at high risk for ventricular arrhythmia. Multicenter Automatic Defibrillator Implantation Trial Investigators. N Engl J Med 1996;335:1933–1940.
80. Touiza A, Etienne Y, Gilard M, et al. Long-term left ventricular pacing: assessment and comparison with biventricular pacing in patients with severe congestive heart failure. J Am Coll Cardiol 2001;38:1966–1970.
81. Leclercq C, Faris O, Tunin R, et al. Systolic improvement and mechanical resynchronization does not require electrical synchrony in the dilated failing heart with left bundle-branch block. Circulation 2002;106:1760–1763.
82. Saxon LA, De Marco T. Cardiac resynchronization: a cornerstone in the foundation of device therapy in heart failure. J Am Coll Cardiol 2001;38:1971–1973.

7 Left Ventricular Assist Devices

Paul L. DiGiorgi, MD,
Yoshifumi Naka, MD, PhD,
and Mehmet C. Oz, MD

CONTENTS

INTRODUCTION

Left ventricular assist devices (LVADs) have become the standard of care for potential heart transplant patients with life-threatening heart failure refractory to medical therapy. Significant advances in both the technology and the clinical experience have taken place. In addition, indications for placement of ventricular assist devices (VADs) have broadened to include patients previously thought unsuitable for device insertion. There is a wide array of devices available and in development. These range from univentricular percutaneous driveline-powered devices to fully implantable total artificial hearts (TAHs). Both patient

From: *Contemporary Cardiology: Surgical Management of Congestive Heart Failure*
Edited by: J. C. Fang and G. S. Couper © Humana Press Inc., Totowa, NJ

and device selection have a great impact on outcome. In addition, the improving long-term success with device support has led to the possibility of permanent support. This review describes indications for VAD placement, reviews current devices, and discusses postoperative management.

INDICATIONS

The traditional indication for VAD support was refractory cardiac failure in patients approved for transplantation. Our patient population has expanded from these patients with chronic heart failure to include a large proportion of patients with acute heart failure. Although some reports have shown better outcomes in stable patients awaiting heart transplant *(1,2)*, acceptable results have been obtained in the emergent patient population *(3–8)*. In addition, our experience suggests similar survival rates between urgent and nonurgent LVAD placements.

There are now several clinical scenarios in which VADs are implanted. These include postcardiotomy cardiogenic shock (PCCS), acute myocardial infarction (AMI), acute decompensation of chronic heart failure, myocarditis, chronic heart failure in transplantation candidates, ventricular arrhythmias, and high-risk cardiac operations.

PCCS patients have shown significant survival benefits if identified early and appropriately treated *(8)*. Because most centers have the capability for short-term but not long-term VAD support/ transplant, we created a network that rapidly identifies and transfers appropriate patients in our region. Initial evaluation optimizes short-term VAD support and transfers patients within 72 hours of decompensation. Long-term LVAD implantation, if necessary, is then performed within 5 days.

AMI patients suffer from cardiogenic shock about 6% of the time and have a mortality of almost 80% *(9,10)*. Even with early revascularization, 1-year survival remains less than 50% *(11)*. Many of these patients suffer either unrecoverable myocardial damage or lack suitable coronary anatomy for revascularization. Advanced mechanical support may be the only therapy available for these patients and can successfully bridge these patients to either recovery or transplant if necessary *(12,13)*.

Patients with long-standing heart failure may decompensate acutely or over longer periods of time. These patients may not have been listed for transplant at the time of failure, although often they are followed at transplant centers. Acute decompensation can be triggered by several etiologies, including new ischemic injuries, arrhythmias, and infections. Patients already listed for heart transplant are the traditional group that

has made up VAD populations. These patients tend to do well with VAD placement as rehabilitation can be optimized before transplant *(14)*.

LVAD implantation in acute myocarditis, particularly in young patients, most often is a bridge to recovery rather than transplantation. Unfortunately, it is difficult to determine which patients will benefit from short-term support or require long-term devices with subsequent transplantation *(15)*. Because recovery is more likely in this population, short-term VADs are more often placed, with subsequent transition to long-term VADs if necessary *(3)*. The patient then proceeds along the same treatment algorithm as other VAD patients.

Patients with ventricular arrhythmias are unique in that, aside from the arrhythmia, their native cardiac function may not be significantly compromised. If pharmacological therapy and defibrillators have failed, VAD support may be warranted. Indeed, VAD support has successfully been implemented in this scenario *(16–18)*.

Patients undergoing high-risk cardiac surgery may need mechanical ventricular support if the surgical procedure is not successful. We routinely arrange for LVAD backup for such cases. The patient is screened for transplant candidacy preoperatively in case of the need for LVAD support and heart transplant.

PATIENT SELECTION

The selection process for VAD implantation must reach a balance between highest risk patients who have unacceptably high mortality rates and too conservative an approach passing over patients who would otherwise benefit from VAD support. Judicious use is also important as VAD implantation incurs significant social and financial investment.

According to the US Food and Drug Administration (FDA), approval for transplant is required for VAD implantation, although this may be difficult in the setting of acute cardiac failure. The generally accepted hemodynamic criteria include systolic blood pressure less than 80 mmHg (or mean arterial blood pressure <65 mmHg), pulmonary capillary wedge pressure more than 20 mmHg, systemic vascular resistance more than 2100 dynes*s/cm^5, urine output less than 20 cc per hour (adults) despite diuretics, and a cardiac index of less than 2 L/min/m^2 despite maximal inotropic or intra-aortic balloon pump (IABP) support *(19)*. In addition, some centers are more specific about the use of inotropic agents, requiring at least two at specified doses *(20)*. Several other factors must be taken into account. We use a system of cardiac and extracardiac factors when evaluating a patient for VAD placement (Table 1).

Table 1
Ventricular Assist Device Considerations

1. Transplant candidate
2. Hemodynamic variables
   a. Cardiac index <2 L/min/m^2
   b. Systolic blood pressure <80 mmHg
   c. Pulmonary capillary wedge pressure >20 mmHg
   d. On maximized medical therapy
3. Cardiac factors
   a. Right ventricular function
   b. Valvular disease/prosthetic valves
   c. Ischemia/bypass grafts
   d. Arrhythmias
4. Noncardiac factors
   a. Neurological function
   b. Infectious diseases
   c. Prolonged prothrombin time
   d. Oliguria
   e. Blood urea nitrogen
   f. Bilirubin
   g. Pulmonary disease
   h. Body surface area <1.5 m^2

Adapted from ref. *20a*.

Cardiac Factors

There are several cardiac factors that must be taken into account when considering VAD placement. Right heart failure (RHF) is one of the most important causes of perioperative mortality *(21,22)*. RHF complicating LVAD placement has been associated with low preoperative mean pulmonary arterial pressure and right ventricle stroke work index *(23)*. Hemodynamic indicators include left atrial pressures less than 10 mmHg, a cardiac index less than 1.8 L/min/m^2, and a decreasing cardiac index developing in the setting of high pulmonary arterial and central venous pressures *(22)*.

Pulmonary vascular resistance/index and the transpulmonary gradient have been used to predict RHF in the post-heart transplant population *(24–26)*. However, we were unable to distinguish survivors from nonsurvivors using these criteria *(22)*. It should be remembered that normal preoperative pulmonary pressures do not necessarily indicate adequate right heart function. Although a patient may have a normal pulmonary vascular resistance in low cardiac output states, a

fixed pulmonary vasculature can translate into pulmonary hypertension and RHF after instituting VAD support.

Although valve disease plays a role in patient selection for VAD implantation, most problems can be addressed at the time of surgery. Aortic insufficiency can cause shunting and loss of forward flow. The degree of aortic insufficiency may be underestimated in the preoperative setting. We therefore recommend intraoperative direct assessment with a left ventricular (LV) vent and believe that all regurgitant flow greater than 1.5 L/min should be addressed.

In patients requiring long-term LVAD support as a bridge to transplant, our preferred strategy is to oversew an incompetent aortic valve. In patients who have the potential for myocardial recovery and subsequent LVAD explant, the valve is repaired by resuspending the prolapsing cusp or by suturing it to the adjacent normal cusp, thereby creating a bicuspid valve. A prosthetic valve should be oversewn to reduce the incidence of thromboembolism.

Mitral stenosis can compromise device inflow and may need to be corrected at the time of implant as well. Repair of other valve pathologies, such as aortic stenosis and mitral regurgitation, should be considered regarding device weaning. A tissue valve should be considered, if replacement is necessary, because of lower risk of thromboembolism and the avoidance of anticoagulation. In addition, bubble studies should be performed and a patent foramen ovale repaired as hypoxia can result from right-to-left shunting after left-sided unloading from an LVAD. Tricuspid stenosis, although rare, should be treated as it will reduce right atrial pressure and improve forward flow through the pulmonary circulation. Correction of tricuspid regurgitation, commonly found, has no benefit unless ascites is present. As LV failure improves on device support, so will right ventricular failure and concomitant tricuspid regurgitation.

Preexisting coronary artery disease (CAD) is common in LVAD candidates. Adequate evaluation of CAD is important to maximize the benefits of VAD implantation. Right-sided bypasses may be necessary when implanting an LVAD to support right ventricular (RV) function. This is especially important for early postoperative RV protection.

In addition, ischemic complications such as angina and arrhythmias may still occur after VAD implantation and can be relieved by coronary bypass. Refractory, malignant arrhythmias themselves can be an indication for VAD implantation *(17,18)*. However, we usually do not perform left-sided bypasses for angina as post-LVAD angina is uncommon. Unless ventricular recovery is likely, left-sided bypasses may not be warranted secondary to a relatively low-flow state after

VAD implantation and the potential for early graft closure. However, there is a possibility that VAD support increases diastolic coronary flows by up to 97% *(27)*. If bypasses are performed, placement of the proximal anastomoses should take into account the LVAD outflow anastomosis site. We, therefore, recommend proximal bypass anastomoses on the lesser curvature of the aorta, providing ample room on the anterolateral aspect of the aorta to accommodate the LVAD outflow graft.

Noncardiac Factors

As more patients with PCCS are evaluated for VAD implantation, neurological status has become an increasingly important and difficult assessment to make and remains an important determinant of mortality in transferred patients *(8)*. It is ethically permissible to discontinue support if patients have unrecoverable neurological function. Ideally, patients should have both thorough neurological and psychiatric evaluations to determine their ability to tolerate mechanical support.

Infection is the Achilles' heal of mechanical support. Infection is the most common complication of long-term VADs and accounts for substantial morbidity and even mortality among VAD patients *(14,24,28–31)*. The location of the infection can have a significant impact on outcome *(29)*. Patients should ideally have negative blood cultures for at least a week prior to VAD implantation. This is especially true for fungal organisms because of the functional T-cell deficiency incurred by these patients *(32)*. Unfortunately, we have been unable to identify either fever or elevated white blood cell count as a risk factor for infection *(33)*. However, others have found elevated white blood cell count, but not fever, as a risk factor for mortality *(20,34)*. As designs and treatments improve, VAD patients with infections do increasingly well posttransplant *(28)*.

In our past experience, renal failure has been the strongest predictor of mortality. We avoid placing devices in patients with serum creatinine levels greater than 5 mg/dL. Patients who have acute cardiac failure may not show an elevated creatinine until later, however. Blood urea nitrogen less than 20 mg/dL has been associated with increased survival *(35)*. We have found urine output to be the best indicator of renal function. Urine output less than 30 mL per hour despite diuretic use has been our most important indicator *(33)*. Although renal impairment is common in this population, recovery during the VAD support period is excellent *(22,36,37)*. In fact, our most recent analysis indicated renal function is no longer predictive of mortality.

Hepatic function is an important factor in post-VAD survival. A prothrombin time greater than 16 seconds is particularly ominous because patients require more blood products. Increased transfusion requirements directly correlate with RHF. Coagulopathies should be aggressively treated with serine protease inhibitors (Aprotinin), vitamin K, and fresh frozen plasma. Hepatic function, evidenced by bilirubin, has been proposed as the best predictor of survival *(38)*. Other studies have failed to associate bilirubin with survival, however *(35)*.

Reoperation can make VAD implantation more challenging technically, but its impact on mortality has varied in published reports *(20,33,35,38)*. We found reoperation was a significant risk factor and use it as part of our screening scale to predict survival postimplant.

Other relative contraindications to VAD implantation include pulmonary failure exclusive of pulmonary edema and malignancy that would preclude survival longer than 2 years. Presently, any condition excluding patients from transplant also excludes them as VAD candidates if this is known preoperatively.

Several studies have attempted to develop simple selection criteria for VAD implantation. These have been based on both unique clinical variables *(20)* and Acute Physiology and Chronic Health Evaluation II (APACHE II) scores *(22)*. In 1995, we published our own scoring scale (Table 2) *(33)*. Scores were based on seven relatively simple variables, including urine output, central venous pressure, mechanical ventilation, prothrombin time, reoperation, white blood cell count, and temperature. We found scores greater than 5 correlated with increased mortality. It is important to remember that no scoring system serves as an absolute predictor for VAD candidacy or success. In addition, as both technology and patient selection evolve, these systems will become obsolete, and new ones will need to be developed.

By appropriately selecting patients for VAD insertion, lives are saved, end-organ impairment is reduced, and transplantation risks are reduced. Ultimately, the utilization of donor hearts will be maximized.

TYPES OF PUMPS

Extracorporeal

Centrifugal Pumps

Centrifugal devices have been the most commonly used pumps for postcardiotomy cardiac support *(39)*. Blood enters axially into the pump, is spun by the magnetically driven blades, and exits peripherally through the outlet port. Although in clinical use for more than 20 years,

Table 2
Risk Factors for Poor Survival After Left Ventricular Assist Device Placement

Risk factor	*Relative risk*	*Score*
Urine output <30 mL per hour	3.9	3
Central venous pressure >20 mmHg	3.1	2
Mechanical ventilation	3.0	2
Prothrombin time >16 seconds	2.4	2
Reoperation	1.8	1
White blood cell count >15,000	1.1	0
Temperature >101.5°F	0	0

Adapted from ref. *166*.

initial enthusiasm waned because of excessive hemolysis. Since then, many new designs have been produced with improved hemodynamics *(40–54)*.

The two most commonly used pumps are the Biomedicus Bio-Pump (Medtronic Inc.) (Fig. 1) and the Sarns/3M Centrifugal System (Sarns/3M). Centrifugal pumps are now considered by many to cause less hemolysis and blood element activation compared to roller pumps *(55–57)*. None of the commonly used pumps has shown significant clinical advantages *(54)*.

Indications for centrifugal pump implantation are extracorporeal membrane oxygenation (ECMO), thoracic aortic surgery, postcardiotomy ventricular failure, bridge to a long-term VAD, and bridge to transplant. Besides thoracic aortic surgery, the major indication has been postcardiotomy ventricular failure *(43,54,58–62)*. Published outcomes have paralleled other short-term devices, with 56 to 68% of patients weaned, and 21 to 44% of patients surviving to discharge *(59,61–63)*. Support duration is shorter than the other commonly used short-term device, the Abiomed BVS 5000 (Abiomed Cardiovascular Inc.), running usually less than 4 days. Popularity of centrifugal pumps has been primarily because of the lower price, ease of use, and greater availability they have historically enjoyed. This may change, however, as more advanced systems like the Abiomed BVS 5000 become more ubiquitous and cost differences diminish *(64)*.

Major limitations include seal disruption, usually within 48 hours, requiring close inspection *(65)*, mandatory anticoagulation, continued sedation with mechanical ventilation, and the inability to ambulate or rehabilitate patients while on the device. In addition, a full-time, bedside

Fig. 1. The centrifugal Biomedicus Biopump. Blood enters the pump apically (top connector) and exits peripherally (lower left connector). (Courtesy of Medtronic Inc., Minneapolis, MN.)

perfusionist is required to run each centrifugal pump system. Finally, the devices are not FDA approved for this purpose. Given these complications and limitations, especially in rehabilitation, centrifugal mechanical assist devices are mainly useful for short-term support in the patient with postcardiotomy ventricular failure and the bridge-to-transplant scenario.

The next generation of centrifugal pumps, however, now in bench and animal testing, is designed for long-term support with partial or total implantability *(66–72)*. Advantages will include their smaller size, potential total implantability, lower energy requirements compared to pusher-plate technologies, and outpatient use. The potential disadvantages of nonpulsatile flow remain to be seen with long-term support.

Abiomed BVS 5000

The Abiomed BVS 5000 is a short-term uni- or biventricular (BV) support system composed of external pumps driven by a computer-controlled drive console (Fig. 2). The FDA first approved the product in 1992 for postcardiotomy support *(73)*. Since then, the indications for use have grown to include AMI, myocarditis, RV support in conjunction

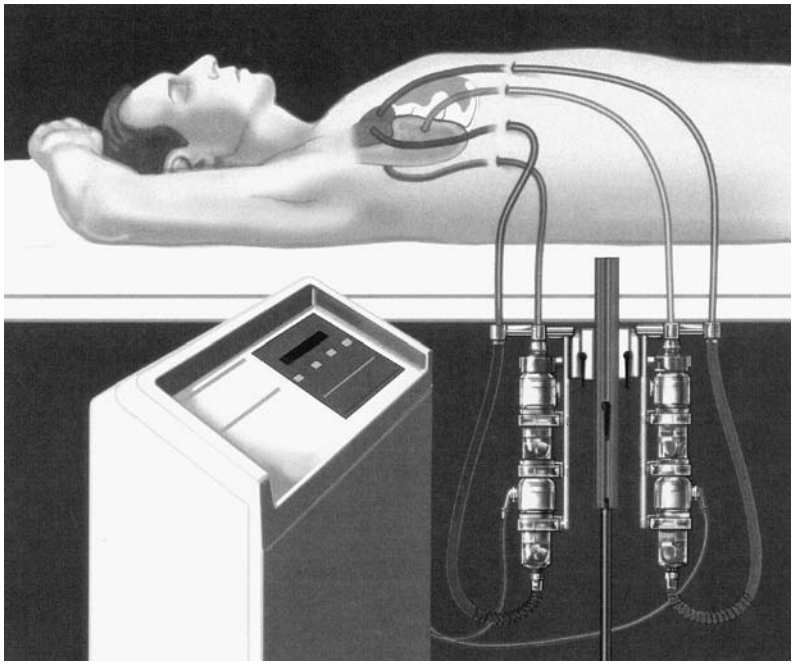


Fig. 2. The Abiomed BVS 5000. Both the pumps and drive console are external. (Courtesy of Abiomed Cardiovascular Inc., Danvers, MA.)

with a long-term LV support device, as a bridge to recovery, and as a bridge to transplant. As a result, the device has become one of the most commonly used means of short-term mechanical cardiac support *(74,75)*. It is the only device approved by the FDA for all patients with potentially reversible heart failure.

Advantages that have made the BVS system popular are the ease of insertion and simplicity in operation, obviating the need for a full-time perfusionist. The system functions reliably for several days, with average support duration between 5 and 9 days. This has been particularly helpful in community hospitals, in which there may be the need to transfer the patient to a transplant center for further treatment *(8,76)*. It has proven its effectiveness in the treatment of both acute myocarditis and PCCS *(3,4,74,77)*. In addition, the cost may be closer to that of centrifugal pumps than previously expected *(64)*. For these reasons, the BVS system has become our standard for bridging patients to longer term devices.

Disadvantages of this device include the requirement for continuous anticoagulation, limited mobility compared to implantable devices,

and the requirement to remain in an intensive care unit. Flow rates are also limited compared to other devices. The maximum flow rate of 6 L per minute may not be enough for septic or large patients. Although patients have been supported as long as 90 days, the device is best suited for short-term use (<10 days). For these reasons, we do not use the device if we feel the support period will be longer than 7 days.

Thoratec Device

The Thoratec VAD (Thoratec Laboratories Corp.) consists of an externalized pneumatic pusher-plate pump positioned subcostally and connected to a drive console. The drive is capable of uni- or BV support with flows up to 7 L per minute. The cannulae are tunneled, exiting out the upper abdominal wall and connected to the extracorporeal pump (Fig. 3). The device was first used clinically in 1982 for postcardiotomy support *(78)* and in 1984 as a bridge to transplantation *(79)*. It has received FDA approval as both a bridge to recovery and a bridge to transplant.

The main advantage of the Thoratec system is the ability to provide long-term BV support. This has become increasingly important with prolonged waiting periods for transplant. The Thoratec system is the only extracorporeal device that is used for long-term support. The paracorporeal position has some particular benefits as well. These include identification of clot and device exchange without invasive surgery. Survival to transplant has been good, up to 74% with support durations longer than 200 days *(80–83)*.

The major limitations of the Thoratec system are the limited mobility and rehabilitation potential because of a large drive console and the need for chronic anticoagulation. New, portable drive units will allow portability, which should overcome the limitations of the original system *(84)*. In addition, the device is not recommended for pediatric patients.

Even with limited portability and the need for chronic anticoagulation, the Thoratec VAD system provides a valuable adjunct to the cardiac assist device armamentarium because of the ability to provide long-term, BV support. At present, we use this device in patients with substantial end-organ injury prior to device insertion and in individuals likely to require BV support

Adult ECMO

ECMO provides mechanical cardiac support (uni- or biventricular) as well as pulmonary support. Although neonatal use has been very successful, the adult experience has been mixed.

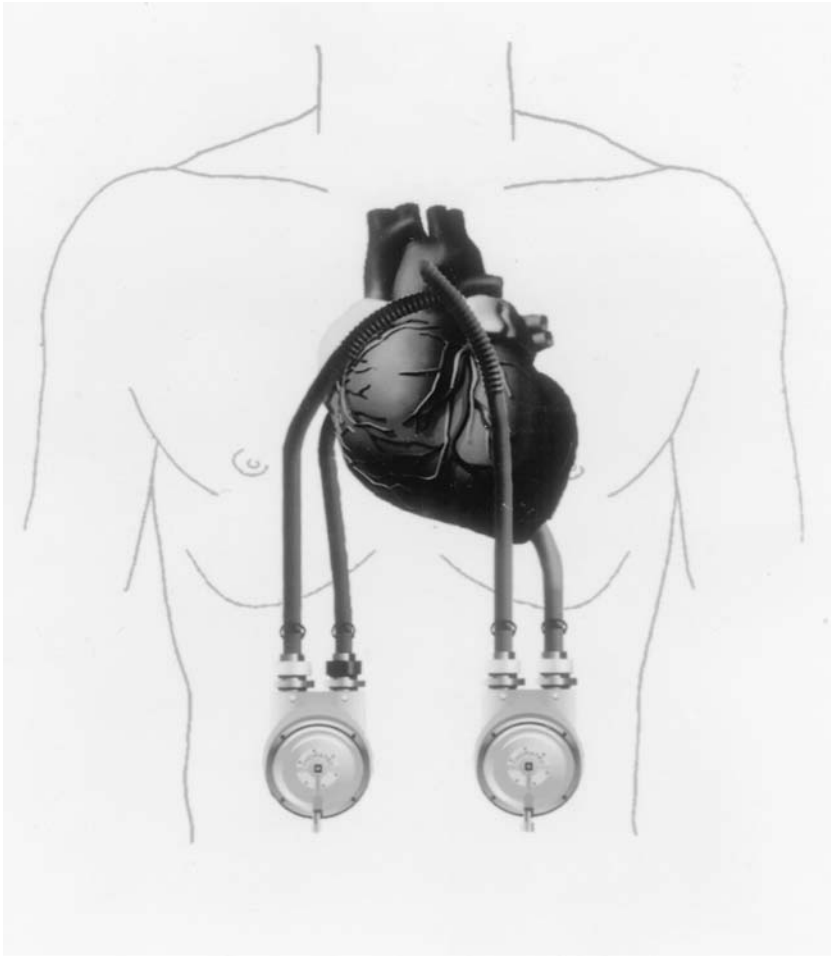


Fig. 3. Thoratec ventricular assist device. Both the pumps and drive console are external. (Courtesy of Thoratec Laboratories Corp., Pleasanton, CA.)

The main indication for ECMO is the need for mechanical assistance when respiratory failure complicates cardiovascular collapse. When initially used for PCCS, survival was low (25%) *(85)*, but with experience and improved circuits, survival increased to 40% *(86)*. ECMO benefits from potential peripheral cannulae insertion and versatility of small consoles. This allows potential implementation in areas outside the operating room for both cardiac and pulmonary support.

Major limitations include requirement for sedation and possible paralysis, heparinization (except in cases of pure respiratory support),

and the potential need for an IABP to reduce afterload. A full-time perfusionist is also necessary to run the equipment. The duration of support is usually only 2 to 3 days, although it can be several days. Complications are common, including leg ischemia, renal failure, bleeding, and oxygenator failure, especially with venoarterial ECMO support.

Overall, the successful use of ECMO in adults has been limited to select centers, and the epidemiological benefits remain minor.

Berlin Heart

The Berlin heart (Mediport Kardiotechnik) is a pneumatically driven paracorporeal support device capable of providing both univentricular and BV mechanical support. The system has been used in Europe since 1988. The blood pumps come in a variety of sizes, down to stroke volumes of about 10 mL, allowing for pediatric use *(87,88)*. Implantation is usually performed via a sternotomy with or without cardiopulmonary bypass and cardioplegic arrest *(89)*. The cannulae are brought out the epigastrium to connect to the external blood pumps. Various drive consoles have been developed, allowing discharge to home while on ventricular support. The duration of implant averages 2 months and has been more than 500 days.

The Berlin heart can provide BV or univentricular support. It has the advantage of pediatric applications and has proven its reliability and low rate of thromboembolic complications. Newer, portable consoles allow patients to be more mobile with better rehabilitation and home discharge.

Coumadin is mandatory (international normalized ratio [INR] 2.5 to 3.5), along with aspirin and dipyridamole *(89)*. The pumps also require twice-weekly inspection for thrombus formation. These high-maintenance requirements should provide reliable service, however, for extended periods of time. This device is not approved by the FDA, so US use is not yet feasible.

Intracorporeal

Intra-Aortic Balloon Pump

In use since the 1960s *(90)*, the IABP is the most commonly used cardiac assist device in use today. It is based on diastolic coronary blood flow augmentation and aortic counterpulsation. As a result, myocardial oxygen consumption is decreased by afterload reduction, and coronary blood flow is increased *(91)*. Percutaneous placement was developed by the 1980s, greatly increasing the use of the devices *(92,93)* by enabling placement by nonsurgeons outside the operating room.

It is most commonly used in cardiogenic shock or ongoing myocardial infarction refractory to medical therapy. Preoperatively, IABP support is commonly used to stabilize patients with myocardial ischemia despite medical therapy before proceeding with revascularization. Survival benefit has been shown with preoperative IABP placement, especially in patients with ejection fractions (EFs) less than 25% *(94)* as well as in those with EFs less than 40% *(95)*. Intraoperatively, it is used for patients who fail weaning from cardiopulmonary bypass despite maximal medical therapy. Insertion of an IABP intraoperatively or postoperatively has been an independent predictor of death. Preoperative insertion has been associated with significantly increased survival *(96)*.

The IABP benefits from relatively rapid and easy insertion without necessarily requiring a surgical approach. The benefits of increased coronary perfusion as well as reduced myocardial oxygen demand are most realized in the ischemic heart, although other forms of cardiomyopathies are also benefited. It does not, however, provide the level of support of other assist devices. Anticoagulation with intravenous heparin is used to prevent thrombotic complications at both the insertion and balloon sites. Postoperative anticoagulation can be started with low-molecular-weight dextran and switched to heparin later.

Vascular complications remain the most common source of morbidity, with rates varying from 9 to 36% *(97,98)*. Most often, this is related to the femoral artery, stressing the importance of common femoral artery insertion (rather than insertion in the superficial femoral artery). Given these complications, however, the IABP has become an important tool in supporting cardiac function without the need for significant surgical intervention.

Thoratec HeartMate

The HeartMate LVAD is an implantable, long-term, univentricular cardiac assist device (Fig. 4). It was developed by Thermo Cardiosystems Inc. (TCI) and is now distributed by Thoratec Laboratories. Based on work started in the mid-1960s, the first clinical implantation of the HeartMate took place in 1986. The HeartMate was the first mechanical circulatory support device to be approved by the FDA for bridging to transplant. Both a pneumatically driven (implantable pneumatic) and an electrically powered (vented electric) version exist. Most hospitals now have converted to the portable electric version, allowing discharge to home on support.

Both systems function with a pusher-plate mechanism delivering up to 10 L per minute of flow. The driveline containing the electric

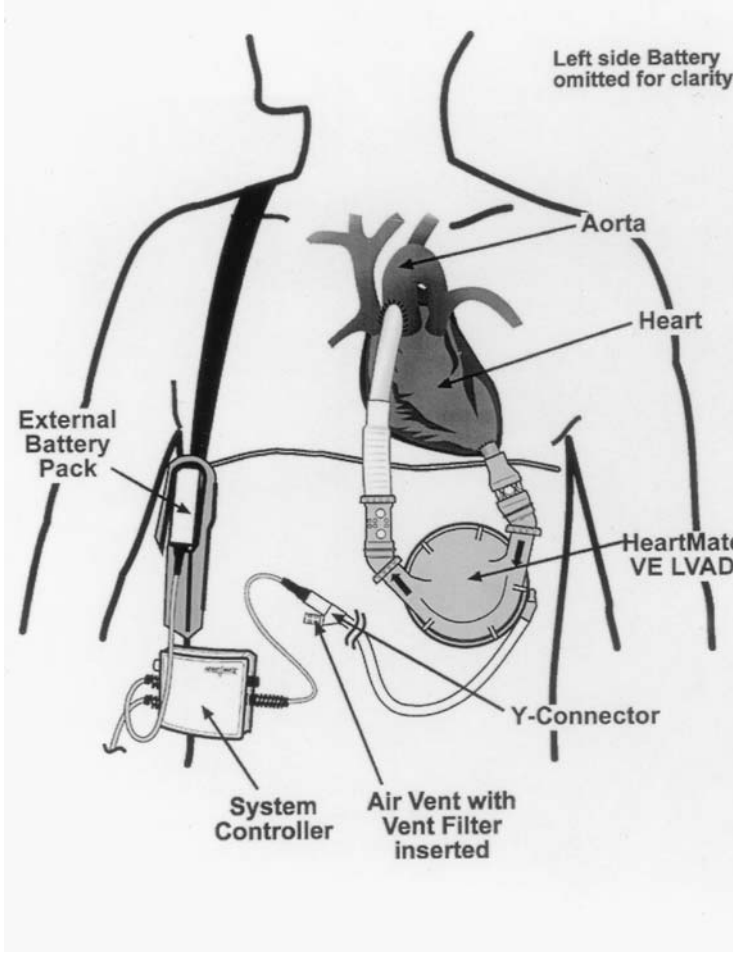


Fig. 4. The HeartMate LVAD. Implantable pump and external drive console. VE, vented electric. (Courtesy of Thoratec Laboratories Corp., Pleasanton, CA.)

cable and an air vent exit the skin to attach to the external drive console. Both inflow and outflow porcine valves are attached to the pump. The inflow cannula is attached to the LV apex, and the outflow is via the ascending aorta. The blood-contacting portion of the pump incorporates titanium microspheres, and the flexible diaphragm is covered with textured polyurethane. This promotes the formation of a pseudointimal layer. This unique surface may be responsible for the low thromboembolic risk associated with the HeartMate despite the lack of anticoagulation *(99–101)*.

The main advantage of the HeartMate is the very low thromboembolic rate (<5%) without anticoagulation *(101–103)*. Patients can be discharged home while awaiting transplant; they can resume almost all their normal activities.

Patients must have a body surface area (BSA) of at least 1.5 m^2 to accommodate the abdominally placed pump. Proper screening of potential recipients is critical *(33)*. Early complications are related to technique. We prefer a preperitoneal drive implantation to avoid intra-abdominal complications, a long driveline tunnel to avoid infectious complications, and a secure, hemostatic ascending aorta/outflow graft anastomosis to avoid bleeding, dissection, and rupture. Other centers prefer intra-abdominal insertion with the benefit of additional tissue around the driveline, including omentum. The major causes of perioperative mortality are hemorrhage and RHF. These have been reduced with the introduction of aprotinin (Bayer) and nitric oxide *(104–108)*. If right-sided mechanical support is necessary, a different device would need to be placed.

Although the HeartMate represents the first generation of reliable mechanical cardiac assist devices, it has enjoyed significant clinical success. As a result, the Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure (REMATCH) study was undertaken using the device as an alternative rather than bridge to transplantation *(109)* (*see* section on postoperative management).

Novacor N1000PC

The Novacor N1000PC (World Heart Corp.) is a wearable LV assist system with implantable pump and externalized vent tube, controller, and batteries (Fig. 5). Its dual pusher-plate design provides symmetrical movement, minimizing mechanical torque *(110,111)*. The pump is lined with a smooth polyurethane sac and has gelatin-sealed inflow and outflow grafts. The first successful bridge-to-transplant implantation took place in 1984, and it received FDA approval for bridge to transplant in 1998. Inflow comes from the LV apex, and outflow is through the ascending aorta, with flows up to 10 L per minute. Patients can ambulate with little impairment after implantation. Many patients have been successfully discharged from the hospital to await transplant. It also has an excellent mechanical reliability rate with few device failures *(112)*.

Successful outcome requires proper patient selection. Device-specific exclusion criteria include blood dyscrasias, presence of a prosthetic aortic valve, and a recipient BSA less than 1.5 m^2 *(113)*. Preoperative multisystem organ failure is predictive of poor outcome

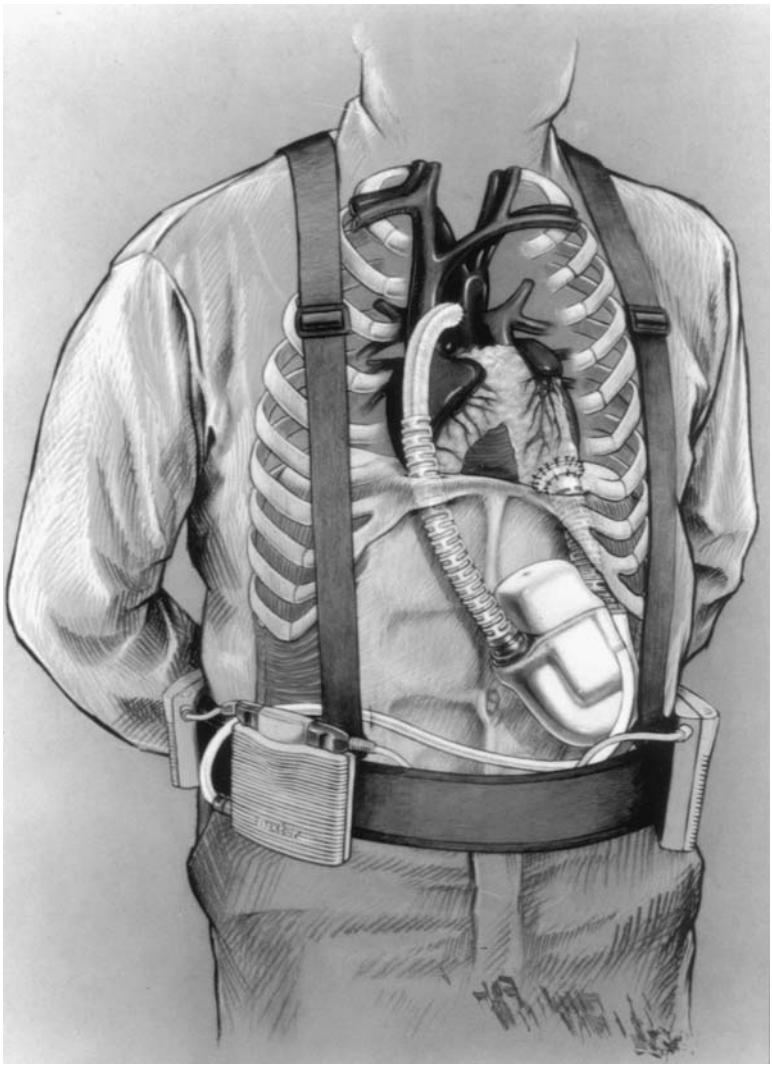


Fig. 5. The Novacor N1000PC. Implantable pump and external drive console. (Courtesy of Baxter Healthcare Corp., Berkeley, CA.)

as well *(33,35,114)*. Like other LVADs, bleeding and RHF are the most significant perioperative complications. Anticoagulation must be maintained with coumadin (INR 2–3) and with aspirin. Despite anticoagulation, the embolic stroke rate associated with the Novacor device has been high (26%). However, recent inflow cannula/conduit modifications have dropped the embolic stroke rate to 12% *(113)*.

Total Artificial Hearts (*see also* Chapter 13)

The CardioWest TAH (CardioWest Technologies Inc.) is a pneumatic, biventricular, orthotopically implanted TAH with an externalized driveline to its console (Fig. 6). It consists of two spherical polyurethane chambers with polyurethane diaphragms. Inflow and outflow conduits are constructed of Dacron™ and contain Medtronic-Hall™ valves. It began as the Jarvik-7 TAH, used in the early 1980s *(115,116)*. Despite early obstacles, a new investigational device exemption study started in 1993. It is the only TAH approved for use in the United States under the FDA investigational device exemption. The trial showed support durations of 12 to 186 days, with a 93% survival to transplant *(117)*. European experience with the CardioWest TAH has been slightly worse, although encouraging *(118,119)*.

The TAH benefits from having the ability to provide excellent, early support, avoiding irreversible end-organ damage in rapidly decompensating critically ill patients *(117)*. Unlike the other biventricular devices, it obviates the presence of the native heart. This is particularly useful when leaving the native heart in place would be detrimental or impossible (infection or cardiac tumors).

Adequate intrathoracic space is required to accommodate the TAH. Fitting criteria includes BSA greater than 1.7 m^2, cardiothoracic ratio 0.5, LV diastolic dimension above 66 mm, AP distance more than 10 cm, and combined ventricular volume of more than 1500 mL. Careful intraoperative fitting is critical. In addition to size requirements, strict anticoagulation with coumadin, aspirin, Persantine, and Trental is needed *(120)*. Rehabilitation is limited as well because of the large console. A portable console for the CardioWest TAH is in development, however.

New TAHs are in development that will allow full implantability and hospital discharge. The AbioCor TAH (Abiomed Cardiovascular) consists of an internal thoracic pump, internal rechargeable battery, internal electronics, and an external battery pack. External power is delivered via a transcutaneous energy transmission coil located on the chest wall. The pump consists of two ventricles with their corresponding mechanical valves. Its stroke volume is between 60 and 65 cc, with an output of between 4 and 10 L per minute. A centrifugal pump moves hydraulic fluid between each ventricle, providing alternate LV and RV pulsatile flow. There is an atrial balance chamber that adjusts for left and right atrial pressures. As with previous TAHs, fitting is critical. The Abiofit system was developed using three-dimensional computed tomography reconstruction to size patients before implantation. Anticoagulation is

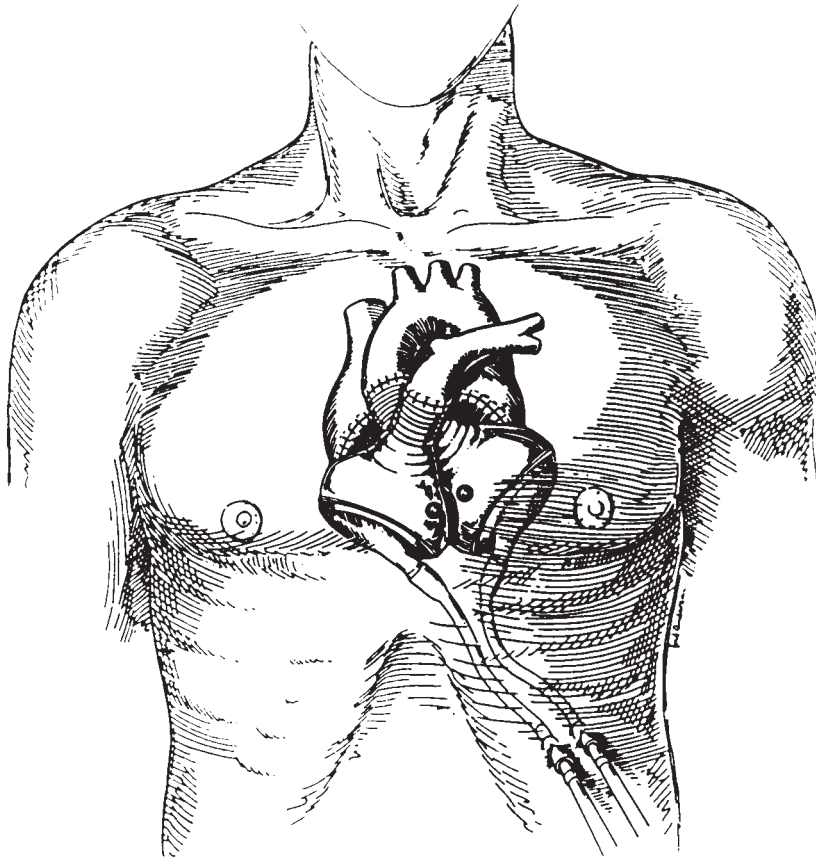


Fig. 6. The CardioWest total artifical heart. Implantable pump and external drive console. (Courtesy of CardioWest Technologies Inc., Tucson, AZ.)

maintained with coumadin and Plavix. The first human implantation took place in July 2001 at Jewish Hospital in Louisville, Kentucky *(121)*. The implantation, part of the initial AbioCor trial, represents the first implantation of a totally implantable TAH. End points include 60-day mortality and quality-of-life measurements, with an anticipated sample size of 15 to 30 patients recruited over 2 years. As of 2004, 5 patients have been implanted, totaling nearly 1 year of support without device malfunction.

Axial Flow Pumps

Axial flow pumps represent one of the newest generations of assist devices. They can provide full cardiac support in a much smaller pump

with fewer moving parts and less blood-contacting surface than pusher-plate devices. In addition to their small size, their design is notable for nonpulsatile flow. Several studies have demonstrated metabolic and neurohumoral changes in organ perfusion compared to pulsatile flow *(122–134)*. However, both clinical and long-term animal studies have failed to show significant differences in morbidity and mortality with axial flow pumps *(135–143)*. The most promising devices are the HeartMate II (Thoratec Laboratories), DeBakey VAD (MicroMed Technology Inc.), and Jarvik 2000 (Jarvik Heart Inc.). These devices weigh between 53 and 176 grams and can generate flows in excess of 10 L per minute.

The Jarvik 2000 axial flow pump, HeartMate II, and the DeBakey axial flow pump all have similar features. Their small size allows implantation into smaller patients than most pulsatile pumps. This also makes placement and explantation easier. With fewer moving parts, there are fewer points of friction, therefore increasing their expected durability. Although there is controversy over long-term nonpulsatile flow, most patients maintain some native cardiac function and therefore continue to have pulsatile blood flow.

Unfortunately, if there is a device failure, there are few options or backup mechanisms in place other than replacement. In addition, because they lack valves, if device malfunction does occur, the patient can develop the equivalent of wide-open aortic insufficiency. The DeBakey pump has already been successfully implanted in a few patients in Europe *(144,145)*. In addition, the HeartMate II and the Jarvik 2000 have been successfully implanted in humans *(146)*.

Cardiac Compression Devices

Epicardial compression devices support the circulation by compressing the failing heart from its epicardial surface. The Anstadt cup was introduced in 1965 *(147)* as a cardiac massage device used for cardiac arrest. This early compression device held the heart in place with vacuum, but did not employ any means to synchronize with the cardiac cycle. Feasibility tests resulted in no device-related complications *(148)*.

Newer devices consist of a cup or cuff with an internal inflatable diaphragm, an electrocardiogram sensor/trigger, and a compression driver console. The force generated by the compression device adds to the ventricular pressure generated by the native, contracting myocardium. Diastolic compliance is lessened, however, requiring higher filling pressures to obtain the same preload *(149,150)*.

Both Abiomed and Cardio Technologies Inc. have compression devices under development. The CardioSupport System of Cardio Technologies is undergoing phase I trials in Europe. Early animal studies demonstrated successful support for up to 7 days *(151)*. The compression devices benefit from not having any blood–device interface, reducing the need for anticoagulation. The epicardial application should be relatively easier without the requirement for cardiopulmonary bypass. With variable compression strength, the devices are easily weaned as well. Potential problems include rhythm disturbances and myocardial injury that may result after prolonged use *(152)*.

DEVICE SELECTION

Device selection is invariably influenced by both availability and physician experience. Although much has been published on individual devices, few studies have compared assist devices at a single institution *(64,153)*. There are two major indications for cardiac assist device support: bridge to recovery and bridge to transplant. Destination therapy, although probable, remains investigational.

There are five FDA-approved assist devices in addition to the IABP for these indications. Table 1 summarizes these devices: the Abiomed BVS 5000, the Thoratec device, the Novacor N1000PC, the TCI HeartMate Implantable Pneumatic, and the TCI HeartMate Vented Electric LVAD. In addition to the FDA-approved devices, there are several other VADs in development and clinical use. Table 3 summarizes most of the current VADs along with their major characteristics.

Important clinical issues in choosing a device include the expected duration of support, need for biventricular support, cost, device-related risks, patient characteristics, and United Network of Organ Sharing classification rules. Institutional standard of care, ranging from community practice to tertiary heart failure/transplant centers, also influences device selection.

Patients who may require mechanical circulatory support can be divided into three main categories; these different clinical scenarios and patient needs dictate the best type of device to use:

1. Acute profound shock, such as from postcardiotomy cardiac arrest, potentially with end-organ failure and RHF.
2. Decompensated chronic congestive heart failure. These individuals are more chronically ill patients who are transplant candidates.
3. Nontransplant candidates. These patients are not at a transplant center and have potentially recoverable myocardium.

Table 3
Ventricular Assist Devices

Class	*Device*	*Implant-able*	*Long-term*	*BiVAD capable*	*Hosp D/C*	*No AC*	*Advantage*	*Disadvantage*
TAH	CardioWest	+	+	+			Greatest TAH clinical experience	Fitting required Immobility Infection (10–90%) Emboli (12%)
TAH	Abiomed	+	+	+	+		Totally implantable	Fitting required
TAH	Penn State	+	+	+	+		Totally implantable	Fitting required
Centrifugal	Biomedicus			+			Simple Easy Inexpensive	Bleeding (45%) Embolus (2–63%) Device failure (15%) RF (35%) Bed bound Perfusionist required
External pneumatic	Abiomed			+			Easy Most common	Flow limit 6 L Bleeding (40%) Hospital bound
External pneumatic	Thoratec		+	+			Only FDA-approved long-term BV VAD	Hospital bound BSA limitation Bleeding (42%) Infection (36%) RF (36%) Embolus (8%)

Pusher plate	Berlin heart		+	+	+		Low-BSA compatible	Pump cleaning required
Pusher plate	HeartMate VE	+	+		+	+	Low CVA rate	Infection BSA >1.5
Pusher plate	Novacor	+	+		+		Reliable (0.8%)	Infection (30–50%) BSA limit CVA (12–26%)
Axial flow	Jarvik	+	+		+		Small size Small drive line	Nonpulsatile? AI with pump failure rpm only
Axial flow	Heart Mate II	+	+		+		Small size Small drive line	Nonpulsatile? AI with pump failure
Axial flow	DeBakey	+	+		+		Small size Small drive line Flow probe 10 L/min	Nonpulsatile? AI with pump failure Fixed pump speed
Epicardial compression	CTI			+		+	Weanable Defibrillation option	Myocardial trauma? Unproven durability
Epicardial compression	Abiomed			+		+	Weanable Defibrillation option	Myocardial trauma? Unproven durability

AC, anticoagulation; AI, aortic insufficiency; BV, biventricular; BSA, body surface area;CVA, cerebrovascular accident; RF, renal failure; rpm, revolutions per minute; TAH, total artifical heart; VAD, ventricular assist device; VE, vented electric.

Patients in profound shock with end-organ dysfunction and RHF need early and reliable support to avoid permanent end-organ damage and increased chances of survival. The preferred devices in such a scenario are the Abiomed BVS 5000, the Thoratec device, and the TAH. These devices provide full BV support, reestablishing near-normal hemodynamics and allowing myocardial recovery *(73)*. Early implementation of BV support is critical in patients with severe BV failure *(3,4,77)*. While on ventricular support, the potential for myocardial recovery and neurological status can be determined. If a prolonged support period is expected, a longer term device should be implanted, such as the Thoratec or TAH. Despite their severe cardiac failure, these patients can be successfully salvaged, with survival rates approaching that of the general cardiac transplantation population *(80,81)*.

Patients who suffer from more chronic congestive heart failure and who are transplant candidates may decompensate before receiving their transplant. In these patients, the potential for long-term support must be considered. Hospital discharge and rehabilitation become important factors in choosing a device for this patient population *(114,154)*. Longer term support with end-organ recovery and better rehabilitation is associated with better long-term survival *(155)*. Therefore, the recommended devices are the implantable HeartMate and the Novacor LVAD. Treatment of RHF, if present, is mandatory. This can be done either medically or with a short-term VAD such as the Abiomed.

Nontransplant candidates may be patients at nontransplant centers or with recoverable cardiac function. Patients at nontransplant centers, who may benefit from a longer term device and transplant workup, can be safely transferred once stabilized on short-term devices *(76)*. Many patients transferred on assist devices are successfully weaned without requiring a long-term implantable LVAD *(8,76)*. The preferred device for use in this setting is the Abiomed BVS 5000. A long-term device can be implanted later as required.

POSTOPERATIVE MANAGEMENT

Early Postoperative Management

There are several factors we have found useful in the postoperative management of LVAD patients. Antibiotic prophylaxis is started preoperatively and continues for at least 3 days postimplant. We treat RHF with milrinone and nitric oxide *(108)*. In addition, we treat vasodilatory hypotension with intravenous arginine vasopressin (Parke-Davis) *(156)*. Aprotinin is continued in the postoperative period until hemorrhage

has stopped. Ventricular arrhythmias are managed with appropriate pharmacological agents and cardioversion if necessary.

Late Postoperative Management

Late postoperative care focuses on rehabilitation and monitoring of the immunological changes *(157)* induced by the LVAD while awaiting heart transplantation. Patients with the vented electric TCI LVAD are eligible for discharge to home while awaiting transplant *(154,158,159)*. Patients are followed weekly in the LVAD clinic. Panel-reactive antibody levels are measured in TCI LVAD patients biweekly.

LVAD Explant vs Transplant

Unless in a study, all LVAD patients are listed as heart transplant candidates. Long-term LVAD explantation is considered only if there is significant myocardial recovery evidenced by an exercise testing protocol. The profound ventricular unload provided by LVAD support can lead to reverse remodeling evident at genetic, biochemical, and histological levels *(160,161)*. Our protocol to assess myocardial recovery is to reduce LVAD flow to 2 L per minute while patients exercise on a treadmill. Right heart catheterization and echocardiography is performed to determine the adequacy of ventricular function *(162)*. Although functional recovery allowing LVAD explantation has been reported *(163)*, our experience has shown only a few patients can be successfully weaned from their devices *(164)*.

Destination Therapy

The first generation of mechanical cardiac assist devices, such as the HeartMate and the Novacor devices, have enjoyed good relatively long-term clinical success. Because of increased long-term survival as well as improved quality of life with these devices, the use of the LVAD for permanent support without transplantation (so-called destination therapy) is under exploration.

The REMATCH study was conducted to test this concept in a randomized controlled trial *(109)*. There were 129 nontransplant candidates in New York Heart Association class IV heart failure randomly assigned to receive a HeartMate LVAD or optimal medical therapy. The patients had very advanced heart failure, as evidenced by the low EFs (17%), low systolic blood pressure (101–103 mmHg), elevated creatinines (1.7–1.8 mg/dL), and the need for intravenous inotropes in 65 to 72% of patients. There was a 48% reduction in the risk of death from any cause in the LVAD group compared to the medical therapy group. The 1- and

2-year survival were 52 vs 25% ($p = 0.002$) and 23 vs 8% ($p = 0.09$) for the LVAD and medical therapy groups, respectively *(165)*. Furthermore, of the 54 deaths in the medical therapy group, 50 were attributable to heart failure. In contrast, of the 41 deaths in the LVAD arm, only 1 was thought secondary to ventricular dysfunction. Quality of life (using the Minnesota Living With Heart Failure questionnaire and New York Heart Association class) was also better in the assist device group.

However, there are reasons for caution. The probability for device failure was 35% at 24 months, and sepsis accounted for 17 of the 41 deaths in the device arm. Furthermore, the Kaplan–Meier survival curves began to come together after 24 months, with a mortality of 77% in the device arm. Finally, cost analyses are pending and will be critical before VADs can be considered a routine strategy for permanent therapy in advanced heart failure.

CONCLUSION

LVADs are the standard of care for potential heart transplant patients with life-threatening heart failure refractory to medical therapy. Significant advances in both the technology and clinical experience have taken place. Increasing technological advances, clinical experience, and broadening indications are allowing more patients to benefit from VAD support. Thus, a critical niche can be filled while patients await heart transplant. For some patients, LVADs may even become an alternative to transplant. In turn, this results in more appropriate transplant candidates, increased survival, and better quality of life for patients who would otherwise not survive.

REFERENCES

1. Schmid C, Deng M, Hammel D, Weyand M, Loick HM, Scheld HH. Emergency vs elective/urgent left ventricular assist device implantation. J Heart Lung Transplant 1998;17:1024–1028.
2. Deng MC, Weyand M, Hammel D, et al. Selection and outcome of ventricular assist device patients: the Muenster experience. J Heart Lung Transplant 1998;17:817–825.
3. Chen JM, Spanier TB, Gonzalez JJ, et al. Improved survival in patients with acute myocarditis using external pulsatile mechanical ventricular assistance. J Heart Lung Transplant 1999;18:351–357.
4. Marelli D, Laks H, Amsel B, et al. Temporary mechanical support with the BVS 5000 assist device during treatment of acute myocarditis. J Card Surg 1997;12: 55–59.
5. Minami K, El Banayosy A, Posival H, et al. Improvement of survival rate in patients with cardiogenic shock by using nonpulsatile and pulsatile ventricular assist device. Int J Artif Organs 1992;15:715–721.

6. Copeland JG, Smith RG, Arabia FA, Nolan PE, Banchy ME. The CardioWest total artificial heart as a bridge to transplantation. Semin Thorac Cardiovasc Surg 2000;12:238–242.
7. Hendry PJ, Masters RG, Mussivand TV, et al. Circulatory support for cardiogenic shock due to acute myocardial infarction: a Canadian experience. Can J Cardiol 1999;15:1090–1094.
8. Helman DN, Morales DL, Edwards NM, et al. Left ventricular assist device bridge-to-transplant network improves survival after failed cardiotomy. Ann Thorac Surg 1999;68:1187–1194.
9. Goldberg RJ, Gore JM, Thompson CA, Gurwitz JH. Recent magnitude of and temporal trends (1994–1997) in the incidence and hospital death rates of cardiogenic shock complicating acute myocardial infarction: The second National Registry of Myocardial Infarction. Am Heart J 2001;141:65–72.
10. Goldberg RJ, Gore JM, Alpert JS, et al. Cardiogenic shock after acute myocardial infarction. Incidence and mortality from a community-wide perspective, 1975 to 1988. N Engl J Med 1991;325:1117–1122.
11. Hochman JS, Sleeper LA, White HD, et al. One-year survival following early revascularization for cardiogenic shock. JAMA 2001;285:190–192.
12. Mueller HS. Role of intra-aortic counterpulsation in cardiogenic shock and acute myocardial infarction. Cardiology 1994;84:168–174.
13. Champsaur G, Ninet J, Vigneron M, Cochet P, Neidecker J, Boissonnat P. Use of the Abiomed BVS System 5000 as a bridge to cardiac transplantation. J Thorac Cardiovasc Surg 1990;100:122–128.
14. Sun BC, Catanese KA, Spanier TB, et al. One hundred long-term implantable left ventricular assist devices: the Columbia Presbyterian interim experience. Ann Thorac Surg 1999;68:688–694.
15. Houel R, Vermes E, Tixier DB, Le Besnerais P, Benhaiem-Sigaux N, Loisance DY. Myocardial recovery after mechanical support for acute myocarditis: is sustained recovery predictable? Ann Thorac Surg 1999;68:2177–2180.
16. Farrar DJ, Hill JD, Gray LA, Galbraith TA, Chow E, Hershon JJ. Successful biventricular circulatory support as a bridge to cardiac transplantation during prolonged ventricular fibrillation and asystole. Circulation 1989;80(5 part 2):III147–III151.
17. Holman WL, Roye GD, Bourge RC, McGiffin DC, Iyer SS, Kirklin JK. Circulatory support for myocardial infarction with ventricular arrhythmias. Ann Thorac Surg 1995;59:1230–1231.
18. Swartz MT, Lowdermilk GA, McBride LR. Refractory ventricular tachycardia as an indication for ventricular assist device support. J Thorac Cardiovasc Surg 1999;118:1119–1120.
19. Oz MC, Rose EA, Levin HR. Selection criteria for placement of left ventricular assist devices. Am Heart J 1995;129:173–177.
20. Swartz MT, Votapka TV, McBride LR, Lohmann DP, Moroney DA, Pennington DG. Risk stratification in patients bridged to cardiac transplantation. Ann Thorac Surg 1994;58:1142–1145.
20a. Williams MR, Oz MC. Indications and patient selection for mechanical ventricular assistance. Ann Thorac Surg 2001;71:S86–S91.
21. Nakatani S, Thomas JD, Savage RM, Vargo RL, Smedira NG, McCarthy PM. Prediction of right ventricular dysfunction after left ventricular assist device implantation. Circulation 1996;94(9 suppl):II216–II221.
22. Gracin N, Johnson MR, Spokas D, et al. The use of APACHE II scores to select candidates for left ventricular assist device placement. Acute Physiology and Chronic Health Evaluation. J Heart Lung Transplant 1998;17:1017–1023.

23. Fukamachi K, McCarthy PM, Smedira NG, Vargo RL, Starling RC, Young JB. Preoperative risk factors for right ventricular failure after implantable left ventricular assist device insertion. Ann Thorac Surg 1999;68:2181–2184.
24. Springer WE, Wasler A, Radovancevic B, et al. Retrospective analysis of infection in patients undergoing support with left ventricular assist systems. ASAIO J 1996; 42:M763–M765.
25. Cloy MJ, Myers TJ, Stutts LA, Macris MP, Frazier OH. Hospital charges for conventional therapy vs left ventricular assist system therapy in heart transplant patients. ASAIO J 1995;41:M535–M539.
26. Macris MP, Myers TJ, Jarvik R, et al. In vivo evaluation of an intraventricular electric axial flow pump for left ventricular assistance. ASAIO J 1994;40: M719–M722.
27. Tedoriya T, Kawasuji M, Sakakibara N, Takemura H, Watanabe Y, Hetzer R. Coronary bypass flow during use of intraaortic balloon pumping and left ventricular assist device. Ann Thorac Surg 1998;66:477–481.
28. Sinha P, Chen JM, Flannery M, Scully BE, Oz MC, Edwards NM. Infections during left ventricular assist device support do not affect posttransplant outcomes. Circulation 2000;102(19 suppl 3):III194–III199.
29. Holman WL, Skinner JL, Waites KB, Benza RL, McGiffin DC, Kirklin JK. Infection during circulatory support with ventricular assist devices. Ann Thorac Surg 1999;68:711–716.
30. Argenziano M, Catanese KA, Moazami N, et al. The influence of infection on survival and successful transplantation in patients with left ventricular assist devices. J Heart Lung Transplant 1997;16:822–831.
31. Herrmann M, Weyand M, Greshake B, et al. Left ventricular assist device infection is associated with increased mortality but is not a contraindication to transplantation. Circulation 1997;95:814–817.
32. Ankersmit HJ, Tugulea S, Spanier T, et al. Activation-induced T-cell death and immune dysfunction after implantation of left-ventricular assist device. Lancet 1999;354:550–555.
33. Oz MC, Goldstein DJ, Pepino P, et al. Screening scale predicts patients successfully receiving long-term implantable left ventricular assist devices. Circulation 1995;92(9 suppl):II169–II173.
34. Pennington DG, McBride LR, Peigh PS, Miller LW, Swartz MT. Eight years' experience with bridging to cardiac transplantation. J Thorac Cardiovasc Surg 1994;107:472–480.
35. Farrar DJ. Preoperative predictors of survival in patients with Thoratec ventricular assist devices as a bridge to heart transplantation. Thoratec ventricular assist device principal investigators. J Heart Lung Transplant 1994;13(1 part 1): 93–100.
36. Friedel N, Viazis P, Schiessler A, et al. Recovery of end-organ failure during mechanical circulatory support. Eur J Cardiothorac Surg 1992;6:519–522.
37. Frazier OH, Macris MP, Myers TJ, et al. Improved survival after extended bridge to cardiac transplantation. Ann Thorac Surg 1994;57:1416–1422.
38. Reinhartz O, Farrar DJ, Hershon JH, Avery GJ Jr, Haeusslein EA, Hill JD. Importance of preoperative liver function as a predictor of survival in patients supported with Thoratec ventricular assist devices as a bridge to transplantation. J Thorac Cardiovasc Surg 1998;116:633–640.
39. Pae WE Jr, Miller CA, Matthews Y, Pierce WS. Ventricular assist devices for postcardiotomy cardiogenic shock. A combined registry experience. J Thorac Cardiovasc Surg 1992;104:541–552.

40. Pennington DG, Merjavy JP, Swartz MT, Willman VL. Clinical experience with a centrifugal pump ventricular assist device. Trans Am Soc Artif Intern Organs 1982;28:93–99.
41. Bianchi JJ, Swartz MT, Raithel SC, et al. Initial clinical experience with centrifugal pumps coated with the Carmeda process. ASAIO J 1992;38:M143–M146.
42. Coselli JS, LeMaire SA, Ledesma DF, Ohtsubo S, Tayama E, Nose Y. Initial experience with the Nikkiso centrifugal pump during thoracoabdominal aortic aneurysm repair. J Vasc Surg 1998;27:378–383.
43. Curtis JJ, Walls JT, Wagner-Mann CC, et al. Centrifugal pumps: description of devices and surgical techniques. Ann Thorac Surg 1999;68:666–671.
44. Mann FA, Wagner-Mann CC, Curtis JJ, Demmy TL, Turk JR. A calf model for left ventricular centrifugal mechanical assist. Artif Organs 1996;20:670–677.
45. Wagner-Mann C, Curtis J, Mann FA, Turk J, Demmy T, Turpin T. Subchronic centrifugal mechanical assist in an unheparinized calf model. Artif Organs 1996; 20:666–669.
46. Curtis J, Wagner-Mann C, Mann F, Demmy T, Walls J, Turk J. Subchronic use of the St. Jude centrifugal pump as a mechanical assist device in calves. Artif Organs 1996;20:662–665.
47. Magovern GJ Jr, Christlieb IY, Kao RL, et al. Recovery of the failing canine heart with biventricular support in a previously fatal experimental model. J Thorac Cardiovasc Surg 1987;94:656–663.
48. Naganuma S, Yambe T, Sonobe T, Kobayashi S, Nitta S. Development of a novel centrifugal pump: magnetic rotary pump. Artif Organs 1997;21:746–750.
49. Ohtsubo S, Naito K, Matsuura M, et al. Initial clinical experience with the Baylor-Nikkiso centrifugal pump. Artif Organs 1995;19:769–773.
50. Taguchi S, Yozu R, Mori A, Aizawa T, Kawada S. A miniaturized centrifugal pump for assist circulation. Artif Organs 1994;18:664–668.
51. Takami Y, Ohara Y, Otsuka G, Nakazawa T, Nose Y. Preclinical evaluation of the Kyocera Gyro centrifugal blood pump for cardiopulmonary bypass. Perfusion 1997;12:335–341.
52. Nakazawa T, Ohara Y, Benkowski R, et al. A pivot bearing-supported centrifugal pump for a long-term assist heart. Int J Artif Organs 1997;20:222–228.
53. Curtis JJ, Walls JT, Schmaltz RA, et al. Improving clinical outcome with centrifugal mechanical assist for postcardiotomy ventricular failure. Artif Organs 1995; 19:761–765.
54. Curtis JJ. Centrifugal mechanical assist for postcardiotomy ventricular failure. Semin Thorac Cardiovasc Surg 1994;6:140–146.
55. Nishinaka T, Nishida H, Endo M, Miyagishima M, Ohtsuka G, Koyanagi H. Less blood damage in the impeller centrifugal pump: a comparative study with the roller pump in open heart surgery. Artif Organs 1996;20:707–710.
56. Yoshikai M, Hamada M, Takarabe K, Okazaki Y, Ito T. Clinical use of centrifugal pumps and the roller pump in open heart surgery: a comparative evaluation. Artif Organs 1996;20:704–706.
57. Morgan IS, Codispoti M, Sanger K, Mankad PS. Superiority of centrifugal pump over roller pump in paediatric cardiac surgery: prospective randomised trial. Eur J Cardiothorac Surg 1998;13:526–532.
58. Noon GP, Ball JW Jr, Papaconstantinou HT. Clinical experience with BioMedicus centrifugal ventricular support in 172 patients. Artif Organs 1995;19:756–760.
59. Noon GP, Ball JW Jr, Short HD. Bio-Medicus centrifugal ventricular support for postcardiotomy cardiac failure: a review of 129 cases. Ann Thorac Surg 1996;61: 291–295.

60. Noon GP, Lafuente JA, Irwin S. Acute and temporary ventricular support with BioMedicus centrifugal pump. Ann Thorac Surg 1999;68:650–654.
61. Hoy FB, Mueller DK, Geiss DM, et al. Bridge to recovery for postcardiotomy failure: is there still a role for centrifugal pumps? Ann Thorac Surg 2000;70: 1259–1263.
62. Joyce LD, Kiser JC, Eales F, King RM, Overton JW Jr, Toninato CJ. Experience with generally accepted centrifugal pumps: personal and collective experience. Ann Thorac Surg 1996;61:287–290.
63. Magovern GJ Jr. The biopump and postoperative circulatory support. Ann Thorac Surg 1993;55:245–249.
64. Couper GS, Dekkers RJ, Adams DH. The logistics and cost-effectiveness of circulatory support: advantages of the Abiomed BVS 5000. Ann Thorac Surg 1999;68:646–649.
65. Curtis JJ, Boley TM, Walls JT, Demmy TL, Schmaltz RA. Frequency of seal disruption with the Sarns centrifugal pump in postcardiotomy circulatory assist. Artif Organs 1994;18:235–237.
66. Hart RM, Filipenco VG, Kung RT. A magnetically suspended and hydrostatically stabilized centrifugal blood pump. Artif Organs 1996;20:591–596.
67. Nojiri C, Kijima T, Maekawa J, et al. Recent progress in the development of Terumo implantable left ventricular assist system. ASAIO J 1999;45:199–203.
68. Ohtsuka G, Nakata K, Yoshikawa M, et al. Long-term in vivo left ventricular assist device study for 284 days with Gyro PI pump. Artif Organs 1999;23: 504–507.
69. Schima H, Schmallegger H, Huber L, et al. An implantable seal-less centrifugal pump with integrated double-disk motor. Artif Organs 1995;19:639–643.
70. Wakisaka Y, Taenaka Y, Chikanari K, Okuzono Y, Endo S, Takano H. Development of an implantable centrifugal blood pump for circulatory assist. ASAIO J 1997;43:M608–M614.
71. Waters T, Allaire P, Tao G, et al. Motor feedback physiological control for a continuous flow ventricular assist device. Artif Organs 1999;23:480–486.
72. Yamazaki K, Litwak P, Tagusari O, et al. An implantable centrifugal blood pump with a recirculating purge system (Cool-Seal system). Artif Organs 1998;22: 466–474.
73. Guyton RA, Schonberger JP, Everts PA, et al. Postcardiotomy shock: clinical evaluation of the BVS 5000 biventricular support system. Ann Thorac Surg 1993;56: 346–356.
74. Jett GK. Abiomed BVS 5000: experience and potential advantages. Ann Thorac Surg 1996;61:301–304.
75. Wassenberg PA. The Abiomed BVS 5000 biventricular support system. Perfusion 2000;15:369–371.
76. McBride LR, Lowdermilk GA, Fiore AC, Moroney DA, Brannan JA, Swartz MT. Transfer of patients receiving advanced mechanical circulatory support. J Thorac Cardiovasc Surg 2000;119:1015–1020.
77. Samuels LE, Kaufman MS, Thomas MP, Holmes EC, Brockman SK, Wechsler AS. Pharmacological criteria for ventricular assist device insertion following postcardiotomy shock: experience with the Abiomed BVS system. J Card Surg 1999; 14:288–293.
78. Pennington DG, Bernhard WF, Golding LR, Berger RL, Khuri SF, Watson JT. Long-term follow-up of postcardiotomy patients with profound cardiogenic shock treated with ventricular assist devices. Circulation 1985;72(3 part 2): II216–II226.

79. Hill JD, Farrar DJ, Hershon JJ, et al. Use of a prosthetic ventricle as a bridge to cardiac transplantation for postinfarction cardiogenic shock. N Engl J Med 1986; 314:626–628.
80. Farrar DJ, Hill JD. Univentricular and biventricular Thoratec VAD support as a bridge to transplantation. Ann Thorac Surg 1993;55:276–282.
81. Farrar DJ, Hill JD, Pennington DG, et al. Preoperative and postoperative comparison of patients with univentricular and biventricular support with the Thoratec ventricular assist device as a bridge to cardiac transplantation. J Thorac Cardiovasc Surg 1997;113:202–209.
82. Korfer R, El Banayosy A, Arusoglu L, et al. Temporary pulsatile ventricular assist devices and biventricular assist devices. Ann Thorac Surg 1999;68:678–683.
83. Farrar DJ. The Thoratec ventricular assist device: a paracorporeal pump for treating acute and chronic heart failure. Semin Thorac Cardiovasc Surg 2000;12: 243–250.
84. Farrar DJ, Buck KE, Coulter JH, Kupa EJ. Portable pneumatic biventricular driver for the Thoratec ventricular assist device. ASAIO J 1997;43:M631–M634.
85. Pennock JL, Pierce WS, Wisman CB, Bull AP, Waldhausen JA. Survival and complications following ventricular assist pumping for cardiogenic shock. Ann Surg 1983;198:469–478.
86. Stolar CJ, Delosh T, Bartlett RH. Extracorporeal Life Support Organization 1993. ASAIO J 1993;39:976–979.
87. Hetzer R, Loebe M, Potapov EV, et al. Circulatory support with pneumatic paracorporeal ventricular assist device in infants and children. Ann Thorac Surg 1998; 66:1498–1506.
88. Ishino K, Alexi-Meskishvili V, Hetzer R. Myocardial recovery through ECMO after repair of total anomalous pulmonary venous connection: the importance of left heart unloading. Eur J Cardiothorac Surg 1997;11:585–587.
89. Loebe M, Hennig E, Muller J, Spiegelsberger S, Weng Y, Hetzer R. Long-term mechanical circulatory support as a bridge to transplantation, for recovery from cardiomyopathy, and for permanent replacement. Eur J Cardiothorac Surg 1997;11 (suppl):S18–S24.
90. Kantrowitz A, Tjonneland S, Freed PS, Phillips SJ, Butner AN, Sherman JL. Initial clinical experience with intraaortic balloon pumping in cardiogenic shock. JAMA 1968;203:113–118.
91. Powell WJ, Daggett WM, Magro AE, et al. Effects of intra-aortic balloon counterpulsation on cardiac performance, oxygen consumption, and coronary blood flow in dogs. Circ Res 1970;26:753–764.
92. Bregman D, Nichols AB, Weiss MB, Powers ER, Martin EC, Casarella WJ. Percutaneous intraaortic balloon insertion. Am J Cardiol 1980;46:261–264.
93. Subramanian VA, Goldstein JE, Sos TA, McCabe JC, Hoover EA, Gay WA. Preliminary clinical experience with percutaneous intraaortic balloon pumping. Circulation 1980;62(2 part 2):I123–I129.
94. Dietl CA, Berkheimer MD, Woods EL, Gilbert CL, Pharr WF, Benoit CH. Efficacy and cost-effectiveness of preoperative IABP in patients with ejection fraction of 0.25 or less. Ann Thorac Surg 1996;62:401–408.
95. Schmid C, Wilhelm M, Reimann A, et al. Use of an intraaortic balloon pump in patients with impaired left ventricular function. Scand Cardiovasc J 1999;33: 194–198.
96. Torchiana DF, Hirsch G, Buckley MJ, et al. Intraaortic balloon pumping for cardiac support: trends in practice and outcome, 1968 to 1995. J Thorac Cardiovasc Surg 1997;113:758–764.

97. Busch T, Sirbu H, Zenker D, Dalichau H. Vascular complications related to intraaortic balloon counterpulsation: an analysis of 10 years experience. Thorac Cardiovasc Surg 1997;45:55–59.
98. Sirbu H, Busch T, Aleksic I, Friedrich M, Dalichau H. Ischaemic complications with intra-aortic balloon counter-pulsation: incidence and management. Cardiovasc Surg 2000;8:66–71.
99. Rose EA, Levin HR, Oz MC, et al. Artificial circulatory support with textured interior surfaces. A counterintuitive approach to minimizing thromboembolism. Circulation 1994;90(5 part 2):II87–II91.
100. Dasse KA, Frazier OH, Lesniak JM, Myers T, Burnett CM, Poirier VL. Clinical responses to ventricular assistance vs transplantation in a series of bridge to transplant patients. ASAIO J 1992;38:M622–M626.
101. Slater JP, Rose EA, Levin HR, et al. Low thromboembolic risk without anticoagulation using advanced-design left ventricular assist devices. Ann Thorac Surg 1996;62:1321–1327.
102. McCarthy PM, Smedira NO, Vargo RL, et al. One hundred patients with the HeartMate left ventricular assist device: evolving concepts and technology. J Thorac Cardiovasc Surg 1998;115:904–912.
103. Goldstein DJ. Thermo Cardiosystems ventricular assist devices. In: Goldstein DJ, Oz MC, eds. Cardiac Assist Devices. Futura, Armonk, NY: 2000, pp. 307–321.
104. Salamonsen RF, Kaye D, Esmore DS. Inhalation of nitric oxide provides selective pulmonary vasodilatation, aiding mechanical cardiac assist with Thoratec left ventricular assist device. Anaesth Intensive Care 1994;22:209–210.
105. Goldstein DJ, Seldomridge JA, Chen JM, et al. Use of aprotinin in LVAD recipients reduces blood loss, blood use, and perioperative mortality. Ann Thorac Surg 1995;59:1063–1067.
106. Chang JC, Sawa Y, Ohtake S, et al. Hemodynamic effect of inhaled nitric oxide in dilated cardiomyopathy patients on LVAD support. ASAIO J 1997;43:M418–M421.
107. Wagner F, Dandel M, Gunther G, et al. Nitric oxide inhalation in the treatment of right ventricular dysfunction following left ventricular assist device implantation. Circulation 1997;96(9 suppl):II-6.
108. Argenziano M, Choudhri AF, Moazami N, et al. Randomized, double-blind trial of inhaled nitric oxide in LVAD recipients with pulmonary hypertension. Ann Thorac Surg 1998;65:340–345.
109. Rose EA, Moskowitz AJ, Packer M, et al. The REMATCH trial: rationale, design, and end points. Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure. Ann Thorac Surg 1999;67:723–730.
110. Portner PM, Oyer PE, Jassawalla JS, et al. An implantable permanent left ventricular assist system for man. Trans Am Soc Artif Intern Organs 1978;24:99–103.
111. Portner PM, Oyer PE, Pennington DG, et al. Implantable electrical left ventricular assist system: bridge to transplantation and the future. Ann Thorac Surg 1989;47:142–150.
112. Lee J, Miller PJ, Chen H, et al. Reliability model from the in vitro durability tests of a left ventricular assist system. ASAIO J 1999;45:595–601.
113. Ramasamy N, Vargo RL, Kormos RL, Portner PM. The Novacor left ventricular assist system. In: Goldstein DJ, Oz MC, eds. Cardiac Assist Devices. Futura, Armonk, NY: 2000, pp. 323–340.
114. Kormos RL, Murali S, Dew MA, et al. Chronic mechanical circulatory support: rehabilitation, low morbidity, and superior survival. Ann Thorac Surg 1994;57: 51–57.

115. Anderson FL, DeVries WC, Anderson JL, Joyce LD. Evaluation of total artificial heart performance in man. Am J Cardiol 1984;54:394–398.
116. DeVries WC, Anderson JL, Joyce LD, et al. Clinical use of the total artificial heart. N Engl J Med 1984;310:273–278.
117. Copeland JG, Arabia FA, Banchy ME, et al. The CardioWest total artificial heart bridge to transplantation: 1993 to 1996 national trial. Ann Thorac Surg 1998;66: 1662–1669.
118. Arabia FA, Copeland JG, Smith RG, et al. International experience with the CardioWest total artificial heart as a bridge to heart transplantation. Eur J Cardiothorac Surg 1997;11(suppl):S5–S10.
119. Copeland JG, Pavie A, Duveau D, et al. Bridge to transplantation with the CardioWest total artificial heart: the international experience 1993 to 1995. J Heart Lung Transplant 1996;15(1 part 1):94–99.
120. Copeland JG, Arabia FA, Smith R, Nolan P. The CardioWest total artificial heart. In: Goldstein DJ, Oz MC, eds. Cardiac Assist Devices. Futura, Armonk, NY: 2000, pp. 341–355.
121. SoRelle R. Cardiovascular news. Totally contained AbioCor artificial heart implanted July 3, 2001. Circulation 2001;104:E9005–E9006.
122. Angell James JE, Daly M. Effects of graded pulsatile pressure on the reflex vasomotor responses elicited by changes of mean pressure in the perfused carotid sinus-aortic arch regions of the dog. J Physiol 1971;214:51–64.
123. Gaer JA, Shaw AD, Wild R, et al. Effect of cardiopulmonary bypass on gastrointestinal perfusion and function. Ann Thorac Surg 1994;57:371–375.
124. Hickey PR, Buckley MJ, Philbin DM. Pulsatile and nonpulsatile cardiopumonary bypass: review of a counterproductive controversy. Ann Thorac Surg 1983;36:720–737.
125. Hornick P, Taylor K. Pulsatile and nonpulsatile perfusion: the continuing controversy. J Cardiothorac Vasc Anesth 1997;11:310–315.
126. Levine FH, Philbin DM, Kono K, et al. Plasma vasopressin levels and urinary sodium excretion during cardiopulmonary bypass with and without pulsatile flow. Ann Thorac Surg 1981;32:63–67.
127. Moores WY, Gago O, Morris JD, Peck CC. Serum and urinary amylase levels following pulsatile and continuous cardiopulmonary bypass. J Thorac Cardiovasc Surg 1977;74:73–76.
128. Noris M, Morigi M, Donadelli R, et al. Nitric oxide synthesis by cultured endothelial cells is modulated by flow conditions. Circ Res 1995;76: 536–543.
129. Taylor KM, Wright GS, Bain WH, Caves PK, Beastall GS. Comparative studies of pulsatile and nonpulsatile flow during cardiopulmonary bypass. III. Response of anterior pituitary gland to thyrotropin-releasing hormone. J Thorac Cardiovasc Surg 1978;75:579–584.
130. Taylor KM, Wright GS, Reid JM, et al. Comparative studies of pulsatile and nonpulsatile flow during cardiopulmonary bypass. II. The effects on adrenal secretion of cortisol. J Thorac Cardiovasc Surg 1978;75:574–578.
131. Watkins WD, Peterson MB, Kong DL, et al. Thromboxane and prostacyclin changes during cardiopulmonary bypass with and without pulsatile flow. J Thorac Cardiovasc Surg 1982;84:250–256.
132. Sezai A, Shiono M, Orime Y, et al. Major organ function under mechanical support: comparative studies of pulsatile and nonpulsatile circulation. Artif Organs 1999;23:280–285.

133. Sezai A, Shiono M, Orime Y, et al. Comparison studies of major organ microcirculations under pulsatile- and nonpulsatile-assisted circulations. Artif Organs 1996;20:139–142.
134. Sezai A, Shiono M, Orime Y, et al. Renal circulation and cellular metabolism during left ventricular assisted circulation: comparison study of pulsatile and nonpulsatile assists. Artif Organs 1997;21:830–835.
135. Wakisaka Y, Taenaka Y, Chikanari K, et al. Long-term evaluation of a nonpulsatile mechanical circulatory support system. Artif Organs 1997;21:639–644.
136. Taenaka Y, Tatsumi E, Sakaki M, et al. Peripheral circulation during nonpulsatile systemic perfusion in chronic awake animals. ASAIO Trans 1991;37:M365–M366.
137. Sakaki M, Taenaka Y, Tatsumi E, Nakatani T, Takano H. Influences of nonpulsatile pulmonary flow on pulmonary function. Evaluation in a chronic animal model. J Thorac Cardiovasc Surg 1994;108:495–502.
138. Reddy RC, Goldstein AH, Pacella JJ, Cattivera GR, Clark RE, Magovern GJ. End organ function with prolonged nonpulsatile circulatory support. ASAIO J 1995;41:M547–M551.
139. Macha M, Litwak P, Yamazaki K, et al. Survival for up to 6 months in calves supported with an implantable axial flow ventricular assist device. ASAIO J 1997;43:311–315.
140. Kawahito K, Damm G, Benkowski R, et al. Ex vivo phase 1 evaluation of the DeBakey/NASA axial flow ventricular assist device. Artif Organs 1996;20:47–52.
141. Hindman BJ, Dexter F, Smith T, Cutkomp J. Pulsatile vs nonpulsatile flow. No difference in cerebral blood flow or metabolism during normothermic cardiopulmonary bypass in rabbits. Anesthesiology 1995;82:241–250.
142. Hindman BJ, Dexter F, Ryu KH, Smith T, Cutkomp J. Pulsatile vs nonpulsatile cardiopulmonary bypass. No difference in brain blood flow or metabolism at 27°C. Anesthesiology 1994;80:1137–1147.
143. Dapper F, Neppl H, Wozniak G, et al. Effects of pulsatile and nonpulsatile perfusion mode during extracorporeal circulation—a comparative clinical study. Thorac Cardiovasc Surg 1992;40:345–351.
144. Wieselthaler GM, Schima H, Hiesmayr M, et al. First clinical experience with the DeBakey VAD continuous-axial-flow pump for bridge to transplantation. Circulation 2000;101:356–359.
145. Potapov EV, Loebe M, Nasseri BA, et al. Pulsatile flow in patients with a novel nonpulsatile implantable ventricular assist device. Circulation 2000;102(19 suppl 3):III183–III187.
146. Westaby S, Banning AP, Jarvik R, et al. First permanent implant of the Jarvik 2000 heart. Lancet 2000;356:900–903.
147. Anstadt GL, Blakemore WS, Baue AE. A new instrument for prolonged mechanical massage [abstract]. Circulation 1965;31(suppl II):43.
148. Anstadt MP, Bartlett RL, Malone JP, et al. Direct mechanical ventricular actuation for cardiac arrest in humans. A clinical feasibility trial. Chest 1991;100: 86–92.
149. Artrip JH, Yi GH, Levin HR, Burkhoff D, Wang J. Physiological and hemodynamic evaluation of nonuniform direct cardiac compression. Circulation 1999;100(19 suppl):II236–II243.
150. Artrip JH, Yi GH, Shimizo J, et al. Maximizing hemodynamic effectiveness of biventricular assistance by direct cardiac compression studied in ex vivo and in vivo canine models of acute heart failure. J Thorac Cardiovasc Surg 2000;120: 379–386.

151. Perez-Tamayo RA, Anstadt MP, Cothran RL, et al. Prolonged total circulatory support using direct mechanical ventricular actuation. ASAIO J 1995;41:M512–M517.
152. Anstadt MP, Perez-Tamayo RA, Banit DM, et al. Myocardial tolerance to mechanical actuation is affected by biomaterial characteristics. ASAIO J 1994;40: M329–M334.
153. El Banayosy A, Arusoglu L, Kizner L, et al. Novacor left ventricular assist system vs HeartMate vented electric left ventricular assist system as a long-term mechanical circulatory support device in bridging patients: a prospective study. J Thorac Cardiovasc Surg 2000;119:581–587.
154. DeRose JJ, Umana JP, Argenziano M, et al. Implantable left ventricular assist devices provide an excellent outpatient bridge to transplantation and recovery. J Am Coll Cardiol 1997;30:1773–1777.
155. Ashton RC, Goldstein DJ, Rose EA, Weinberg AD, Levin HR, Oz MC. Duration of left ventricular assist device support affects transplant survival. J Heart Lung Transplant 1996;15:1151–1157.
156. Argenziano M, Choudhri AF, Oz MC, Rose EA, Smith CR, Landry DW. A prospective randomized trial of arginine vasopressin in the treatment of vasodilatory shock after left ventricular assist device placement. Circulation 1997;96 (9 suppl):II-90.
157. Ankersmit H-J, Itescu S. Immunobiology of left ventricular assist devices. In: Goldstein DJ, Oz MC, eds. Cardiac Assist Devices. Futura, Armonk, NY: 2000, pp. 193–211.
158. Morales DL, Catanese KA, Helman DN, et al. Six-year experience of caring for forty-four patients with a left ventricular assist device at home: safe, economical, necessary. J Thorac Cardiovasc Surg 2000;119:251–259.
159. Catanese KA, Goldstein DJ, Williams DL, et al. Outpatient left ventricular assist device support: a destination rather than a bridge. Ann Thorac Surg 1996;62: 646–652.
160. Levin HR, Oz MC, Chen JM, Packer M, Rose EA, Burkhoff D. Reversal of chronic ventricular dilation in patients with end-stage cardiomyopathy by prolonged mechanical unloading. Circulation 1995;91:2717–2720.
161. Frazier OH, Benedict CR, Radovancevic B, et al. Improved left ventricular function after chronic left ventricular unloading. Ann Thorac Surg 1996;62:675–681.
162. Foray A, Williams D, Reemtsma K, Oz M, Mancini D. Assessment of submaximal exercise capacity in patients with left ventricular assist devices. Circulation 1996;94(9 suppl):II222–II226.
163. Mueller J, Wallukat G, Weng Y, et al. Predictive factors for weaning from a cardiac assist device. An analysis of clinical, gene expression, and protein data. J Heart Lung Transplant 2001;20:202.
164. Mancini DM, Beniaminovitz A, Levin H, et al. Low incidence of myocardial recovery after left ventricular assist device implantation in patients with chronic heart failure. Circulation 1998;98:2383–2389.
165. Rose EA, Gelijns AC, Moskowitz AJ, et al. Long-term use of a left ventricular assist device for end-stage heart failure. N Engl J Med 2001;345:1435–1443.
166. Oz MC, Argenziano M, Catanese KA, et al. Bridge experience with long-term implantable left ventricular assist devices. Are they an alternative to transplantation? Circulation 1997;95:1844–1852.

8 Left Ventricular Volume Reduction Surgery for Idiopathic Dilated Cardiomyopathy

Richard Lee, MD, MBA,
Mohammed A. Quader, MD,
Katherine J. Hoercher, RN,
and Patrick M. McCarthy, MD

CONTENTS

INTRODUCTION

In the United States alone, 4.8 million people suffer from congestive heart failure (CHF). Approximately 550,000 new cases of CHF are diagnosed each year *(1)*. As the population ages, the magnitude of this problem is projected to increase *(2)*. After diagnosis, despite improvements in medical management, 5-year mortality is 60% for men and

From: *Contemporary Cardiology: Surgical Management of Congestive Heart Failure*
Edited by: J. C. Fang and G. S. Couper © Humana Press Inc., Totowa, NJ

45% for women *(1)*. There are 150,000 people in the end stage of this disease, and there is a 5-year mortality that approaches 100% despite the use of angiotensin II-converting enzyme inhibitors *(3)*. Approximately half of these patients have heart failure from idiopathic, infectious, or valvular etiologies unrelated to coronary artery disease *(4)*.

Nearly 2500 heart transplants each year offer hope to a fraction of these patients, but the majority are faced with a short, limited life. In an effort to improve symptoms and survival in these patients, several innovative strategies have been attempted. One of the most widely publicized has been left ventricular (LV) volume reduction, the Batista procedure *(5)*. This chapter discusses the theory and technique of the surgery, the early results, the present status, and the future role of ventricular reconstruction in nonischemic, end-stage CHF.

THEORY AND SURGICAL TECHNIQUE

Ventricular reconstruction for ischemic heart disease was performed as early as 1934 by Claude Beck *(6)* and was performed clinically without cardiopulmonary bypass by Charles Bailey in 1957 *(7)*. One year later, Denton Cooley performed the procedure on cardiopulmonary bypass *(8)*. Vincent Dor expanded the indications to include akinetic as well as dyskinetic myocardial segments in 1985 *(9)*. However, it was not until 1994 that Randas Batista popularized the concept of ventricular volume reduction to nonischemic myocardial segments in patients with idiopathic cardiomyopathy, Chagas disease, or valvular disease *(5)*.

Batista's bold move was based on Laplace's law (Wall tension = Pressure × Radius/2 × Wall thickness), where wall stress is a function of chamber diameter. He also observed that muscle mass is proportional to the cube of the radius in animal hearts. He postulated that an increase in the left ventricle diameter would require a compensatory cubic increase in muscle mass to maintain normal LV function. The partial left ventriculectomy attempted to restore the diameter of the left ventricle by excising a portion of the lateral LV wall, usually between the papillary muscles, or with papillary muscle transection and reimplantation (Fig. 1). This would reduce wall stress and decrease the hypertrophic demand placed on the myocardium. The procedure was most commonly accompanied by a mitral valve repair or replacement. Although the concept of the surgical technique was straightforward, the actual application varied widely. In addition, the geometry of the left ventricle led to a variable mass of tissue excised.

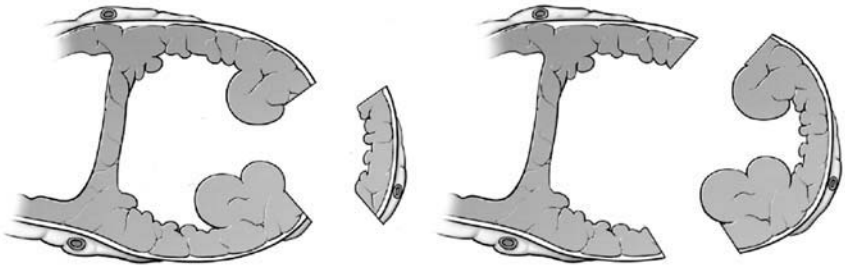


Fig. 1. The partial left ventriculectomy is performed by a wedge-shape excision of myocardium, usually between papillary muscles. However, it often leads to a variable amount of excised myocardium.

EARLY RESULTS

From its inception, the partial left ventriculectomy was plagued by high early mortality. Batista's earliest series in Brazil did not have adequate follow-up to draw any conclusions. However, in 1997, combined results from Brazil and Buffalo General Hospital in New York reported on 120 patients undergoing partial left ventriculectomy *(10)*. The 30-day mortality was 22%, and 2-year survival was 55%. Although all of the patients were in New York Heart Association (NYHA) class IV preoperatively, 57% of the survivors were in NYHA class I, and 33% were in NYHA class II. Unfortunately, only 23 of the 120 patients underwent surgery in Buffalo and had adequate follow-up.

In the same year, McCarthy et al. at the Cleveland Clinic in Ohio reported on 53 patients undergoing partial left ventriculectomy *(11)*. Preoperatively, 60% were in NYHA class IV, and 40% were in NYHA class III. We had only 1 perioperative death (1.9%). However, 15% of our patients required a left ventricular assist device (VAD). With aggressive application of VADs and transplantation, at 11 months actuarial survival was 87%, and freedom from relisting for heart transplantation was 72%. Of the discharged patients, 35% were in NHYA class I, and 32% were in class II.

In 1998, Moreira et al. reported the San Paulo experience in Brazil *(12)*. Left ventriculectomy was performed in 27 patients, 11 in NYHA class III and 16 in NYHA class IV. Hospital mortality was 14.8%, and survival between 6 and 24 months was 59.2%. However, in survivors, NYHA class improved from 3.6 to 1.4. Gradinac had a similar experience in Belgrade with 22 patients *(13)*. The 1-year survival was 68%, but NYHA class improved from 3.8 to 1.4 in those who survived.

Although there were clearly some patients who benefited from the operation, the high early mortality and unpredictable results tempered the initial enthusiasm for the widespread application of this procedure.

In May 2000, the Cleveland Clinic presented its late experience with the partial left ventriculectomy *(14)*. Sixty-two patients underwent partial left ventriculectomy between May 1996 and December 1998. All patients were in NYHA class III (38%) or IV (63%), with 95% transplant candidates. LV end-diastolic diameter (LVEDD) was reduced from 8.4 to 5.9 cm. LV end-diastolic volume (LVED) index was reduced from 133 to 64 mL. Ejection fraction (EF) increased from 16 to 31%. There were only 2 (3.2%) hospital deaths.

Unfortunately, these excellent perioperative results were not durable. Survival was 80% at 1 year and 60% at 3 years. Event-free survival (EFS) was 49% at 1 year and 26% at 3 years. Eleven patients (18%) received left VADs as rescue therapy, and 8 received a heart transplant. Thirty-two patients returned to class IV heart failure. Freedom from class IV was 57% at 1 year and 42% at 3 years. Although there was a small group of patients who appeared to benefit from the operation, we concluded that early and late failures precluded the widespread application of the partial left ventriculectomy. Subsequently, we abandoned the procedure because of the high surgical mortality, concern for diastolic dysfunction, return of heart failure, and occasional postoperative malignant ventricular arrhythmia.

A number of reports helped elucidate some of the reasons that partial left ventriculectomy was unsuccessful. Using mathematical modeling, the group at Columbia found that the geometric rearrangement associated with this operation led to a reduction in wall stress for a given level of pressure generation, thus implying an increase in the efficiency with which wall stress is transduced into intraventricular pressure. However, changes in systolic function were accompanied by offsetting changes in diastolic function; consequently, overall pump function (the Frank-Starling relationship) was depressed *(15)*.

Gorcsan et al. found that partial left ventriculectomy did increase EF and right ventricular ejection by reducing ventricular volumes, but it also resulted in an increase in LV stiffness *(16)*. This may explain why postoperative estimates of LV performance varied with the degree of myocardial fibrosis *(16)*. This may also explain why the effect varied with the preoperative function of the resected segment *(17)*. Artrip et al. found a beneficial effect on this relationship of resecting dyskinetic tissue, an equivocal effect of akinetic scar resection, and a negative effect of removing contracting myocardium *(17)*.

PRESENT STATUS

Despite this information, a few centers persisted with partial left ventriculectomy, especially when transplantation was not a realistic option. An elective international registry reported on 287 patients undergoing partial left ventriculectomy at 48 institutions *(18)*. Several risk factors for EFS, defined by absence of death or ventricular failure that required a VAD or listing for transplantation, were identified. The 1-year EFS was 58% after elective operations, but only 19% after emergent operations. Preoperative NYHA class IV led to a 2-year EFS of 39%. When the preoperative NYHA class was less than IV, EFS was 59% at 2 years. The experience of the center also had a strong impact on outcome. After 20 cases, the 1-year EFS was 69%, as compared to 46% before 20 cases. As few as 5 cases in a single hospital led to a better outcome. Other indicators for a worse outcome included fractional shortening below 5% and duration of preoperative symptoms longer than 9 years. Previous reports have also implicated postoperative mitral regurgitation *(19)* and extent of interstitial fibrosis *(20)* as prognostic indicators.

Suma and members of the RESTORE group reported a series of 82 patients undergoing partial left ventriculectomy for nonischemic cardiomyopathy *(21)*; 40% were in NYHA class III, and 60% were in class IV. During this experience, they changed several aspects of treatment. These included a change to ventriculectomy on-pump on a beating heart, mitral valve replacement via the left ventriculotomy, resection limited to the area between the papillary muscles, and a more targeted resection location based on intraoperative echocardiography. This led to an anterior resection in 12 patients. Overall hospital mortality was 20%, but was only 8% for elective surgeries. When the site was selectively chosen rather than the standard site, hospital mortality decreased from 33 to 15%. The 4-year survival was 53% overall, but 0% for emergencies and 69% for elective procedures. The survivors remain in NYHA class I or II with only 1 patient with a left VAD awaiting transplant.

At the Cleveland Clinic, we recently reviewed our 5-year outcomes from the 62 patients who underwent partial left ventriculectomy between May 1996 and December 1998 *(22)*. Mean follow-up was 3.3 ± 1.9 years. Survival at 1, 2, and 5 years was 82, 78, and 52%, respectively. Survival was similar for patients on preoperative inotropic support: 84, 80, and 56% at 1, 2, and 5 years, respectively. The risk of death consisted of two phases, an early phase that peaked at

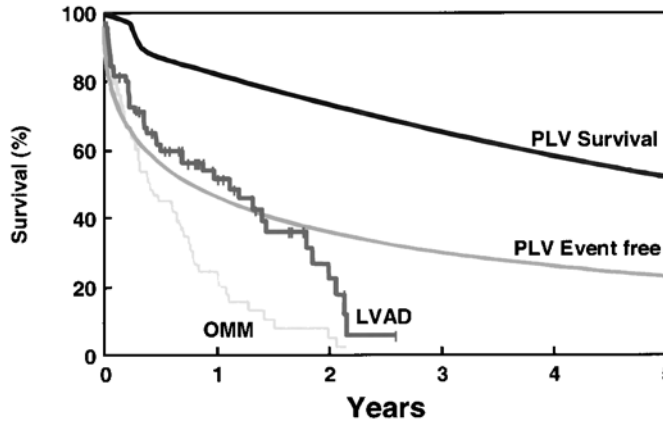


Fig. 2. Comparison of the REMATCH trial results and the Cleveland Clinic results after partial left ventriculectomy (PLV). OMM stands for optimal medical management in the REMATCH trial. LVAD represents the outcome of patients after implantation of a left ventricular device in the REMATCH trial.

4 months and a constant-hazard phase of 11% per year. EFS was 46, 41, and 23% at 1, 2, and 5 years, respectively.

FUTURE ROLE

Although the results of the partial left ventriculectomy have precluded its widespread application, it has shown that certain patients can benefit from ventricular volume reduction, even in nonischemic myocardial disease. To put the results of the partial left ventriculectomy into perspective, we compared them to the results of the Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure (REMATCH) trial (Fig. 2). In patients with similar NYHA classifications, 2-year survival was 23% after left VAD placement in the REMATCH trial. In comparison, at the Cleveland Clinic, 5-year EFS for patients after partial left ventriculectomy was 23%.

Perhaps more important, the partial left ventriculectomy showed that some patients do benefit from LV volume reduction. From lessons learned with dynamic cardiomyoplasty and partial left ventriculectomy, two new devices have been developed either to prevent myocyte overstretch and provide passive LV constraint (Acorn cardiac support device [CSD; ACORN Cardiovascular Inc.]) or reshape the left ventricle altogether without removal of functioning myocardium (Myosplint) *(23)*.

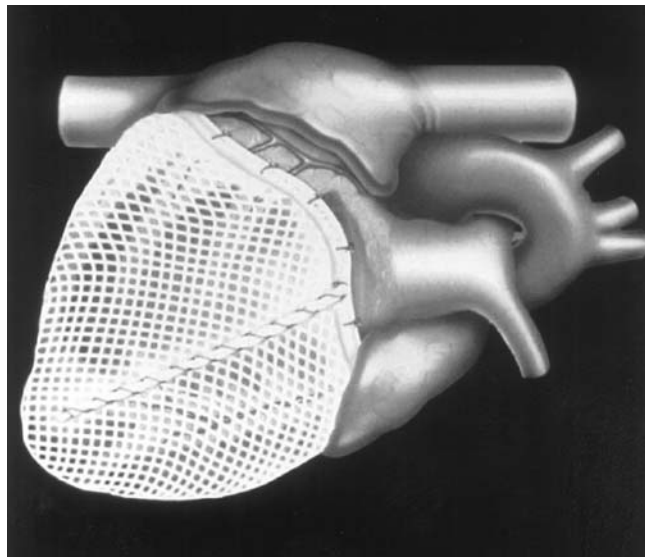


Fig. 3. The Acorn cardiac support device is a custom-made meshlike polyester jacket surgically placed around the ventricles of the heart.

Acorn Cardiac Support Device

The first example of such a device is the Acorn CSD, a custom-made meshlike polyester jacket that is surgically placed around the ventricles of the heart (Fig. 3). Constructed from a compliant woven mesh, it is designed to provide both flexibility and strength. The design of the mesh permits bidirectional compliance of the fabric, which allows it to conform easily to the heart, hence allowing the heart to return to a more normal ellipsoidal shape *(24)*. CSD placement is often performed with concomitant valve repair or coronary artery bypass.

Preclinical studies with CSDs have been reported from two different heart failure models. In an intracoronary microembolization canine heart failure model, Saavedra et al. showed that long-term use of a CSD resulted in decreased end-diastolic and end-systolic volumes and shifted the end-systolic pressure volume relation to the left, compatible with reverse remodeling *(25)*. Chaudrey et al., in a canine heart failure model, showed improved LV diastolic function and chamber sphericity, decreased wall stress, and no evidence of functional mitral regurgitation *(26)*.

In CSD testing on the ovine heart failure model, Power et al. reported similar findings of improved cardiac function, as evidenced

by increased EF, fractional shortening, positive dp/dt, and negative dp/dt *(27)*. Sabbah et al. found downregulation of a stretch-mediated p21 ras and sarcoplasmic reticulum adenosine triphosphatase after wrap placement in the canine model. This suggests that the CSD can alter gene expression and promote reverse remodeling *(28)*.

The effect of CSD on akinetic area development following acute myocardial infarction in an ovine model was investigated. Following a baseline magnetic resonance imaging study after creation of an anterior infarct in 10 sheep, a CSD was placed in 5 sheep, with 5 remaining animals serving as controls. The terminal study done at 2 months postinfarction revealed a significantly diminished area of akinesis in the CSD group, with the relative area of akinesis following a similar pattern *(29)*.

Konertz et al. *(30)* examined the safety and efficacy of the CSD in a series of 27 patients suffering from cardiomyopathy and with a mean NYHA of 2.6 ± 0.1. Of these, 16 received concomitant cardiac surgery, principally mitral valve repair or replacement. The remaining 11 patients received a CSD only. In the CSD-only group, 5 of the 11 patients experienced adverse events, including 2 deaths, during an average follow-up of 12.2 ± 1.1 months, but none of the events were device related. Follow-up at 3 and 6 months reflected a significant improvement from pretreatment in EF (21 to 28 and 33%) and NYHA functional class (2.5 to 1.6 and 1.7), as well as a significant decrease in LVEDD (74 to 68 and 65 mm) and left ventricular end-systolic volume (LVESD) (65 to 62 and 57 mm).

Raman et al. *(31)* reported similar findings in a cohort of five patients undergoing CSD with concomitant coronary artery bypass graft. Midterm outcomes at 12-month follow-up demonstrated a significant decrease in LVEDD and LVESD, with an improvement in LVEF and NYHA functional class *(31)*.

From these early studies, it appears the CSD is useful for preventing further cardiac dilation and improves symptoms of heart failure without device-related morbidity or mortality. A randomized, prospective clinical trial of the CSD is currently under way in Europe, the United States, and Australia.

Myosplint

The Myosplint was designed to change the geometry of the left ventricle to decrease wall stress and improve hemodynamics. The implant consists of two epicardial pads and a transventricular tension member. The two pads are located on the surface of the heart, with the load-bearing tension member passing through the ventricle, connecting the pads and drawing the ventricular walls toward one another. Typically,

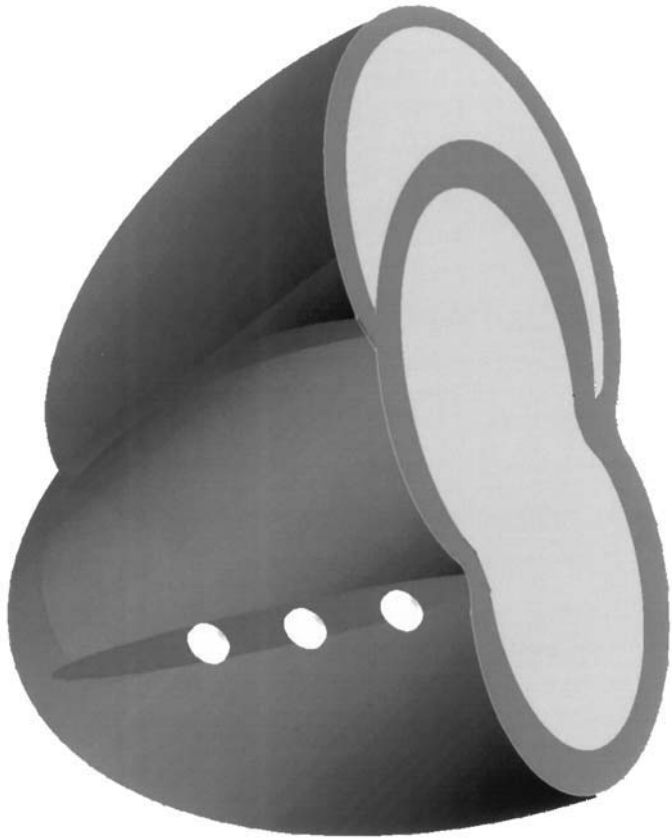


Fig. 4. The Myosplint consists of two epicardial pads and a transventricular tension member. The two pads are located on the surface of the heart with the load-bearing tension member passing through the ventricle connecting the pads and drawing the ventricular walls toward one another. The three Myosplints are tightened to create a bilobular ventricular shape.

three Myosplints are placed on the beating heart, from the lateral left ventricle through the posterior intraventricular septum. The splints are then tightened to create a bilobular shape (Fig. 4).

The Myosplint was initially studied in the canine heart failure model to assess outcomes at 1 month following application. In this trial, heart failure was induced in 15 dogs over a period of 27 days *(32)*. Of these, 7 animals underwent sham surgery, and 8 animals received the Myosplint device. By three-dimensional echocardiographic calculations, LVEF significantly increased from 19% at baseline to 36% acutely and remained at 39% at 1 month after Myosplint

implant. Also, LVEDV and LVESV significantly decreased and were sustained at 1 month. End-systolic wall stress (EDWS) significantly decreased by 39% acutely and by 31% at 1 month. Also, EDWS was significantly reduced by 30% acutely and by 41% at 1 month.

Chronic human studies were first performed in seven patients with dilated cardiomyopathy who were NYHA class III–IV. LVEDD in this group ranged from 72 to 102 mm. Mitral valve regurgitation was mild in three patients and moderate in four cases. Four patients underwent concomitant mitral valve repair at the time of Myosplint implant. At 3-month follow-up, one patient experienced worsening heart failure attributed to unrepaired and significant mitral regurgitation. The remaining six patients showed improvement in symptoms of heart failure, with two of the patients removed from the transplant waiting list. This early experience demonstrated that Myosplint implantation can be safely performed without significant adverse affects; however, these investigators noted that mitral valve repair should be done in any patient undergoing the Myosplint implant *(33)*.

The long-term effect of Myosplint therapy on cardiac function awaits results from a larger, randomized study. The Myosplint is undergoing US Food and Drug Administration feasibility testing, with a total of 40 patients enrolled to date.

CONCLUSION

The Batista procedure was unpredictable, suffered from many early failures, worsened diastolic function, and gave only temporary relief to highly selected patients. However, the Batista "concept" of LV reconstruction for idiopathic dilated cardiomyopathy may prove to be a useful adjunct for selected patients with congestive heart failure if patient selection, surgical techniques, or therapeutic devices can be refined.

REFERENCES

1. Levy D, Kenchaiah S, Larson MG, et al. Long-term trends in the incidence and survival with heart failure. N Engl J Med 2002;347:1397–1402.
2. Loop FD. Coronary artery surgery: the end of the beginning. Eur J Cardiothorac Surg 1998;14:554–571.
3. Swedberg K, Kjekshus J, Snapinn S. Long-term survival in severe heart failure in patients treated with enalapril. Ten year follow-up of CONSENSUS I. Eur Heart J 1999;20:136–139.
4. McMurray JJ, Stewart S. Epidemiology, aetiology and prognosis of heart failure. Heart 2000;83:596–602.
5. Batista RJV, Santos JLV, Takeshita N, et al. Partial left ventriculectomy to improve left ventricular function in end-stage heart disease. J Card Surg 1996;11:96–97.
6. Beck CS. Operation for aneurysm of the heart. Ann Surg 1944;120:34–50.

7. Likoff W, Bailey CP. Ventriculoplasty: excision of myocardial aneurysm. JAMA 1958;915–928.
8. Cooley DA, Collins HA, Morris GC, et al. Ventricular aneurysm after myocardial infarction: surgical excision with the use of cardiopulmonary bypass. JAMA 1958; 167:557.
9. Dor V, Kreitmann P, Jourdan J, et al. Interest of physiological closure (circumferential plasty on contractile areas) of left ventricle after resection and endocardectomy for aneurysm of akinetic zone comparison with classical technique about a series of 209 left ventricular resections. J Cardiovasc Surg 1985;26:73.
10. Batista RJV, Verde J, Nery P, et al. Partial left ventriculectomy to treat end-stage heart disease. Ann Thorac Surg 1997;64:634–638.
11. McCarthy PM, Starling RC, Wong J, et al. Early results with partial left ventriculectomy. J Thorac Cardiovasc Surg 1997;114:755–765.
12. Moreira LF, Stolff NAG, Bocchi EA, et al. Partial left ventriculectomy with mitral valve preservation in the treatment of dilated cardiomyopathy. J Thorac Cardiovasc Surg 1998;115:800–807.
13. Gradinac S, Miric M, Popovic Z, et al. Partial left ventriculectomy for idiopathic dilated cardiomyopathy: early results and 6-month follow-up. Ann Thorac Surg 1998;66:1963–1968.
14. Franco-Cereceda A, McCarthy PM, Blackstone EH, et al. Partial left ventriculectomy for dilated cardiomyopathy: is this an alternative to transplantation? J Thorac Cardiovasc Surg 2001;121:879–893.
15. Dickstein ML, Spotnitz HM, Rose EA, Burkhoff D. Heart reduction surgery: an analysis of the impact on cardiac function. J Thorac Cardiovasc Surg 1997;113: 1032–1040.
16. Gorcsan J 3rd, Feldman AM, Kormos RL, Mandarino WA, Demetris AJ, Batista RJ. Heterogeneous immediate effects of partial left ventriculectomy on cardiac performance. Circulation 1998;97:839–842.
17. Artrip JH, Oz MC, Burhoff D. Left ventricular volume reduction surgery for heart failure: a physiologic perspective. J Thorac Cardiovasc Surg 2001;122:775–782.
18. Kawaguchi AT, Suma H, Konertz W, et al. Partial left ventriculectomy: the Second International Registry Report 2000. J Card Surg 2001;16:10–23.
19. Bhat G, Dowling RD. Evaluation of predictors of clinical outcome after partial left ventriculectomy. Ann Thorac Surg 2001;72:91–95.
20. Kawaguchi AT, Bergsland J, Ishibashi-Ueda H, et al. Partial left ventriculectomy in patients with dilated failing ventricle. J Card Surg 1998;13:335–342
21. Suma H, the RESTORE group. Left ventriculoplasty for nonischemic dilated cardiomyopathy. Semin Thorac Cardiovasc Surg 2001;13:514–521.
22. Hoercher KJ, Starling RC, McCarthy PM, Blackstone EH, Young JB. Partial left ventriculectomy: lessons learned and future implications for surgical trials. Circulation 2002;106:II-418.
23. Kaplon R, Lombardi P. Passive constraint and new shape-change devices for heart failure. Semin Thorac Cardiovasc Surg 2002;14:150–156.
24. Oz MC. Passive ventricular constraint for the treatment of congestive heart failure. Ann Thorac Surg 2001;71:S185–S187.
25. Saavedra FW, Tunn R, Mishima T, et al. Reverse remodeling and enhanced adrenergic reserve from a passive external ventricular support in experimental dilated heart failure. Circulation 2000;102(suppl II):II-501.
26. Chaudry PA, Mishima T, Sharov VG, et al. Passive epicardial containment prevents ventricular remodeling in heart failure. Ann Thorac Surg 2000;70: 1275–1280.

27. Power J, Raman J, Byrne M. Passive ventricular constraint is a trigger for a significant degree of reverse remodeling in an experimental model of degenerative heart failure and dilated cardiomyopathy. Circulation 2000;102(suppl II):II-502.
28. Sabbah HN, Gupta RC, Sharov VG, et al. Prevention of progressive left ventricular dilation with the Acorn cardiac support device (CSD) down regulates stretch-mediated P21ras, attenuates myocardial hypertrophy, and improves sarcoplasmic reticulum calcium cycling in dogs with heart failure. Circulation 2000;102 (suppl II):II-683.
29. Pilla JJ, Blom AS, Brockman DJ, et al. Ventricular constraint using the Acorn cardiac support device reduces myocardial akinetic area in an ovine model of acute infarction. Circulation 2002;106(12 suppl 1):I207–I211.
30. Konertz WF, Shapland JE, Hotz H, et al. Passive containment and reverse remodeling by a novel textile cardiac support device. Circulation 2001;104:I-270–I-275.
31. Raman JS, Hata M, Storere JM, et al. The mid-term results of ventricular containment (Acorn Wrap) for end stage ischemic cardiomyopathy. Ann Thorac Cardiovasc Surg 2001;5:278–281.
32. McCarthy PM, Takagaki M, Ochiai Y, et al. Device-based change in left ventricular shape: a new concept for the treatment of dilated cardiomyopathy. J Thorac Cardiovasc Surg 2001;122:482–490.
33. Schenk S, Reichenspurner H, Boehm DH, et al. Myosplint implant and shape-change procedure: intra- and peri-operative safety and feasibility. J Heart Lung Transplant 2002;21:680–686.

9 Surgical Management of Hypertrophic Cardiomyopathy

William G. Williams, MD,
E. Douglas Wigle, MD,
Harry Rakowski, MD,
Anthony C. Ralph-Edwards, MD,
and Leonard Schwartz, MD

CONTENTS

DEFINITIONS

Hypertrophic cardiomyopathy (HCM) is a genetic disorder characterized by ventricular hypertrophy in the absence of an identifiable cause for the hypertrophy *(1–4)*. The hypertrophy is usually asymmetric and involves the interventricular septum in 90% of patients. Most commonly, the outflow septum (i.e., subaortic area) is the major focus

From: *Contemporary Cardiology: Surgical Management of Congestive Heart Failure*
Edited by: J. C. Fang and G. S. Couper © Humana Press Inc., Totowa, NJ

of hypertrophy, but the midventricular or apical septum may occur in isolation or concomitantly. Rarely (5%) the right ventricle is involved. The extent of the hypertrophy varies tremendously and accounts for different manifestations of the disease *(1–5)*. The hypertrophy is associated with myocardial fiber disarray on microscopy.

The disorder is an inherited autosomal dominant mutation or arises by spontaneous mutation. HCM is a heterogeneous disorder of the sarcomere, and to date 10 genes and more than 200 mutations have been described affecting β-myosin heavy chain, cardiac myosin-binding protein C, cardiac troponin T, troponin I, α-tropomyosin, regulatory myosin light chains, actin, and titin *(4,6,7)*. Although not practical as yet, genetic screening may provide better detection and outcome prediction. The troponin T and some β-myosin heavy-chain mutations have been associated with a poor outcome.

PREVALENCE

Within the general population, HCM may affect as many as 1 per 500 individuals and represents about one-quarter the prevalence of all forms of congenital heart disease *(3,4,7)*. However, many individuals with HCM are asymptomatic and may remain so indefinitely.

CLASSIFICATION OF HCM

The clinical manifestations of HCM are varied and dependent on the extent and location of the hypertrophy and the secondary effects of the hypertrophy *(8)*. Based on hemodynamic criteria, patients may have either an obstructive or nonobstructive form of the disease (Table 1). The obstruction may occur at rest, with provocation (latent), or intermittently (labile). The degree of obstruction varies directly with the inotropic state of the heart and inversely with the systemic vascular resistance and preload.

CLINICAL PRESENTATION

The clinical manifestations of HCM are extremely varied. Many patients are asymptomatic *(3–5,9)*. Symptoms in children are very uncommon, although they are not immune to sudden death *(10,11)*. Symptoms may first develop during adolescence, possibly because of an accelerated growth of myocardial hypertrophy. Most patients become symptomatic in their fourth or fifth decade. Because of the dynamic nature of the obstructive form of HCM, symptoms will vary in intensity from day to day, depending on normal variation in periph-

Table 1
Hemodynamic Characteristics of Hypertrophic Cardiomyopathy

Nonobstructive HCM
Abnormal diastolic function
Impaired relaxation and impaired compliance
Normal or supernormal systolic function
Impaired systolic (end-stage) systolic function secondary to myocardial fibrosis
Obstructive HCM
Subaortic obstruction
Midventricular obstruction
Apical obstruction

eral vascular resistance. The most common presenting symptoms are dyspnea and fatigue; angina; palpitations; and presyncope, syncope, and sudden death.

Dyspnea and Fatigue

Dyspnea and fatigue are the most common symptoms and may be caused by poor diastolic filling of the left ventricle, from reduced compliance secondary to the hypertrophy or to impaired diastolic relaxation. With increased myocardial fibrosis late in the course of the disease, the ventricle may dilate, and compliance may further deteriorate.

In patients with obstruction, the associated mitral valve insufficiency (*see* Physiology of Obstructive HCM section) increases left atrial (LA) pressure, which results in exercise intolerance, dyspnea, fatigue, and atrial arrhythmias.

Angina

Extensive hypertrophy may result in inadequate blood supply to the endocardium. Concomitant arteriosclerosis of the coronary arteries will lead to regional ischemia, with the hypertrophied area at increased risk. In about 5% of patients with HCM, one or more of the coronary arteries may have an intramyocardial course. The intramyocardial segment is compressed by the surrounding muscle contraction during each systole. The systolic obstruction affects the diastolic flow pattern and has been linked to angina as well as an increased risk of sudden death *(10,11)*.

Palpitations

Poor diastolic function of the left ventricle and the presence of mitral regurgitation will lead to atrial dilation and the onset of supraventricular arrhythmias. Patients with a LA diameter greater than

50 mm are at increased risk of atrial fibrillation (AF). The onset of supraventricular arrhythmias usually precipitates a marked increase in symptoms. The onset of AF also increases the risk of stroke.

Ventricular arrhythmias may occur with HCM and are an ominous sign of increased risk of sudden death *(12–17)*. The mechanism of ventricular arrhythmias is not completely understood, but precipitating factors include the marginal blood supply, myocardial fibrosis, and in some patients, an intramyocardial coronary artery.

Presyncope, Syncope, and Sudden Death

The cause of syncope in these patients may be outflow obstruction, vasovagal reflexes, or arrhythmias, including ventricular tachycardia (VT) or fibrillation (VF). A history of sudden death is not uncommon among patients with HCM and among their families. Syncope is a risk factor for sudden death, and the septal thickness has been correlated with the risk of sudden death *(12,18)*. Brief periods of VT may not be associated with an increased risk of sudden death *(16)*.

HCM accounts for about one-third of sudden deaths among young athletes *(4)*. The outcome of 16 patients with HCM who were resuscitated from VT or VF demonstrated that they are at increased risk of further fatal arrhythmia *(19)*.

PHYSIOLOGY OF OBSTRUCTIVE HCM

Patients with asymmetric septal hypertrophy develop left ventricular (LV) outlet obstruction at the apex, the midventricle, or most commonly in the subaortic area *(1,8,20)*. In the most common variant of subaortic stenosis, the thickened septal wall protrudes into the left ventricular outflow tract (LVOT) just caudal to the aortic valve and opposite the mitral valve annulus and anterior mitral leaflet *(21)*. The thickened septum narrows the subaortic outflow. To maintain a normal cardiac output, the left ventricle must contract more vigorously to force blood through the diminishing diameter of the subaortic channel. Consequently, there is flow acceleration in the subaortic outflow tract, and a pressure gradient develops between the body of the left ventricle and the aorta. The left ventricle responds to this increased systolic pressure demand by hypertrophy, and the hypertrophy occurs in the body of the left ventricle as well as in the septum. Therefore, a vicious circle occurs consisting of the hypertrophied septum obstructing the outflow tract, causing increased LV work and subsequent hypertrophy, which aggravates the outflow obstruction further.

The flow acceleration in the subaortic outflow tract affects the mitral valve and left atrium *(22)*. The mitral valve leaflet, usually the anterior one, is "lifted" by the venturi forces of flow acceleration toward the ventricular septum in midsystole, much as the airflow over an airplane wing lifts the airplane into the air *(23)*. The anterior mitral valve leaflet displacement into the outflow tract is referred to as *systolic anterior motion* (SAM). Because the leaflet of the valve is displaced toward the septum during systole, it prevents normal coaptation and results in mitral regurgitation. The regurgitant jet is typically posteriorly directed and occurs late in systole. The degree of regurgitation is affected by the severity of the obstruction: Factors that increase contractility or decrease peripheral resistance will increase the severity of mitral regurgitation. Although the regurgitation is typically posteriorly directed, intrinsic valve anomalies, such as leaflet prolapse, may cause centrally or anteriorly directed jets of regurgitation.

It is very important to recognize that the regurgitation associated with subaortic obstruction occurs after SAM–septal contact and will therefore resolve when the outlet obstruction is relieved. In contrast, mitral regurgitation that occurs prior to SAM–septal contact is unrelated to the obstruction and will persist after relief of the obstruction. Many patients will have regurgitation because of a combination of intrinsic valve anomalies and SAM.

TREATMENT FOR HCM

Medical Treatment

Many patients remain asymptomatic or have mild symptoms and therefore do not require treatment. They should, however, be assessed for the risk of sudden death. Patients who are symptomatic because of nonobstructive HCM are managed medically with drugs that improve compliance, such as β-blockers, which slow the heart rate and improve ventricular filling. Calcium channel blockers improve diastolic relaxation and may improve filling as well. The combination of β-blockers and verapamil should be used cautiously because the combination may produce excessive atrioventricular (AV) nodal block. Some have also advocated the use of the sodium channel blocker disopyramide because of its negative inotropic effects. However, its routine use is often limited by excessive anticholinergic side effects.

Antiarrhythmic drugs may be indicated for patients at risk of AF or of sudden death. Amiodarone is most commonly used, and its efficacy has been supported by McKenna and others *(24,25)*. However, a com-

parison of antiarrhythmics vs implantable defibrillators for patients with HCM who have been resuscitated following near-fatal ventricular arrhythmias suggested that the defibrillators may be more effective *(26)*.

Anticoagulants should be considered for patients with AF as they are at risk of stroke.

Implantable Defibrillators

Patients with HCM and resuscitation from sudden death, documented VT, or a strong family history of sudden death should be considered for an implantable cardioverter defibrillator (ICD). In a multicenter study of 128 patients with ICDs, Maron et al. reported appropriate defibrillator discharges at a rate of 7% per year *(26)*. However, a similar proportion of patients had inappropriate ICD discharges.

Pacemakers

Patients with HCM may require permanent pacing for control of atrial or ventricular arrhythmias. Furthermore, patients with the obstructive form of HCM may benefit from dual-chamber pacing in other ways, as first reported by McDonald et al. *(27)*. The mechanisms by which pacing may improve symptoms are not clear, but various hypotheses have been proposed and include the induction of paradoxical septal motion through asynchronous depolarization, a negative inotropic effect, a reduction in mitral valve SAM, an increase in end-systolic volume, and altered myocardial perfusion. However, the clinical benefit of pacing in HCM is controversial. A prospective randomized double-blind crossover trial recommended that pacing not be used as primary therapy *(28)*. Pacing was associated with some symptomatic improvement and a modest reduction in outflow tract gradient of 40%, but objective exercise testing demonstrated no benefit, and there was no change in LV wall thickness on echocardiographic follow-up. The authors did concede that the elderly patient (>65 years) may benefit from atrioventricular pacing.

Heart Transplantation

It has been estimated that approx 5 to 10% of patients with HCM may reach a terminal end stage with dilated cardiomyopathy *(1–4)*. Thinning of the ventricular walls precedes this stage and leads to markedly dilated atrial and ventricular chambers. Transplantation is the only effective therapy at this stage.

Surgical Myectomy

Patients who are symptomatic with the obstructive form of HCM will benefit from subaortic myectomy *(29–33)*. The usual indications

for surgery are medically refractory symptoms or intolerance of effective medications. Some centers would also consider high-risk groups (young patient with a very thick septum or a strong family history of sudden death) as an indication as well. When genetic mapping becomes practical, it may help triage the high-risk groups toward a surgical myectomy.

Preoperative Assessment

A careful clinical history and family history are important in assessing risk with and without surgery. Identification of concomitant disease is important because such problems, or the necessity to manage associated pathology surgically, may affect the patient's risk.

The echocardiogram is essential is assessing both the extent and the severity of the hypertrophy and in clarifying the status of the mitral valve *(22,23,34)*. Although this information should be available and reviewed before surgical consultation, a transesophageal echocardiography (TEE) assessment is essential intraoperatively, both before and after the myectomy *(34)*.

In adults suitable for myectomy, the interventricular septum thickness should be greater than 17 mm and may be considerably thicker. The echo measurement is useful in gaging the depth of resection required. The length of the hypertrophied septum is measured to determine the length of the excision. Associated midventricular obstruction, which can be masked by upper septal outflow obstruction, requires a longer resection to a level below the head of the papillary muscles.

The mitral valve should be assessed for the quantity, direction, and timing of regurgitation. Mitral regurgitation secondary to dynamic obstruction occurs after the SAM–septal contact and is typically posteriorly directed. Alterations in this pattern do exist and usually resolve following successful myectomy, but regurgitation unrelated to obstruction may require mitral valve repair or replacement.

Because of the association of coronary artery myocardial bridges with HCM and the potential association with sudden death, every patient considered for surgery should have a coronary angiogram to document the presence or absence of both coronary artery disease and these myocardial bridges.

Operative Technique of Myectomy

Myectomy is performed during cardiopulmonary bypass with single right atrial cannulation and LA venting of the LV. Mild hypothermia is used during bypass, but we avoid cooling until after the myocardium is arrested with blood cardioplegia at normal temperature. Once the cardioplegia arrests the heart at normothermia, the cardioplegia is cooled

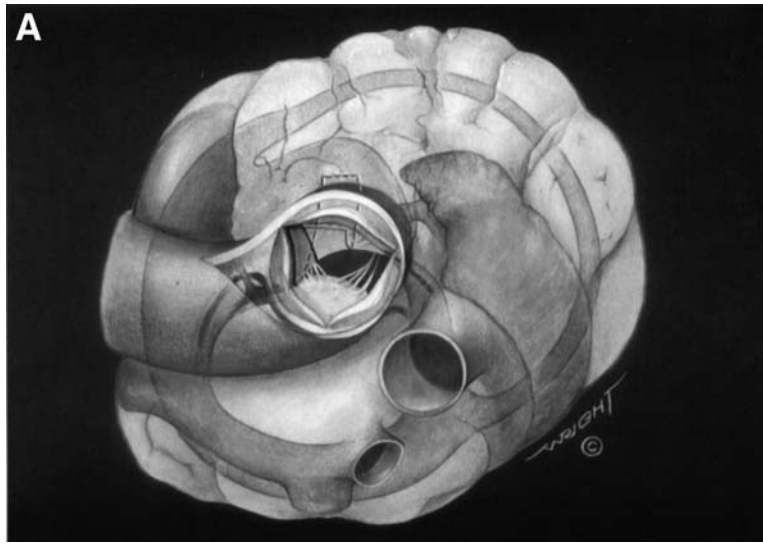


Fig. 1. (A) A surgeon's view of the heart from the patient's right side, looking toward the apex. The ascending aorta is shown open through an oblique aortotomy, exposing the trileaflet aortic valve. The protruding septum narrows the outflow tract opposite the mitral valve. The stippling indicates the thickness of the ventricular septum. The three incisions to complete the myectomy are illustrated and described in the text.

and continued until the myocardium reaches 15°C, generally requiring about 1500 cc. Cooling the beating perfused heart is dangerous because the hypertrophied heart may fibrillate, and cardioplegic perfusion may not be distributed evenly, which leads to poor diastolic relaxation and difficulty in defibrillation following reperfusion. With warm induction cardioplegia, the heart usually recovers spontaneously with reperfusion, with or without terminal warm cardioplegia.

The septal resection is done through an oblique aortotomy extending to, but not across, the sino-tubular junction. Before the myectomy, the outflow tract and mitral and aortic valves should be carefully examined and the septal thickness and length of hypertrophy palpated to confirm the echo findings. Transmural palpation of the free LV wall apex to the septum is a good guide regarding what the septal thickness should be following resection.

The excision requires three incisions into the septum (Fig. 1A). The initial septal subaortic incision is made with a no. 11 scalpel blade and starts 2 mm below the right cusp of the aortic valve and 2 to 3 mm to the right of its nadir. If this incision is started too far to the right, it may

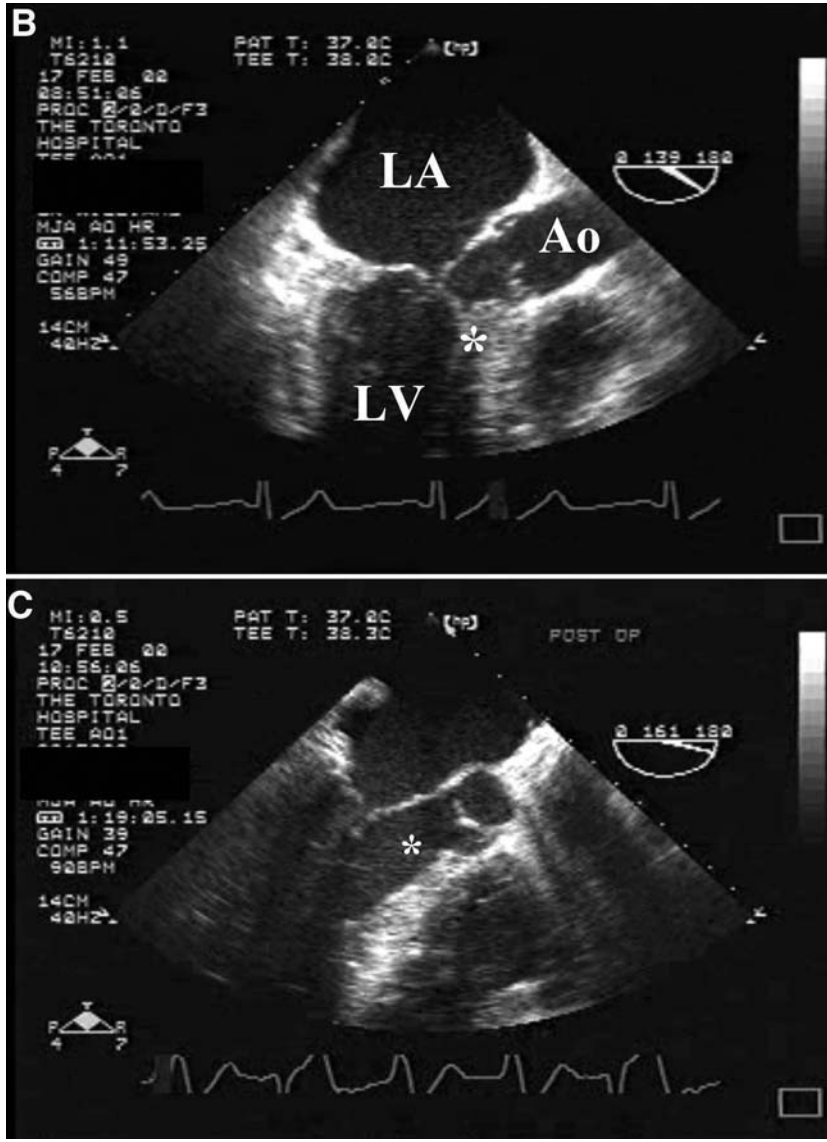


Fig. 1. (B) The systolic anterior motion (SAM) of the mitral valve results in contact of the leaflets with the ventricular septum. The SAM-septal contact obstructs the left ventricular outlet (*) and prevents complete coaptation of the mitral leaflets that results in posteriorly directed mitral regurgitation. **(C)** After successful myectomy, the mitral leaflets close in a normal plane, regurgitation is eliminated, and the left ventricular outlet (*) is no longer obstructed. LA, left atrium; Ao, aorta; LV, left ventricle; * left ventricular outlet.

damage the His bundle. If the hypertrophy is unusually prominent on the right side of the outflow tract, the initial incision may be made further to the right but lower (10 mm from the aortic valve) in the septum and slanted to the left as it extends upward toward the aortic annulus. The depth of this initial incision depends on the estimate, by echo and palpation, of the septal thickness. The depth should leave a residual septal thickness of 8 mm, similar to the LV free wall below the septum. The direction of the initial incision is toward the apex. For right-handed surgeons, the tendency is to direct the incision too far to the left of the apex. To avoid this, the incision can be made with the left hand. The length of the initial incision depends on the extent of the hypertrophy, but generally is 35 to 50 mm long in the adult. For patients with midventricular obstruction, the incision should extend at least to the level of the anteroseptal papillary muscle head. Transmural palpation of the incision is used to judge the adequacy of both its depth and its length.

The second incision is made parallel to the first and 2 mm anterior to the mitral valve insertion. The septum is narrower here than on the right, so the second incision is not as long. Its depth is again determined by palpation, leaving a residual septal thickness of 8 mm.

The third incision is made 2 mm below the aortic annulus and parallel to it. It extends from the proximal extent of the first incision to the proximal extent of the second. The depth of this incision is only 2 mm because a deeper incision would become too shallow. Once the septum is exposed with this incision, it allows a second cut, also 2 mm deep, in a more anterior direction. A third 2-mm incision may be required to establish the depth of the resection, guided by transmural palpation and the depth of the first and second incisions. The purpose of the superficial incisions 2 mm deep is somewhat analogous to a series of short straight lines, each at an angle to one another, creating a circle.

Once the appropriate depth of the third incision is established, the block of muscle to be excised is dissected distally toward the apex, confirming by repeated palpation that the direction and residual septal depth are leaving a residual septal thickness of 5 to 8 mm. Under the right-left aortic commissure, the top of the resection is an acute angle because of the convergence of the annulus. As the dissection continues caudally, the resection more distally under the commissure must be rounded to avoid perforating the septum below the pulmonary valve. On palpation of the residual septum, there should be no difference in thickness compared to the free LV wall below the septum.

The area of the specimen resected should be approximately the area of the aortic valve. On average, the resection measures 25 mm wide, 45 mm long, and 15 mm deep.

Before closing the aortic incision, the mitral and aortic valves are inspected for inadvertent damage. The LV cavity is irrigated to remove any loose pieces of muscle, and the bed of the resection is checked for muscle fragments.

Intraoperative Postmyectomy TEE

Once off bypass, the adequacy of the myectomy is checked by TEE *(22,23,34)*. The outflow tract should be a normal diameter, and the mitral valve SAM should be absent, allowing the mitral valve to close in a normal plane of apposition (Fig. 1B,C). On Doppler interrogation, the mitral regurgitation should be considerably less or absent, and the LV outflow gradient should be less than 10 mmHg, with minimal or no increase in gradient after an induced extrasystole. It is not uncommon for some chordal SAM to persist. Color flow Doppler should rule out a ventricular septal perforation and usually identifies divided septal perforators in the base of the resection.

Because the plane of the echo lies at a 30° angle to the plane of the myectomy, the medial wall of the resection appears on TEE as a prominent right-angled divot. Within 1 week of myectomy, this edge of the myectomy atrophies, thereby increasing the outlet diameter.

Unroofing Coronary Artery Myocardial Bridges

An intramyocardial course of a coronary artery, usually the left anterior descending, may be associated with sudden death, even in patients with HCM without obstruction *(10,11)*. Systolic compression of the coronary may be impressive. Among our surgical patients with obstructive HCM, 26 of 333 (7.8%) had a myocardial bridge. Whether unroofing these bridges decreases the risk of death is unknown, but we attempt to unroof the bridge if a myectomy is performed.

The coronary artery distal to the tunnel is identified, and its superficial (anterior) surface is exposed by sharp dissection. The sharp dissection is then extended proximally by staying along the plane of the artery until it reemerges onto the epicardial surface. The divided myocardium over the artery is usually 3 to 5 mm thick. Unfortunately, the course of the artery may be so deep that trabeculations of the right ventricular cavity are entered. In this situation, after the myocardial bridge has been divided, the opening into the ventricle is repaired by pledgeted sutures placed deep to the coronary.

Postoperative Management

Postmyectomy patients are managed very similar to most cardiac patients and benefit from an early extubation protocol *(35)*. They

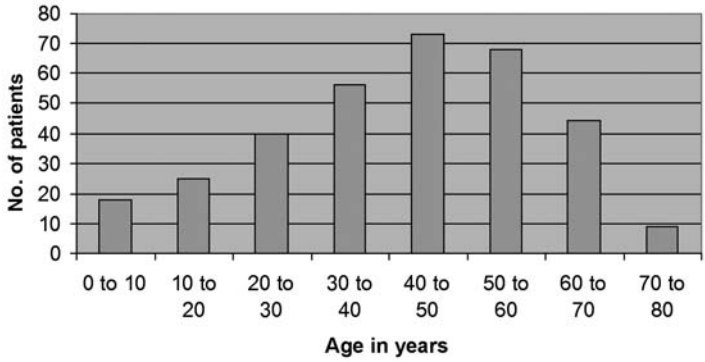


Fig. 2. The histogram illustrates the age range at myectomy by decade. Median age is 44.2 years.

seldom need either inotropic or afterload-reducing drugs. Patients with HCM have increased myocardial contractility and require an adequate preload. They seldom need inotropic support or afterload reduction, and both are generally contraindicated in patients with obstruction.

Postoperative AV block is uncommon (1%). However, all patients should have temporary atrial and ventricular pacing wires placed at the time of surgery with backup ventricular demand pacing capacity. It is not uncommon for postmyectomy patients to require temporary AV pacing for a few hours. Most patients develop left bundle branch block (BBB); therefore, those with preoperative right BBB are at high risk of developing postoperative complete AV block. Overall, about 4 to 5% postmyectomy patients need permanent pacing.

Atrial arrhythmias, typically AF, are not uncommon a few days after myectomy. We routinely use sotalol to prevent or control AF.

Surgical Results of Myectomy

Since 1972, we have operated on 333 patients with HCM. The median age at surgery was 44.2 years, with the range 0.2 to 76.4 years (Fig. 2). Men comprised 60.4% of this series. Thirty-eight patients were children (<18 years). Most patients were symptomatic prior to myectomy; the majority (58%) were New York Heart Association (NYHA) class III (Fig. 3). Some younger children with high gradients and very thick septa were operated on in the absence of symptoms. Lesions in addition to HCM were present in 129 (39%) of patients (Table 2). A previous myectomy had been performed in 23 patients. Three of the previous operations were done by an author of this chapter and 20 by other surgeons.

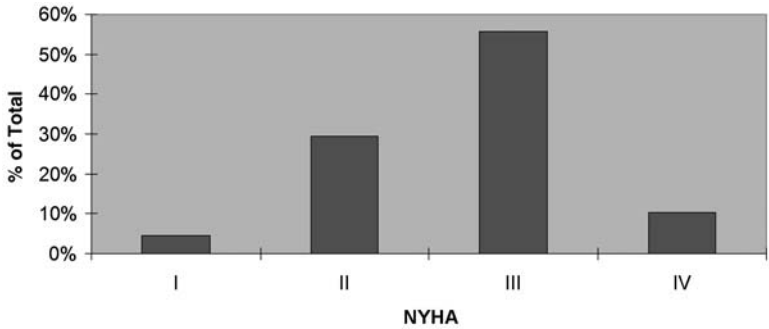


Fig. 3. Preoperative New York Heart Association class.

Table 2
Concomitant Pathology at Time of Surgery

Associated pathology	*n*	*%*
None	204	61
Coronary artery	30	9
Mitral disease	29	8
Coronary muscle bridge	26	8
Other	20	6
Midventricular stenosis	15	4
Aortic disease	11	3
RVOTO	8	2
	343*	

*Some patients had more than one associated problem.

There were 6 early deaths (1.8%), and during a follow-up period of 6.7 years (median 5.4, range 0 to 24.4 years), there have been 37 late deaths (Fig. 4). Survival 10 years postmyectomy is estimated as 82% (–3%). Survival is better among the 243 patients who did not require concomitant procedures at the time of myectomy: 86 vs 68% at 10 years after myectomy (Fig. 5).

Older age at myectomy, poorer preoperative NYHA class (Fig. 6), and coronary artery disease appear to be associated with an increased risk of early or late mortality (Table 3). Unroofing of a myocardial coronary artery bridge was not associated with early or late mortality, and there were no deaths among the 6 patients in whom a known myocardial bridge was not unroofed. Permanent pacing, either pre-myectomy (n = 14) or postmyectomy (n = 24), did not affect overall mortality. Early postoperative complications occurred in 16% of patients,

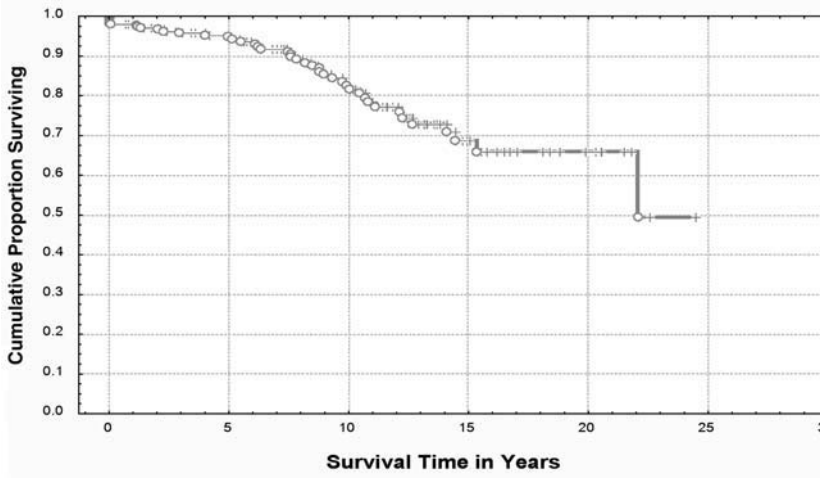


Fig. 4. The Kaplan-Meier plot shows the survival after myectomy for 333 patients with obstructive hypertrophic cardiomyopathy. Survival at 10 years is 82%.

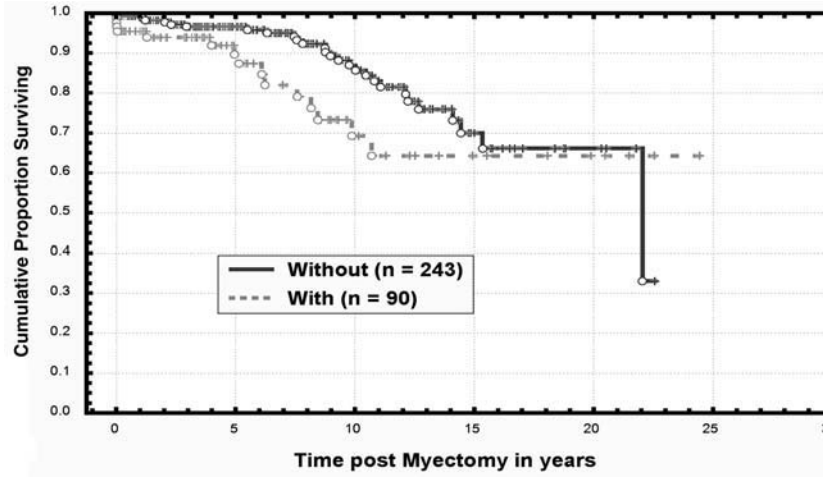


Fig. 5. Survival among patients with concomitant procedures at myectomy was less favorable than those having a myectomy alone.

the most important of which were strokes in 7 patients, 1 of whom had permanent, severe long-term damage.

Symptomatic improvement after myectomy is impressive, with 95% of patients becoming NYHA class I at the most recent follow-up (Fig. 7). Symptomatic improvement persists in most patients.

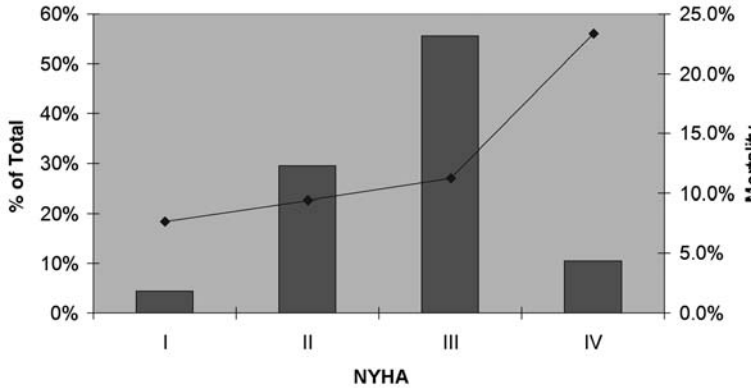


Fig. 6. The total mortality, early and late, is higher among the patients with class IV symptoms prior to myectomy.

Table 3
Risk Factors for Death

	N	*Early death*	*Late death*	*Total mortality (%)*	*Mortality without (%)*
Coronary artery bypass	30	3	7	33.3	10.9
Age >70 years	9	1	3	44.4	12.0
Mitral valve surgery	13	2	2	30.8	12.2
NYHA class IV	30	3	4	23.3	11.9
Previous myectomy	23	0	6	26.1	11.9
Myocardial bridge unroofing	20	0	0	0.0	13.7
Permanent pacemaker	46	1	7	17.4	12.2

Note: The rightmost column indicates the mortality for all patients without the risk factor in the first column.

Reoperation has been required in only 10 patients, including 3 for recurrent (more likely persistent) outlet obstruction, and one for mid-ventricular obstruction. The median time to reoperation was 3.2 years (range 0 to 19 years). The indications for reoperation are shown in Table 4. The probability of reoperation (n = 10) is illustrated by the Kaplan–Meier plot in Fig. 8. Freedom from reoperation is 96 ± 1.5% at 10 years after myectomy.

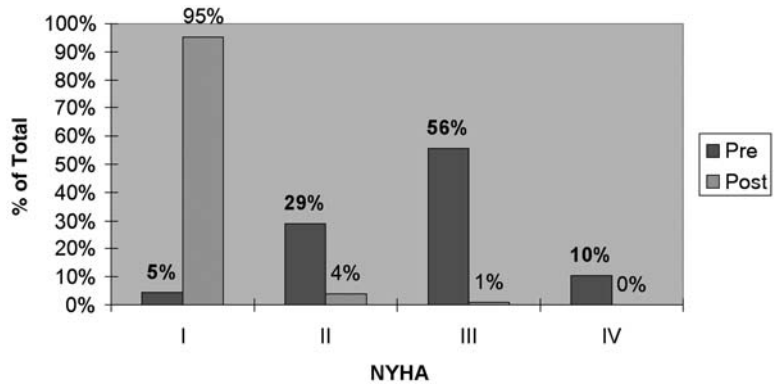


Fig. 7. Symptomatic improvement following myectomy for patients with the obstructive form of hypertrophic cardiomyopathy is impressive, with 95% becoming class I.

Table 4
Indications for Reoperation

	N
Myectomy	3
Heart transplant	2
LV-Ao conduit	1
Mid-ventricular stenosis	1
Mitral valve replacement/maze	1
Aortic valve replacement for SBE	1
Ventricular septal defect and atrial lead recall	1
Total	10

Septal Alcohol Ablation

In 1994, Sigwart introduced a catheter-based treatment for reducing the LVOT obstruction for patients with HCM *(36)*. This was based on the observation that the first septal perforating branch of the left anterior descending artery supplied the area of the intraventricular septum contributing to the production of the LVOT gradient. Sigwart, using standard coronary angioplasty technique, found that temporary occlusion of this branch (up to 30 minutes) resulted in a remarkable decrease in the outflow gradient, with reappearance of the gradient with balloon deflation.

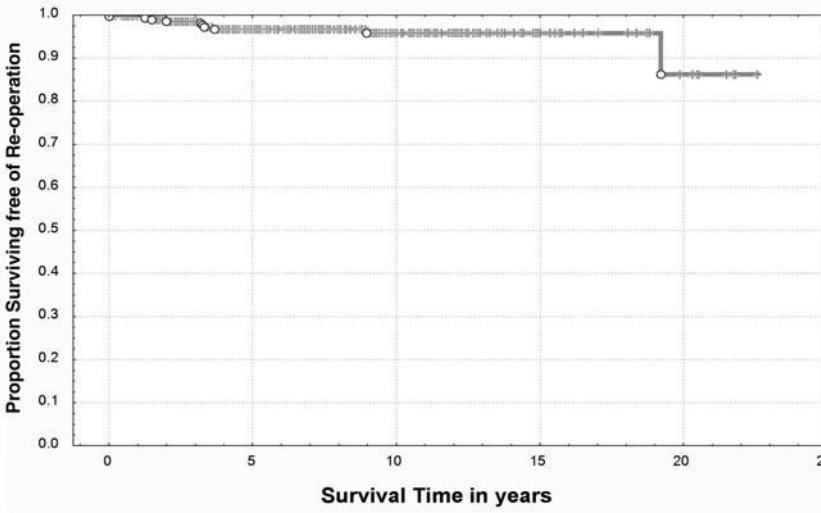


Fig. 8. Only 4% (n = 10) of patients required reoperation after myectomy. Among these, only three patients had recurrent outlet obstruction.

To produce a permanent result, he exploited the intraarterial chemical ablation properties of ethyl alcohol *(36)*. The hyperosmolality of ethanol results in acute dehydration of the endothelial cells, with desquamation and occlusion of the injected artery. The rapidity of the toxicity exceeds even that of an acute vascular occlusion, suggesting a direct parenchymal tissue effect as well. The resultant myocardial infarction and scar are extremely well defined histologically in experimental studies and on magnetic resonance imaging in humans. Sigwart slowly injected 3 mL of 95% ethanol through the inflated balloon into the septal branch and deflated the balloon after 5 minutes. The pressure gradient was abolished immediately and did not reappear. In a minority of patients, the proximal septum is supplied by a number of small septal branches rather than by one large branch, and he found that on occasion it was necessary to ablate more than one. The major risk of the procedure is the appearance of conduction abnormalities. In our experience, about 60% develop a right BBB, and in about 10% of cases, complete heart block occurs requiring a permanent pacemaker.

The most important addition to the technique was the introduction of myocardial contrast echocardiography by Faber et al. *(37)*. This involves the forceful bolus injection of 1 mL contrast echo agent through the inflated balloon lumen with on-line continuous echocardiography. This "lights up" the myocardium supplied by the branch, per-

mitting the accurate and specific demarcation of its vascular supply. If this includes the region of SAM–septal contact and no other important other area of supply is identified (such as posterior wall or papillary muscles), then this branch is ablated. The introduction of myocardial contrast echocardiography has reduced the number of branches ablated and resulted in smaller infarct by creatinine kinase measurement, and the need for long-term pacing has become less common. Other complications are rare. Concern regarding the short- and long-term appearance of serious ventricular arrhythmias has not materialized. There have been no documented cases of ventricular septal defects.

The mechanism of relief of the gradient with septal alcohol ablation is complex and temporal *(38)*. It is not unusual for the gradient to disappear completely during the procedure only to reappear in the next few days postprocedure. The immediate effect appears to be because of global changes of LV ejection. There is immediate basal septal dysfunction (hypo- or akinesis) with no change in the mitral valve motion, with the anterior leaflet continuing to move toward the septum. Peak acceleration rate just proximal to the LVOT obstruction is significantly lower, and conduction abnormalities such as the right BBB and the resultant dyssynchrony in LV contraction reduces the acceleration rate even more. The partial reappearance of the gradient early on is almost always temporary, with gradual reduction of the gradient over the succeeding weeks to an average resting value of 9 mmHg at 8 weeks (from 60 mmHg preprocedure) and to an average provocable gradient of 32 mmHg (from 114 mmHg preprocedure).

By 1 year, the average resting gradient is 4 mmHg, and the provocable gradient is 32 mmHg. One group found complete elimination of the LVOT gradient in 67% of patients *(39)*. Regression of LV hypertrophy is present at 1 year and continues for at least 2 years, with LV mass decreasing from a baseline of 301–78 g to 223–5 g at 1 year and 190–58 g at 2 years *(40)*. This long-term benefit is because of LVOT widening as a consequence of the infarction necrosis and replacement fibrosis, which is apparent at 6 weeks, with further widening developing at later follow-up in some cases. We have seen some patients whose improvement has continued beyond 1 year.

In a minority of patients (approx 10%), the LVOT gradient reappears at about 6 weeks even after the usual initial acute reduction. In these patients, peak acceleration rates at follow-up approach baseline values, and the LVOT diameter shows minimal increase from baseline. These patients at the time of the ablation had a smaller septal area opacified by intracoronary contrast injection (3.3–1.9 cm^2) compared to those with a good long-term result (6.5–1.5 cm^2).

Septal alcohol ablation can be considered when there are reasonably large proximal septal perforators (>1.5 mm in diameter) and there are no coexistent abnormalities that require surgical treatment (such as significant myocardial bridging, nonangioplastable coronary disease requiring revascularization, and structural mitral or aortic valvular disease).

SUMMARY

HCM is a myocardial disease that results from a genetic mutation. Protein synthesis is altered in the subaortic region compared to elsewhere in the left ventricular wall *(41,42)*. HCM is not uncommon among the general population, occurring in perhaps 1 in 500 people. Manifestations of the disease are very diverse. The majority of patients are asymptomatic and have a normal life expectancy. However, symptoms from altered diastolic function or from outlet obstruction and associated mitral valve regurgitation may be severe and associated with early death.

Surgical treatment is a useful therapeutic option for some patients with HCM. For those with HCM at high risk of sudden death, an implantable defibrillator should be considered. For the small number of patients with end-stage myocardial dysfunction, heart transplantation may be the only option.

Surgical myectomy for symptomatic patients with the obstructive form of HCM is a low risk (1.8% mortality) procedure, improves symptoms in 95% of patients, and may extend longevity. The results of surgical myectomy are a standard against which the recent advent of catheter alcohol ablation of the blood supply to the septum should be compared *(43,44)*.

REFERENCES

1. Wigle ED, Rakowski H, Kimball BP, Williams WG. Hypertrophic cardiomyopathy. Clinical spectrum and treatment. Circulation 1995;92:1680–1692.
2. Spirito P, Sideman CE, McKenna WJ, Maron BJ. The management of hypertrophic cardiomyopathy. N Engl J Med 1997;336:775–785.
3. Maron BJ. Hypertrophic cardiomyopathy. Lancet 1997;350:127–133.
4. Maron BJ, Salberg L. Hypertrophic Cardiomyopathy: For Patients, Their Families, and Interested Physicians. Futura, New York: 2001.
5. Maron BJ, Casey SA, Poliac LC, et al. Clinical course of hypertrophic cardiomyopathy in a regional United States cohort. JAMA 1999;281:650–655.
6. Maron BJ, Moller JH, Seidman CE, et al. Impact of laboratory molecular diagnostic criteria for genetically transmitted cardiovascular diseases: hypertrophic cardiomyopathy. Long QT syndrome, and Marfan syndrome. Circulation 1998;98:1460–1471.
7. Maron BJ, Gardin JM, Flack JM, Gidding SS, Kurosaki TT, Bild DE. Prevalence of hypertrophic cardiomyopathy in a general population of young adults: echocardiographic analysis of 4111 subjects in the CARDIA study. Circulation 1995;92: 785–789.

8. Wigle ED, Sasson Z, Henderson MA, et al. Hypertrophic cardiomyopathy. The importance of the site and extent of the hypertrophy. A review. Prog Cardiovasc Dis 1985;28:1–83.
9. Hecht GM, Panza JA, Maron BJ. Clinical course of middle-aged asymptomatic patients with hypertrophic cardiomyopathy. Am J Cardiol 1992;69:935–940.
10. Yetman A, Hamilton R, Benson L, McCrindle BW. Factors associated with outcome in children with hypertrophic cardiomyopathy. Can J Cardiol 1997;13:88C.
11. Yetman AT, McCrindle BW, MacDonald C, Freedom RM, Gow R. Myocardial bridging in children with hypertrophic cardiomyopathy—a risk factor for sudden death. N Engl J Med 1998;339:1201–1209.
12. Spirito P, Bellone P, Harris KM, Bernabo P, Bruzzi P, Maron BJ. Magnitude of left ventricular hypertrophy and risk of sudden death in hypertrophic cardiomyopathy. N Engl J Med 2000;342:1778–1785.
13. Maron BJ, Olivotto I, Spirito P, et al. Epidemiology of hypertrophic cardiomyopathy-related death. Circulation 2000;102:858–864.
14. Doevendans PA. Hypertrophic cardiomyopathy: do we have the algorithm for life and death? Circulation 2000;101:1224–1226.
15. Drory Y, Turetz Y, Hiss Y, et al. Sudden unexpected death in persons < 40 years of age. Am J Cardiol 1991;68:1388–1392.
16. Spirito P, Rapezzi C, Autore C, et al. Prognosis of asymptomatic patients with hypertrophic cardiomyopathy and nonsustained ventricular tachycardia. Circulation 1994;90:2743–2747.
17. Elliott PM, Poloniecki J, Dickie S, et al. Sudden death in hypertrophic cardiomyopathy: identification of high risk patient. J Am Coll Cardiol 2000; 36:2212–2218.
18. McKenna WJ, Camm AJ. Sudden death in hypertrophic cardiomyopathy: assessment of patients at high risk. Circulation 1989;80:1489–1492.
19. Elliott PM, Sharma S, Varnava A, Poloniecki J, McKenna WJ. Survival after cardiac arrest or sustained ventricular tachycardia in patients with hypertrophic cardiomyopathy. J Am Coll Cardiol 1999;33:1596–1601.
20. Wigle ED, Rakowski H. Hypertrophic cardiomyopathy: when do you diagnose midventricular obstruction vs apical cavity obliteration with a small nonobliterated area at the apex of the left ventricle? J Am Coll Cardiol 1992;19:525–526.
21. Grigg LE, Wigle ED, Williams WG, Daniel LB, Rakowski H. Transesophageal Doppler echocardiography in obstructive hypertrophic cardiomyopathy: clarification of pathophysiology and importance in intraoperative decision making. J Am Coll Cardiol 1992;20:53–54.
22. Yu E, Chiam C, Siu S, Rakowski H, Wigle ED, O'Kelly B. Left atrial structure and function post myectomy in patients with hypertrophic obstructive cardiomyopathy. Can J Cardiol 1997;13:95C.
23. Yu EHC, Omran AS, Wigle D, Williams WG, Siu SC, Rakowski H. Mitral regurgitation in hypertrophic obstructive cardiomyopathy: relationship to obstruction and relief with myectomy. J Am Coll Cardiol 2000;36:2219–2225.
24. McKenna WJ, Oakley CM, Krikler DM, Goodwin JF. Improved survival with amiodarone in patients with hypertrophic cardiomyopathy and ventricular tachycardia. Br Heart J 1985;53:412–416.
25. Gilligan DM, Missouris CG, Boyd MJ, Oakley CM. Sudden death due to ventricular tachycardia during Amiodarone therapy in familial hypertrophic cardiomyopathy. Am J Cardiol 1991;68:971–973.

26. Maron BJ, Shen W-K, Link MS, et al. Efficacy of implantable cardioverter-defibrillators for the prevention of sudden death in patients with hypertrophic cardiomyopathy. N Engl J Med 2000;342:365–373.
27. McDonald K, McWilliams E, O'Keefe B, Maurer B. Functional assessment of patients treated with permanent dual chamber pacing as a primary treatment for hypertrophic cardiomyopathy. Eur Heart J 1988;9:893–898.
28. Maron BJ, Nishimura RA, McKenna WJ, Rakowski H, Josephson ME, Kieval RS. Assessment of permanent dual-chamber pacing as a treatment for drug-refractory symptomatic patients with obstructive hypertrophic cardiomyopathy. Circulation 1999;99:2927–2933.
29. Williams WG, Wigle ED, Rakowski H, Smallhorn J, Leblanc J, Trusler GA. Results of surgery for hypertrophic obstructive cardiomyopathy. Circulation 1987; 76:V104–V108.
30. Williams WG, Ralph-Edwards AC, Wigle ED. Surgical management of hypertrophic obstructive cardiomyopathy. Cardiol Rev 1997;5:40–49.
31. Theodoro DA, Danielson GK, Feldt RH, Anderson BJ. Hypertrophic obstructive cardiomyopathy in pediatric patients: results of surgical treatment. J Thorac Cardiovasc Surg 1996;112:1589–1599.
32. Heric B, Lytle BW, Miller DP, et al. Surgical management of hypertrophic obstructive cardiomyopathy. Early and late results. J Thorac Cardiovasc Surg 1995;110:195–208.
33. McCully RB, Nishimura RA, Tajik AJ, et al. Extent of clinical improvement after surgical treatment of hypertrophic obstructive cardiomyopathy. Circulation 1999; 99:2927–2933.
34. Grigg LE, Wigle ED, Williams WG, Daniel LB, Rakowski H. Transesophageal echocardiography in obstructive hypertrophic cardiomyopathy: clarification of pathophysiology and importance of intraoperative decision making. J Am Coll Cardiol 1992;53:42–52.
35. Cregg N, Cheng DCH, Karski JM, Williams WG, Webb G, Wigle ED. Morbidity outcome in patients with hypertrophic obstructive cardiomyopathy undergoing cardiac septal myectomy: early-extubation anesthesia vs high-dose opioid anesthesia technique. J Cardiothorac Vasc Anesthesia 1999;13:47–52.
36. Sigwart U. Nonsurgical myocardial reduction for hypertrophic obstructive cardiomyopathy. Lancet 1995;346:211–214.
37. Faber L, Seggewiss H, Fassbender D, et al. Identification of the target vessel (TV) in percutaneous transluminal ablation (PTSMA) in hypertrophic obstructive cardiomyopathy by myocardial contrast echocardiography (MCE) [abstract]. Circulation 1997;96(suppl I):I-639.
38. Flores-Ramirez R, Lakkis NM, Middleton KJ, Killip D, Spencer WH, Nagueh SF. Echocardiographic insight into the mechanisms of relief of left ventricular obstruction after nonsurgical septal reduction therapy in patients with hypertrophic obstructive cardiomyopathy. J Am Coll Cardiol 2001;37:208–214.
39. Woo A, Schwartz L, Wigle ED, Ross J, Rakowski H. Myocardial contrast echocardiography during septal ethanol ablation for obstructive hypertrophic cardiomyopathy. In: Goldberg BB, Raichlen JS, Forsberg F, eds. Ultrasound Contrast Agents. Martin Dunitz: 2000, pp. 197–211.
40. Mazur W, Nagueh SF, Lakkis NM, et al. Regression of left ventricular hypertrophy after nonsurgical septal reduction therapy for hypertrophic obstructive cardiomyopathy. Circulation 2001;103:1492–1496.

41. Li G, Li R-K, Mickle DAG, et al. Elevated insulin-like growth factor-1 and transforming growth factor-BI and their receptors in patients with idiopathic hypertrophic obstructive cardiomyopathy. Circulation 1998;98:II-144–II-150.
42. Li G, Li R-K, Borger MA, et al. Regional overexpression of IGF-1 and TGF-B1 in the myocardium of hypertrophic obstructive cardiomyopathy patients. J Thorac Cardiovasc Surg 2002;123:89–95.
43. Seggewiss H, Gleichman U, Faber L, et al. Percutaneous transluminal septal myocardial ablation in hypertrophic obstructive cardiomyopathy: acute results and 3 month follow-up in 25 patients. J Am Coll Cardiol 1998;31:252–258.
44. Maron BJ. Role of alcohol septal ablation in treatment of obstructive hypertrophic cardiomyopathy. Lancet 2000;355:425–426.

10 Dynamic Cardiomyoplasty and New Prosthetic LV Girdling Devices

Michael A. Acker, MD

CONTENTS

INTRODUCTION

Dynamic cardiomyoplasty (DCMP) is a promising but unproven surgical treatment for patients with end-stage heart failure. Today, the procedure is no longer performed in the Unites States. The procedure, first performed by Alain Carpentier in 1985 *(1)*, involves mobilization of the latissimus dorsi muscle, which is then wrapped circumferentially around the heart. The muscle wrap is then, after a period of training, stimulated to contract in synchrony with cardiac systole. Chronic repetitive stimulation induces biochemical and physiological transformations of the muscle, altering its characteristics toward cardiac muscle. These changes include fatigue resistance, increased aerobic capacity, prolonged contraction duration, diminished size, and reduced maximal power *(2–5)*.

From: *Contemporary Cardiology: Surgical Management of Congestive Heart Failure*
Edited by: J. C. Fang and G. S. Couper © Humana Press Inc., Totowa, NJ

CLINICAL EXPERIENCE WITH DYNAMIC CARDIOMYOPLASTY

Since 1985, more than 1000 patients have had DCMP performed worldwide. The majority had significant improvement in New York Heart Association (NYHA) functional class and overall quality of life *(6–8)*. Despite this dramatic improvement, consistent objective hemodynamic beneficial effects have not been consistently demonstrated, and a survival advantage has not been proven over medical therapy alone *(9)*. Further clouding the picture have been evolving indications, uncertainty over risk stratification, a past relatively high operative mortality, limitations of a first-generation cardiomyostimulator, concomitant surgery, and a mechanism of action that remains unclear. Lack of a clear survival advantage and ongoing misunderstanding of its mechanism of action hindered its acceptance as a treatment alternative for patients with end-stage heart failure. Recruitment for the definitive phase III US Food and Drug Administration (FDA) study was slow, and the study was terminated early, ending its clinical use in the United States.

In more than several hundred to 1000 patients implanted with Medtronic cardiomyostimulators, consistent clinical improvement has been noted in 80 to 85% of hospital survivors. On the average, the NYHA class improves 1.2 classes. The improvement begins within the first 6 months of surgery and has been sustained for years. Quality-of-life (QoL) measures assessing daily activity, social activity, quality of interaction, and mental health all improve significantly *(10)*. In addition, the number of hospitalizations for heart failure has been seen to decrease *(11)*.

Similar clinical improvement was demonstrated in the phase II FDA trial of DCMP. This was a multicenter prospective trial to evaluate the safety of the device in 68 patients. Outcomes were compared to those of a reference group of medically treated patients with matched demographic, etiologic, clinical, and hemodynamic parameters. In both groups, almost all patients were in NYHA class III heart failure, suffered from either ischemic or idiopathic cardiomyopathy, and were on optimized medical therapy. Operative mortality was 12%. Of the patients, 80% were functionally improved at 6 and 12 months (3 ± 0.1 to 1.7 ± 0.1 NYHA class), which was significantly better than the reference group *(9)*. Patients remained functionally improved to 2 years.

Despite the overwhelming evidence for clinical improvement, consistent evidence of clinically significant hemodynamic benefit is lacking. In the phase II trial, left ventricular ejection fraction (LVEF) increased from $22.7 \pm 1.0\%$ to $25.5 \pm 1.9\%$, and LV stroke work index increased from 26 ± 1 to 30 ± 2 g/m^2 per beat. Both changes were

statistically significant. No change, however, was seen in cardiac index, pulmonary capillary wedge pressure, right ventricular (RV)EF, and maximal O_2 consumption. Recent reports continue to demonstrate a small but statistically significant improvement in LVEF *(11–16)*.

The operative mortality associated with cardiomyoplasty has progressively decreased over the last decade. During a FDA phase I feasibility study (1988–1991), 31% of patients did not survive their hospitalization. Many of these patients were NYHA class IV. During the FDA phase II study, in which almost all patients were class III, hospital mortality decreased to 12%. During the recently terminated phase III trial, patients undergoing cardiomyoplasty had a hospital mortality of less than 3% *(10)*. Three-quarters of the hospital deaths were related to progressive heart failure. The remaining deaths were related to sepsis or multisystem organ failure. Deaths that occurred following initial hospital discharge were 80% cardiac in origin, with 38% sudden and 41% nonsudden. Among the approx 20% noncardiac deaths, about half were caused by pneumonia and sepsis; the rest were caused by noncardiac unknown causes *(10)*.

During cardiomyoplasty's initial experience, survival for class IV patients was clearly shown to be much worse than survival for class III. Today, NYHA class IV patients are not considered candidates for DCMP. Actuarial survival appeared to be improving further (1 year 78%, 2 years 70%) for class III patients (n = 103) at experienced centers *(10)*.

Furnary et al. *(16)* performed a multivariate analysis of risk factors for poor overall survival in 127 patients who underwent the DCMP from three major centers. They found that predictors of poor results were atrial fibrillation, NYHA class IV status, high pulmonary capillary wedge pressure, and need for intra-aortic balloon pump. When peak oxygen consumption (VO_2) was analyzed, pulmonary capillary wedge pressure and NYHA class were eliminated from the model.

Analysis of 117 patients from the phase II DCMP study group demonstrated VO_2 and LVEF provided independent prognostic information for procedure-related death according to logistic regression analysis *(17)*. Rector et al. *(18)* updated the earlier multicenter analysis (n = 166) and found, in addition to VO_2 and LVEF, center experience and significant coronary artery disease (coronary arteries with stenosis lesions <70%) were predictors of cardiac mortality within 2 months after cardiomyoplasty. Moreira et al. *(19)* reported 5-year follow-up on 31 patients post-DCMP. Multivariate analysis of factors influencing outcome showed that preoperative functional class and pulmonary vascular resistance significantly affected long-term survival.

Cardiomyoplasty was originally conceived as a method to assist the heart mechanically during ejection by "squeezing," thereby increasing

beat-to-beat EF, stroke volume, and cardiac output. Although a few investigators *(20,21)* have demonstrated the direct active synchronous assistance of the wrap on the failing heart, convincing hemodynamic evidence of clinically important beat-to-beat systolic assist is at best modest and often not seen at all despite significant improvement in functional status *(22)*. Others have suggested that the primary action is a girdling effect by which the muscle wrap acts to prevent further ventricular remodeling *(12,22,23)*.

There continues to be substantial evidence supporting active systolic assistance in both clinical and animal studies. One year following DCMP in 13 patients, Jatene et al. showed that LVEF increased with stimulator on vs off *(20)*. Cho et al. *(24)* and Aklog et al. *(25)* showed augmentation of end-systolic elastance for assisted beats in normal canine hearts. We showed that, in chronic cardiomyopathic canine hearts, active cardiomyoplasty assist will result in a beat-to-beat increase in load-independent indices of contractility *(26)*. In at least some patients Schreuder et al. showed, quite convincingly, that 1 year after DCMP, optimization of stimulation parameters will result in significant beat-to-beat improvement in cardiac function *(21)*.

Although most patients demonstrated no significant change, in about 50% of patients, Hagege et al. saw a decrease in LVEF and dP/dt when the stimulator was turned off for 24 hours, suggesting a heterogeneous response of muscle wrap contraction. This may be related to the individual degree of latissimus dorsi muscle damage *(12)*. Atrophy and fibrosis of the distal part of the latissimus dorsi muscle flap is thought to be caused by ischemia. This contributes to weakening the overall effect of the latissimus dorsi muscle contraction, limiting its ability to improve active systolic assistance.

Carraro et al. *(27,28)* have developed an intermittent "demand" stimulation protocol that produces and maintains a long-term partial transformation (intermediate fiber type) of the latissimus dorsi muscle. This muscle is relatively fatigue resistant, yet faster and more powerful than a fully transformed muscle. It is a muscle more capable of beat-to-beat assistance of the heart. Arpesella et al. have recently demonstrated in animal study that *in situ* conditioning and two-stage mobilization improves the distal perfusion and capillary density *(29)*. Kashem et al. also demonstrated in dogs that intermittent stimulation results in a more powerful muscle capable of increased LV assistance *(30)*.

This suggests that cardiomyoplasty should be done in two stages: the first to mobilize the muscle partially and to place electrodes to begin preconditioning *in situ* and the second stage to complete the muscle flap mobilization, followed by the actual cardiac wrap. Such a

strategy, not done in the past, would be expected to result in a more powerful muscle with preserved distal perfusion, avoiding muscle fibrosis seen to date.

EFFECTS OF PASSIVE GIRDLING

Passive girdling effects have been proposed as an additional mechanism of benefit. Carpentier et al. demonstrated a stable cardiothoracic ratio for up to 3 years following DCMP, whereas progressive dilatation would otherwise be anticipated in such patients *(6)*. Capouya et al. reported that placement of an unstimulated wrap around a normal heart followed by rapid ventricular pacing attenuated LV enlargement *(23)*. Our laboratory demonstrated that, in a chronic canine cardiomyopathic model, DCMP limited the remodeling process of ongoing heart failure *(26)*, and this effect can also be demonstrated without chronic systolic assistance *(31)*.

Kass et al. *(22)* demonstrated in three patients a leftward shift of end-systolic pressure volume relationship and stabilization of the end-diastolic pressure volume relationship at 6 and 12 months after DCMP, suggesting a reversal of the remodeling process. Although no active systolic beat-to-beat assistance could be demonstrated, objective measures of systolic function improved dramatically. Evidence of reverse remodeling has also been demonstrated by Lorusso et al., who reported a significant reduction in left ventricular end-diastolic diameter up to 3 years after DCMP in 22 patients *(11)*.

Hagege et al. *(12)* reported further evidence that active beat-to-beat assistance is not necessary for overall benefit from DCMP. They reported that in 13 patients, all longer than 1 year after DCMP, there was no change in overall indexes of systolic or diastolic left ventricular function after stopping muscle wrap stimulation for 24 hours. All patients were clinically improved, and overall LVEF was improved. Jondeau et al. reported similar results *(14)*.

Finally, there have been several anecdotal reports of clinical deterioration when the stimulator was dysfunctional for more than 1 to 2 weeks. This speaks more to the importance of synchronous stimulation chronically than its active beat-to-beat assistance.

Kawaguchi and associates showed that mechanical artificial external synchronous systolic compression that mimics DCMP will decrease wall stress and myocardial oxygen consumption *(32,33)*. In acute experiments utilizing unconditioned muscle and normal hearts, Lee et al. *(34)*, Chen et al. *(35)*, and Aklog et al. *(25)* demonstrated decreased wall stress with active muscle wrap assistance.

Our laboratory demonstrated *(36)*, in a chronic canine cardiomyopathic model, that DCMP results chronically in an improvement in preload recruitable stroke work and myocardial efficiency when compared to control heart failure animals. In addition, muscle wrap stimulation further increased preload recruitable stroke work and myocardial efficiency, and potential energy decreased. This was seen without a change in stroke volume or cardiac output.

Oh et al. postulated that the muscle wrap of DCMP decreases wall stress according to Laplace's law (by increased wall thickness) *(37)*. For this to occur, the muscle wrap must develop and share tension with the myocardium even if there is no change acutely in overall LV function *(37)*. These findings may explain why significant improvement in LVEF and other standard measurements of LV function may not be found in patients who improve clinically.

In some patients with ischemic cardiomyopathy, DCMP may induce increase collateral blood flow to ischemic areas of the ventricle. Mannion et al. demonstrated evidence of this in an ischemic animal model *(38)*, and collaterals have been found in autopsy studies between the myocardium and the muscle wrap *(39)*.

Finally, the possibility that stimulation of the latissimus dorsi nerve may affect the neurohormonal milieu via a central pathway must be investigated. In the future, staged mobilization procedures and new intermittent stimulation protocols may limit muscle damage and produce a stronger, yet still fatigue-resistant, muscle with more potential for powerful cardiac assistance *(27,28,40,41)*.

THE C-SMART TRIAL

The phase III randomized clinical trial, also known as C-SMART (Cardiomyoplasty-Skeletal Muscle Assist Randomized Trial) commenced in June 1995 and was terminated near the end of 1998. Slightly more than 100 patients had been entered into the study. There were to be 400 patients (200 for DCMP and 200 for standard medical therapy) recruited. The study utilized the new Transform cardiomyostimulator (Medtronic Inc.). C-SMART was designed to test the hypothesis that DCMP improves the functional status and quality of life of patients with NYHA class III heart failure compared to a control group with comparable morbidity and mortality evaluated 12 months postenrollment in the trial.

There were 103 patients randomly assigned to C-SMART from 1994 to 1998. At 6 months, 79% of patients with DCMP were NYHA class I or II compared to 25% in the medical group. There was also statistical

improvement in QoL scores and 6-minute walk. The 6-month survival was similar between medical and surgical groups *(42)*. Despite these encouraging preliminary results, the trial was halted by Medtronic, the trial's sponsor, because of slowness of recruiting patients. The cardiomyostimulator is no longer produced, and the operation has not been done in the United States since the trial stopped.

Legitimate doubts about the efficacy of DCMP remain. Although patients are improved functionally, no statistically significant hemodynamic or survival benefit has been demonstrated. Many cardiologists and cardiac surgeons agree with Leier, who stated in an editorial, "In short, those who need it, don't survive it and those who survive it, don't need it" *(43)*. Unfortunately, although many patients with class III heart failure can be managed effectively with medication alone, there are clearly many patients on maximal medical therapy whose quality of life and exercise capacity have worsened, yet are not sick enough to consider transplantation. Comparison of Minnesota Living With Heart Failure scores of recent DCMP patients with those of the class II and III patients in the Studies of Left Ventricular Dysfunction (SOLVD) treatment arm demonstrated that the cardiomyoplasty candidates perceived significantly greater limitations of daily living *(11)*, which motivated them to seek a surgical treatment for their heart failure in lieu of medication alone. It is clear that a more potent treatment alternative for these patients must be sought.

Chronic dilatation and remodeling are initial valuable adaptations that allow weakened hearts to achieve near-normal systolic pressure and flows at increased, but still tolerable, diastolic pressures. Although initially adaptive, ongoing remodeling and dilatation is maladaptive and a major risk factor for mortality *(22)*. The remodeled ventricle has a larger chamber with an increased radius of curvature, increased wall stress, increased myocardial oxygen consumption, impaired subendocardial blood flow, impaired myocardial energetics, and increased risk of arrhythmias *(44)*. It is likely that DCMP, through a combination of a chronic elastic constraint and active dynamic assistance, decreases myocardial wall stress and attenuates ventricular dilatation and the remodeling process associated with progressive heart failure (Fig. 1).

It is well accepted that the small, but important, survival benefit attributed to angiotensin-converting enzyme inhibitors in patients with heart failure is secondary to an attenuation of progressive cardiac enlargement. This important but subtle effect was not realized until completion of large prospective randomized studies (SOLVD) *(44)*. What is abundantly clear by now is that DCMP can be shown to limit the remodeling process of heart failure in animal studies and in some patients.

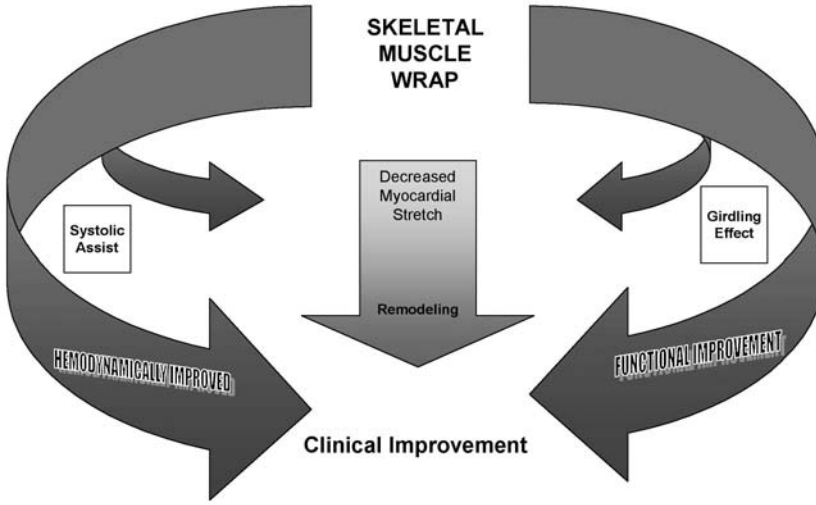


Fig. 1. Dynamic cardiomyoplasty probably acts by at least two mechanisms, ultimately limiting the remodeling process of progressive heart failure.

OTHER STRATEGIES

Stimulated by the potential importance of the passive girdling of the muscle wrap in DCMP, new prosthetic passive girdling devices have been developed. One such device is a polyester jacket (CorCap™, Acorn Cardiovascular Inc.). In animal studies of dilated cardiomyopathy, it promoted reverse remodeling and improved indexes of systolic function. The jacket also has partially reversed the heart failure phenotype on a cellular and molecular level *(45,46)*. It is hypothesized that the CorCap jacket reduces diastolic wall stress (Fig. 2). In an animal model of an acute myocardial infarct, placement of the jacket post-infarct prevents subsequent LV dilatation and remodeling and preserves LV systolic function *(47)*.

During the initial safety trial in Europe, the CorCap was placed in patients with NYHA class III congestive heart failure with dilated cardiomyopathy and was often combined with mitral valve repair. No device-related complications were noted, and very importantly, no cases of constrictive pericarditis developed in over 2 years of follow-up. Although not designed as an efficacy trial, several patients who had the CorCap alone have demonstrated significant improvement in LVEF, with LV volumes stabilizing or reversing. There is currently an ongoing FDA-sponsored phase II multiinstitutional, randomized study of

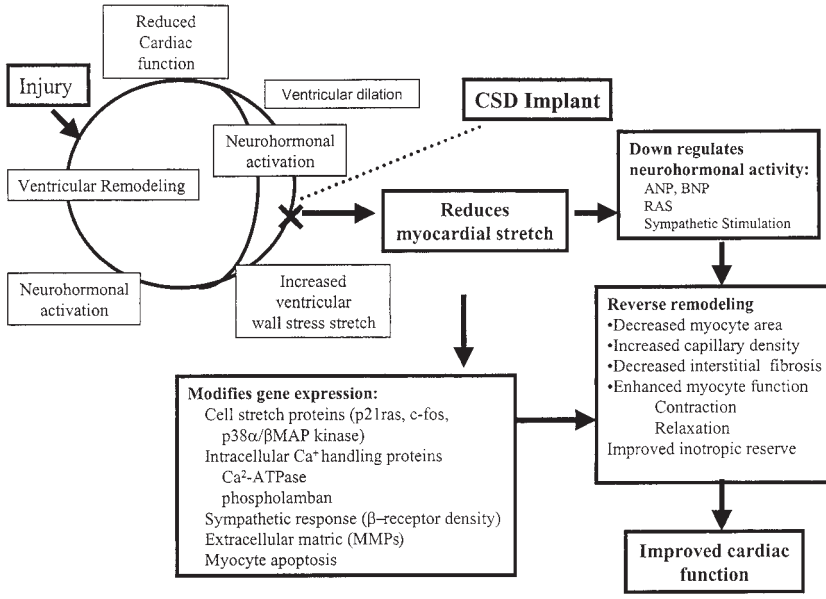


Fig. 2. Decreased myocardial stretch and stress have been demonstrated to modify the heart failure phenotype on global, cellular, and molecular levels. ANP, atrial natriuretic peptide; BNP, brain natriuretic peptide; RAS, renin angiotensin system; MMP, matrix metalloproteinase.

patients with NYHA class III heart failure and dilated ventricles with and without mitral insufficiency (Fig. 3).

Another device still in development is the Myocor Myosplint, which is designed to decrease left ventricular wall stress by changing LV shape, thus improving contractile function. This shape change is accomplished by surgically placing three myosplints perpendicular to the LV long axis, drawing LV walls inward, and creating a symmetric bilobular left ventricle. The bilobular left ventricle has decreased wall stress compared to the original spherical, ellipsoidal shape *(48)*. In contrast to the CorCap, this device decreases wall stress acutely, but is more invasive to place. It has been demonstrated to decrease wall stress in canine models of heart failure and is awaiting human evaluation.

With C-SMART's termination, the potential clinical benefit of cardiomyoplasty will never be totally known. Its ultimate role in the treatment of heart failure depended on the outcome of properly designed randomized controlled studies, such as C-SMART. With termination of the FDA phase III trial, clinical cardiomyopathy has ceased in the United States, although in Europe the procedure is still performed. The

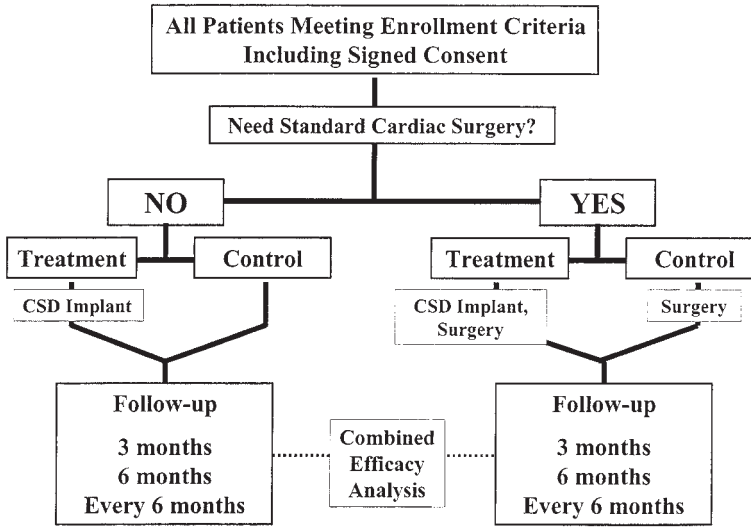


Fig. 3. US multicenter randomized trial of Acorn jacket in patients with NYHA class III heart failure and dilated left ventricles.

lessons learned from cardiomyoplasty (i.e., that an external constraint can be used effectively to limit the remodeling process of heart failure) however, may still prove of larger clinical significance.

REFERENCES

1. Carpentier A, Chacques JC. Myocardial substitution with a stimulated skeletal muscle: first successful clinical case [letter]. Lancet 1985;1:1267.
2. Mannion JD, Bitto T, Hammond RL, et al. Histochemical and fatigue characteristics of conditioned canine latissimus dorsi muscle. Circ Res 1986;58: 298–304.
3. Salmons S, Sreter FA. Significance of impulse activity in the transformation of skeletal muscle type. Nature 1967;263:30–34.
4. Sreter FA, Gergely J, Salmons S, Romanul F. Synthesis by fast muscle of myosin light chains characteristic of slow muscle in response to long-term stimulation. Nature 1973;241:17–19.
5. Clark BJ, Acker MA, McCully K, et al. In vivo ^{31}P-NMR spectroscopy of chronically stimulated canine skeletal muscle. Am J Physiol 1988;254: C-258–C-266.
6. Carpentier A, Chachques JC, Acar C, et al. Dynamic cardiomyoplasty at 7 years. J Thorac Cardiovasc Surg 1993;106:42–52.
7. Moreira LF, Stolf NA, Braile DM, Jatene AD. Dynamic cardiomyoplasty in South America. Ann Thorac Surg 1996;61:408–412.
8. Magovern GJ, Simpson A. Clinical cardiomyoplasty: review of the 10-year United States experience. Ann Thorac Surg 1996;61:413–419.

9. Furnary AP, Jessup M, Moreira LF. Multicenter trial of dynamic cardiomyoplasty for chronic heart failure. The American Cardiomyplasty Group. J Am Coll Cardiol 1996;28:1175–1180.
10. Medtronic dynamic cardiomyoplasty clinical database. 1996.
11. Lorusso R, Milane E, Volterrani M, et al. Cardiomyoplasty as isolated procedure to treat refractory heart failure. Eur J Cardiothorac Surg 1997;363–372.
12. Hagege AA, Desnos M, Fernandez F, et al. Clinical study of the effect of latissimus dorsi muscle flap stimulation after cardiomyoplasty. Circulation 1995;92 (suppl II):II210–II215.
13. Bocchi EA, Bellotti G, Moreira LF. Mid-term results of heart transplantation, cardiomyoplasty and medical treatment of refractory heart failure caused by idiopathic dilated cardiomyopathy. J Heart Lung Transplant 1996;75:736–745.
14. Jondeau G, Dorent R, Dib JC, et al. Dynamic cardiomyoplasty: effect of discontinuing latissimus dorsi stimulation on left ventricular systolic and diastolic performance and exercise capacity. J Am Coll Cardiol 1995;26:129–134.
15. Tasdemir O, Kucukaksu SD, Vural KM, et al. A comparison of early and mid-term results after dynamic cardiomyoplasty in patients with ischemic and idiopathic cardiomyoplasty. J Thorac Cardiovasc Surg 1997;113:173–181.
16. Furnary AP, Chacques JC, Moreira LP, et al. Long-term outcome survival analysis and risk stimulation of dynamic cardiomyoplasty. J Thorac Cardiovasc Surg 1996;112:1640–1650.
17. Phase II Dynamic Cardiomyoplasty Study Group. Factors associated with acute hospital mortality following a latissimus dorsi cardiomyoplasty. Maastricht, The Netherlands, 1994.
18. Rector TS, Benditt D, Chachques J, et al. Retrospective risk analysis for early heart-related death after cardiomyoplasty. The Worldwide Cardiomyoplasty Group. J Heart Lung Transplant 1997;16:1018–1025.
19. Moreira LF, Stolf NA, Bocchi EA, et al. Clinical and left ventricular function outcomes up to 5 years after dynamic cardiomyoplasty. J Thorac Cardiovasc Surg 1995;109:353–362.
20. Jatene AD, Moreira LF, Stolf NA, et al. Left ventricular function changes after cardiomyoplasty in patients with dilated cardiomyopathy. J Thorac Cardiovasc Surg 1991;102:132–139.
21. Schreuder JJ, van der Veen FH, van der Velde ET, et al. Beat-to-beat analysis of left ventricular pressure volume relation and stroke volume by conductance catheter and aortic model flow in cardiomyoplasty patients. Circulation 1995; 91:2010–2017.
22. Kass DA, Baughman KL, Pak PH, et al. Reverse remodeling from cardiomyoplasty in human heart failure. Circulation 1995;91:2314–2318.
23. Capouya ER, Gerber RS, Drinkwater DC, et al. Girdling effect of non-stimulated cardiomyoplasty on left ventricular function. Ann Thorac Surg 1993;56:867–871.
24. Cho PW, Levin HR, Curtis WE, et al. Pressure-volume analysis of changes in cardiac function in chronic cardiomyoplasty. Ann Thorac Surg 1993;56: 38–45.
25. Aklog L, Murphy MP, Chen FY, et al. Right latissimus dorsi cardiomyoplasty improves left ventricular function by increasing peak systolic elastance. Circulation 1994;90(part II):II-112–II-119.
26. Patel HJ, Lankford EB, Polidori DJ, et al. Dynamic cardiomyoplasty: its chronic and acute effects on the failing heart. J Thorac Cardiovasc Surg 1997;114: 169–178.
27. Muneretto C, Carraro U, Barbiero M, et al. Shortened conditioning and lighter

stimulation regimen for dynamic cardiomyoplasty: preliminary results. Basic Appl Myol 1997;7:55–56.
28. Carraro U, Docali G, Barbiero M, et al. Demand dynamic cardiomyoplasty: improved clinical benefits by non-invasive monitoring of LD flap and long-term tuning of its dynamic contractile characteristics by activity-rest regime. Basic Appl Myol 1998;8:11–15.
29. Arpesella G, Carraro V, Mikus PM, et al. Activity–rest stimulation of latissimus dorsi for cardiomyoplasty: 1 year results in sheep. Ann Thorac Surg 1998;66: 1983–1990.
30. Kashem A, Santamore WP, Chiang B, et al. Vascular delay and intermittent stimulation: keys to successful latissimus dorsi muscle stimulation. Ann Thorac Surg 2001;71:1866–1873.
31. Patel HJ, Polidori DJ, Pilla JJ, et al. Stabilization of chronic remodeling by asynchronous cardiomyoplasty in dilated cardiomyopathy: the effects of a conditioned wrap. Circulation 1997;96:3665–3671.
32. Kawaguchi O, Goto Y, Futai S, et al. Mechanical enhancement and myocardial oxygen saving by synchronized dynamic left ventricular compression. J Thorac Cardiovasc Surg 1992;103:573–581.
33. Kawaguchi O, Goto Y, Futaki S, et al. The effects of dynamic cardiac compression on ventricular mechanics and energetics. J Thorac Cardiovasc Surg 1994;107: 850–859.
34. Lee KJ, Dignan RJ, Parmar JM, et al. Effects of dynamic cardiomyoplasty on left ventricular performance and myocardial mechanics in dilated cardiomyopathy. J Thorac Cardiovasc Surg 1991;102:124–131.
35. Chen FY, Aklog L, deGuzman BJ, et al. New technique measures decreased transmural myocardial pressure in cardiomyoplasty. Ann Thorac Surg 1995;60: 1678–1682.
36. Patel HJ, Pilla JJ, Polidori D, et al. Long-term dynamic cardiomyoplasty improves chronic and acute myocardial energetics in a model of left ventricular dysfunction. Circulation 1998;98:II346–II351.
37. Oh JH, Badhwar V, Chiu RC. Mechanism of dynamic cardiomyoplasty. J Card Surg 1996;11:194–199.
38. Mannion JD, Blood V, Bailey W, et al. The effect of basic fibroblast growth factor on blood flow and morphologic features of a latissimus dorsi cardiomyoplasty. J Thorac Cardiovasc Surg 1996;111:19–28.
39. Mott BD, Misawa Y, Lough JO, et al. Clinicopathological correlation of dynamic cardiomyoplasty. Am J Cardiol 1996;11:133E.
40. Carroll SM, Heilman SJ, Steimel RW, et al. Vascular delay improves latissimus dorsi muscle perfusion and muscle function for use in cardiomyoplasty. Plast Reconstr Surg 1997;99:1329–1337.
41. Ianuzzo CD, Ianuzzo SE, Anderson WA. Cardiomyoplasty: transformation of the assisting muscle using intermittent vs continuous stimulation. J Card Surg 1996; 11:293–303.
42. Young JB, Kirklin JK, C-SMART investigators. Cardiomyoplasty-Skeletal Muscle Assist Randomized Trial (C-SMART): 6 month results [abstract]. American Heart Association, 1999.
43. Leier CV. Cardiomyoplasty: is it time to wrap it up? J Am Coll Cardiol 1996;28: 1101–1102.
44. Cohn JN. Structural basis for heart failure: ventricular remodeling and its pharmacologic inhibition. Circulation 1995;91:2504–2507.

45. Chaudhry PA, Mishima T, Sharov UG, et al. Passive epicardial containment prevents ventricular remodeling in heart failure. Ann Thorac Surg 2000;70:1275–1280.
46. Sabbah HN, Chaudhry PA, Paone G, et al. Passive ventricular constraint with Acorn prosthetic jacket prevents progressive left ventricular dilation and improves ejection fraction in dogs with moderate heart failure. Paper presented at: American College of Cardiology Advanced Meeting; March 1999; New Orleans, LA.
47. Pilla JJ, Blom AS, Brockman DJ, et al. Ventricular constraint using the Acorn cardiac support device (CSD) reduces myocardial infarct size in an ovine model of acute infarction. Circulation 2002;106:I207–I211.
48. Takagaki M, McCarthy PM, Ochiai Y, et al. Novel device to change left ventricular shape for heart failure treatment: device design and implantation procedure. ASAIO J 2001;47:244–248.

11 Xenotransplantation

Joren C. Madsen, MD, DPhil
and Ruediger Hoerbelt, MD

CONTENTS

INTRODUCTION

Data from the United Network for Organ Sharing (UNOS) indicated that status 1 patients waiting for a heart transplant in the United States have a mortality rate as high as 45% because of the shortage of donor organs *(1)*. The discrepancy between the number of patients waiting for an organ transplant and the number of organs that become available each year is increasing. In 1999, the number of heart transplant candidates on US waiting lists was 4277, but less than 50% received an organ *(1)*. Although it is difficult to determine the overall number of patients who would benefit from cardiac transplantation in the United States if the source of donor organs were unlimited, estimates range from 35,000 to 100,000 patients (reviewed in ref. *2*).

From: *Contemporary Cardiology: Surgical Management of Congestive Heart Failure*
Edited by: J. C. Fang and G. S. Couper © Humana Press Inc., Totowa, NJ

This scarcity of donor organs has led to a strong resurgence of interest in xenotransplantation. However, there are formidable immunological barriers to overcome before the full potential of transspecies organ transplantation can be realized. This chapter primarily examines the immunological barriers to xenotransplantation and the experimental strategies currently employed to overcome them. Because the most excitement in recent years has been in the area of hyperacute rejection and cellular rejection, these two areas are the primary focus of this review. The physiological barriers to cardiac xenotransplantation, although important, are less critical than in liver or kidney xenotransplantation. This subject is reviewed in the Choice of Animal Donor section. Infectious disease issues are summarized at the end of the chapter. The many ethical ramifications of xenotransplantation are beyond the scope of this chapter; excellent reviews are provided in refs. *2–6*.

ADVANTAGES OF XENOTRANSPLANTATION

Although the traditional rationale for pursuing xenotransplantation as a treatment for end-stage heart disease has been its promise to provide an unlimited supply of donor organs, there are other advantages that could be realized by bringing xenotransplantation to the clinic. By identifying and preparing the donor and recipient in advance of the transplant, the potentially devastating effects of brain death on the donor organ *(7)* would be eliminated, and the ischemia/reperfusion injury associated with prolonged preservation times *(8)* would be greatly reduced. Optimizing the physiological state of the donor organ and the timing of organ procurement would have significant short- and long-term benefits. Indeed, the combined clinical impact of brain death, prolonged preservation times, and associated ischemia/reperfusion injury on whole organ transplantation is highlighted by the fact that kidney allografts from human lymphocyte antigen (HLA)-mismatched living donors survive longer than allografts from HLA-identical cadaveric donors *(9)*.

There is also the exciting potential for modifying the host and the donor organs prior to transplantation, not only to mitigate the vigorous xenogeneic immune response, but also to create "customized" donor organs. From an immunological standpoint, the human host may one day be preconditioned to induce immunological tolerance to the xenograft, for instance, by donor bone marrow transplantation *(10)* or gene therapy *(11)*. Alternatively, the xenograft could be derived from animals genetically engineered for the lifelong expression of transgenes that mitigate the hyperacute response to natural antibody *(12)* or that prevent acute vascular rejection *(13)* (*see* Prevention of Hyperacute

Rejection section). Most important, scientists have now successfully cloned swine through nuclear transfer from adult somatic cells *(14)* and have been able to "knock out" genes relevant to hyperacute xenograft rejection in the process. This is a major step in bringing xenotransplantation to the clinic (*see* Prevention of Hyperacute Rejection section). Of note, the ability to customize the xenogeneic organ donor genetically may obviate the need for some of the investigative approaches described here.

From a physiological standpoint, gene transfer techniques could be used to overexpress genes of functional value to the organ and donor. For instance, right heart dysfunction/failure might be prevented in a donor heart engineered to overexpress *SERCA2a* (to optimize the utilization of myocardial calcium), β*2-AR* (to improve β-adrenergic signaling), or *Bcl-2* (to block cardiomyocyte apoptosis) *(15)*. Alternatively, an animal heart might be "trained" for implantation into a recipient with fixed pulmonary hypertension by banding or balloon-occluding the main pulmonary artery of the donor prior to procurement *(16,17)*. The resulting pressure load would induce rapid hypertrophy of the right ventricle *(18)*, making it a more suitable organ for a recipient with high pulmonary vascular resistance. Possibilities such as these add to the utility of xenotransplantation.

CHOICE OF ANIMAL DONOR

Early studies of xenotransplantation in several different species demonstrated that hyperacute rejection did not occur in every combination of species, but only in species of great phylogenetic diversity. The greater the phylogenetic distance between species, the more rapid the rejection response was. Realizing this, Calne suggested the terms *concordant*, to describe species combinations in which hyperacute rejection did not occur, and *discordant*, to describe combinations in which it did occur *(19)*. Because hyperacute rejection is the result of preformed, naturally occurring antibodies directed against tissue from other species, these terms have more recently been used to distinguish between (concordant) combinations of species in which there are no preformed natural antibodies (i.e., hamster to rat or monkey to baboon) and (discordant) species combination in which natural antibodies do exist (i.e., guinea pig to rat or pig to baboon).

Understandably, early efforts to apply xenotransplantation in the clinic were directed toward the use of nonhuman primates (chimpanzee) as donors because they were phylogenetically closest to humans and therefore provided concordant xenografts. However, nonhuman primates such as chimpanzees and baboons present other problems that make

their use as xenograft donors unlikely. They are small compared to adult humans, their availability is limited, and their potential for transmitting infectious diseases is real. The US Food and Drug Administration has expressed growing concern over the use of nonhuman primate-derived tissues for human transplantation *(20)*.

Most investigators now believe that the pig will be the most suitable source of organs and tissues for humans, even though swine provide discordant xenografts. The advantages of swine include unlimited availability, favorable breeding characteristics, and organs similar in size and function to their human counterparts. Since the late 1970s, a herd of miniature swine has been bred selectively to homozygosity at the porcine major histocompatibility complex (MHC) *(21,22)*. These partially inbred miniature swine provide a number of unique advantages as potential xenograft donors. In contrast to domestic swine, which reach 450 kg, adult miniature swine achieve weights of 120 to 140 kg, making it possible to obtain a miniature swine organ of appropriate size for any potential human recipient.

To identify which miniature swine would donate the best size-matched heart for a particular human recipient, our laboratory performed a morphometric study of the miniature swine heart using transthoracic echocardiography. By comparing the morphometric measurements of aortic annulus diameter in the miniature swine with normative human data, we were able to develop a nomogram, relating swine length to human height, to make the prediction (Fig. 1) *(23)*.

The physiology of the porcine circulatory system is similar to that of humans. To address whether a size-matched miniature swine heart would meet the physiological needs of a human host, we performed a preliminary analysis of the hemodynamic parameters of ejection fraction, stroke volume, and cardiac output in pigs chosen as the appropriate size to donate hearts to a 70-kg human. Swine were placed on cardiopulmonary bypass to vary preload and afterload conditions independent of the right and left ventricles at a fixed heart rate. We found that left ventricular performance was never limiting in the face of high volume and pressure loads. Right ventricular performance was also maintained with increased right ventricular afterload. However, progressive volume loading of the right ventricle under conditions of fixed systemic afterload eventually led to dilatation of the tricuspid annulus and tricuspid regurgitation. These data suggest that the function of a size-matched cardiac xenograft from a miniature swine would be adequate to meet the hemodynamic requirements of a human recipient, but efforts should be made to avoid volume overload in the early postoperative period *(23)*.

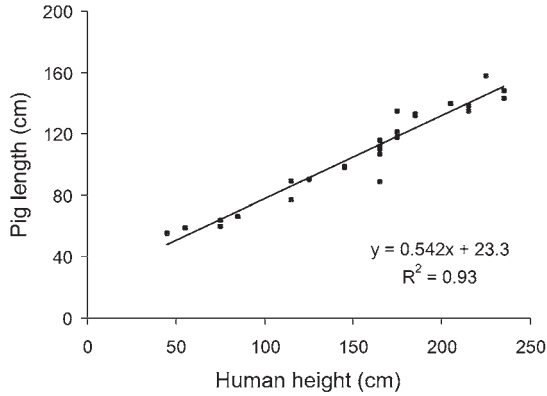


Fig. 1. Swine-to-human cardiac size-matching nomogram. Swine aortic dimensions are highly correlated with a pig's body length. By analogy, human aortic annulus diameter is also highly correlated with a person's height. By comparing echocardiographic swine data to normative human data, we were able to construct a size-matching nomogram. This nomogram predicts the best size-matched pig for a prospective human cardiac xenograft recipient by matching for aortic annulus diameter. (Reproduced with permission from ref. *23*.)

There are additional advantages to using MHC-inbred miniature swine as xenograft donors. Swine express blood groups equivalent to human ABO blood groups. To diminish an immune response against AB antigens, group H (equivalent to human blood group O) miniature swine have been selectively bred for the purpose of transplantation. From the perspective of genetic engineering, incorporating transgenes into a line of pigs from the same inbred herd would permit quicker crossbreeding than possible if different breeding stocks were used. Also, because the major MHC of inbred miniature swine donors has been fully characterized *(24–26)*, a strategy of introducing relevant porcine MHC genes into the bone marrow of human recipients before transplantation could be undertaken possibly to induce tolerance. This process, termed *molecular chimerism*, has proven effective in prolonging the survival of allografts *(11,27)*. Finally, whereas primates may harbor infectious agents such as herpes B virus that can be lethal for human recipients, pigs can be bred to exclude serious human pathogens *(28)*.

HISTORY OF XENOTRANSPLANTATION

Keith Reemtsma introduced xenotransplantation to clinical medicine in 1963 when he performed the first chimpanzee-to-human renal

transplant *(29)*. The following year, James Hardy attempted the first human cardiac xenotransplant in the first reported attempt to transplant a heart of any sort into a human recipient *(30)*. The chimpanzee heart that Hardy grafted into his 68-year-old patient dying of end-stage heart failure survived for approx 1 hour after the cessation of cardiopulmonary bypass, but was subsequently "judged incapable of accepting the large venous return" because of an obvious size mismatch *(30)*. In retrospect, the rapidity of spontaneous cardiac dysfunction strongly implicated hyperacute rejection as the mediator of graft loss. Although others have attempted cardiac xenotransplantation, none achieved patient or graft survival *(31)*. These early failures, combined with the dramatic increase in available organ donors because of the widespread acceptance of the concept of brain death in the late 1960s *(32)*, led to a diminished interest in xenotransplantation over the next 15 years.

In 1984, clinical interest in xenotransplantation was rekindled when Bailey transplanted an ABO-incompatible baboon heart into a neonate born with hypoplastic left heart syndrome *(33)*. Using an intensive immunosuppression regimen and a baboon donor selected for eliciting the weakest xenogeneic response in mixed lymphocyte cultures, Bailey and colleagues successfully avoided hyperacute rejection. However, on postoperative day 20, the patient succumbed to an infection, most likely related to the high levels of immunosuppression necessary to abrogate hyperacute rejection. Postmortem microscopic analysis revealed a mononuclear cellular infiltrate with capillary thrombosis suggestive of acute vascular rejection.

Since Bailey et al.'s report *(33)*, there have been at least two attempts at pig-to-human heart transplantation in addition to attempts at pig-to-human liver *(34)* and islet cell *(35)* and baboon-to-human bone marrow transplantation *(36)*, but none of these endeavors resulted in a clear-cut clinical benefit. Perhaps the most encouraging xenotransplantation results to date are in the treatment of neurological disorders *(37,38)*, for which fetal pig neural cells transplanted into the brain of a patient suffering from Parkinson's disease survived over 7 months with appropriate growth of nonhuman dopaminergic neurons using only cyclosporine for immunosuppression *(39)*.

Although advances in the clinical arena have been modest, enormous progress has been made in the scientific investigation of xenotransplantation. Not only have the immunological barriers to successful xenotransplantation been more clearly defined, but also the potential solutions to these problems have increased in number and promise.

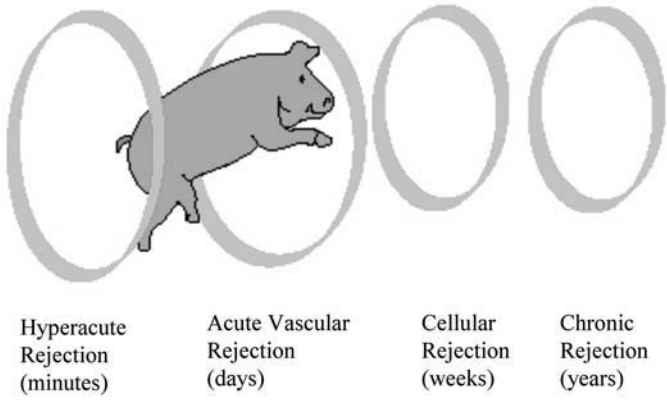


Fig. 2. Immunological obstacles in pig-to-primate transplantation. Xenografts will have to pass through four immunological "hoops" (phases) of the host response before long-term graft acceptance can be achieved. (Modified with permission from ref. *185*.)

IMMUNOLOGICAL OBSTACLES

The earliest and perhaps most devastating immunological barrier to xenotransplantation is that of *hyperacute rejection*, which results from the binding of natural antibody to the vascular endothelium of the donor, fixation of complement, activation of the endothelium, and finally the initiation of the coagulation cascade. As illustrated in Fig. 2, other important but less well-understood immunological barriers include (1) acute vascular rejection (also called delayed xenograft rejection or acute humoral xenograft rejection), which probably involves multiple pathways, including antibodies and/or immune cells binding to endothelium and endothelial cell activation; (2) cellular rejection, which involves mechanisms similar in nature, albeit stronger in intensity, to those responsible for clinical allograft rejection; and (3) chronic rejection, which remains enigmatic in both allogeneic and xenogeneic transplantation, but would likely develop following pig organ transplantation in a human unless all immune mechanisms of rejection had been overcome. Because little is known about chronic xenograft rejection, it is not discussed further.

Hyperacute Rejection

When a heart is transplanted from one species into a phylogenetically disparate species (i.e., pig to primate), an extremely fulminant immunological reaction ensues within minutes of organ reperfusion.

Fig. 3. (A) Photograph taken of a normal pig heart transplanted into the neck of an untreated baboon just after the arterial and venous anastomoses are opened.

The once-normal-appearing myocardium becomes dusky and cyanotic, with diminished, if not absent, contractility (Fig. 3). Widespread intravascular thrombosis and interstitial hemorrhage characteristic of a hypercoagulable state mark the histology of this hyperacute rejection response (Fig. 4). The three major physiological components responsible for this hyperacute rejection response are (1) binding of preformed xenoreactive natural antibodies to carbohydrate moieties on the vascular endothelium of the donor organ, (2) activation of the complement cascade within the recipient, and (3) endothelial cell activation.

Preformed Natural Antibodies

It was realized as early as the mid-1960s that hyperacute rejection was caused by antibody-mediated complement activation *(40,41)*. However, it was not until the early 1990s that it became clear just

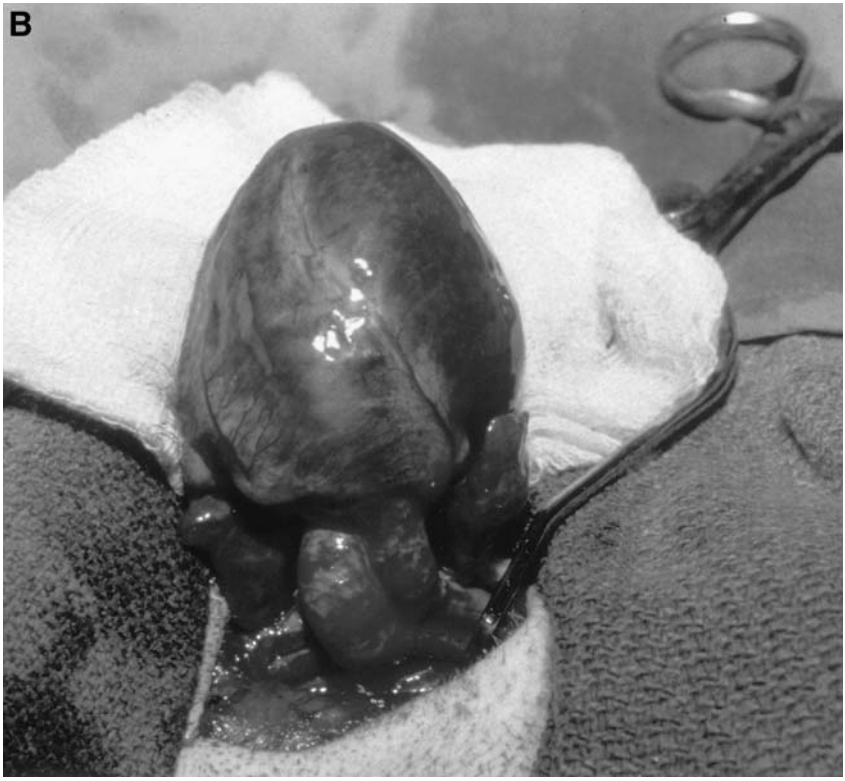


Fig. 3. (B) Photograph of the same pig heart taken 10 minutes after reestablishment of blood flow showing the dusky, cyanotic appearance typical of hyperacute rejection.

what porcine antigen was targeted by human natural antibodies. Although it might be imagined that human natural antibodies would recognize a wide array of antigens on pig organs, it has been documented that more than 80% of human complement-fixing natural antibodies recognize a single structure, Galα1-3Gal, a carbohydrate structurally similar to blood group antigens A and B. It was the seminal work of Good and Cooper *(42,43)* and Galili and colleagues *(44,45)* that clearly established the Galα1-3Gal terminal residue (abbreviated as αGal) on pig endothelium as the determinant responsible for binding the major portion of preformed human natural antibodies.

Expression of the αGal epitope is governed by the presence of an α-galactosyltransferase (αGT) enzyme that catalyzes the reaction *(44)*

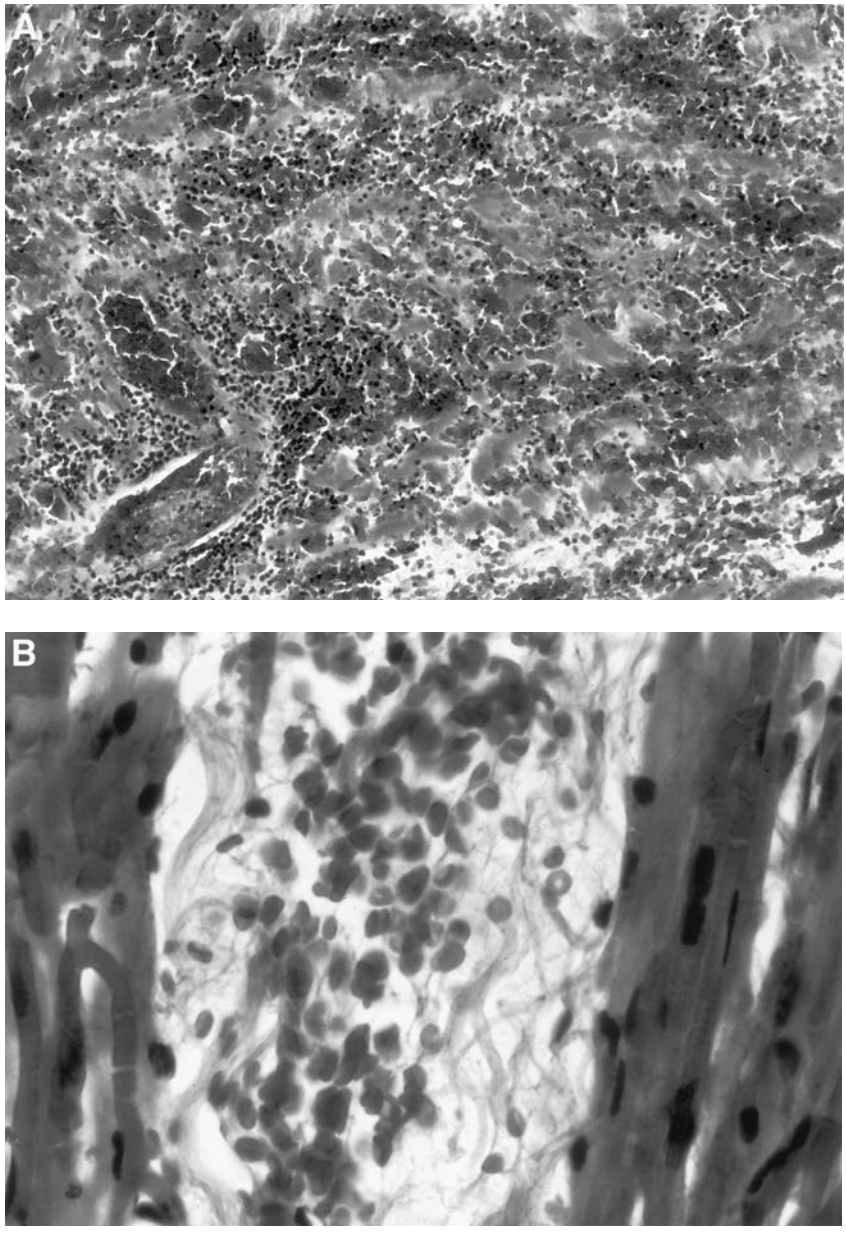


Fig. 4. Photomicrograph of a myocardial biopsy from a hyperacutely rejected pig heart stained with hematoxylin and eosin showing **(A)** interstitial hemorrhage and **(B)** intravascular thrombosis.

$$Gal\beta 1\text{-}4GlcNAc\text{-}R + UDP - Gal\alpha^{\alpha 1,3GT} > Gal\alpha 1\text{-}3Gal\beta 1\text{-}4GlcNAc\text{-}R + UDP$$

This enzyme is found in New World monkeys and all lower order mammals (including swine). As a result, these species express the αGal epitope on their vascular endothelium and do not have circulating anti-αGal antibody. In contrast, humans and all higher order primates (e.g., chimpanzees, baboons, and Old World monkeys) have lost the gene for αGT. The lack of constitutive αGal expression in these higher order species permits the formation of antibodies directed against the endothelial αGal determinant.

These anti-αGal antibodies are not a constitutive part of the immunoglobulin repertoire of the developing fetus and therefore do not exist at birth. Transplantation of a porcine organ into a newborn baboon that lacks xenoreactive antibodies but has an intact complement system does not result in hyperacute rejection *(46)*. It is believed that, like the natural antibodies that bind blood group antigens, immunoglobulins that bind to the αGal epitope develop as a consequence of exposure to environmental microorganisms that express the same carbohydrate determinants *(47)*. Parenthetically, the loss of the α-galactosyltransferase gene during evolution may have provided a survival advantage by allowing the development of anti-αGal antibodies that could defend against environmental pathogens, including viruses that express this determinant *(48)*.

The majority of natural antibody responsible for binding the αGal epitope on the pig endothelium is of the immunoglobulin (Ig)M isotype; it accounts for as much as 4% of the total circulating IgM in humans *(49)*. It is highly likely that only IgM (but not IgG) natural antibodies can cause hyperacute rejection, probably because the greater number of receptors on the IgM compared to IgG antibodies increase its binding avidity sufficiently to trigger complement activation *(49,50)*. Interestingly, when humans are exposed to pig tissue, either through extracorporeal perfusion of a pig organ, pig islet cell, or bone marrow transplantation, the rise in levels of anti-αGal IgG is significantly greater than the corresponding rise in anti-αGal IgM *(51)*. It is thought that these IgG anti-αGal antibodies may promote antibody-dependent cell-mediated cytotoxicity by binding natural killer cells and macrophages through the Fc portion of the antibody. This mechanism of xenograft destruction is probably more important in acute vascular rejection than in hyperacute rejection (*see* Acute Vascular Rejection section). Although antibodies to foreign alloantigens may exist in prospective recipients because of prior exposure, preformed IgG

antibodies directed against foreign MHC molecules do not seem to play a major role in hyperacute rejection *(52)*, but may become important in acute vascular rejection *(53)*.

Complement Activation

The development of hyperacute rejection depends on the activation of complement. In some models of discordant xenotransplantation (i.e., guinea pig to rat), complement is activated through the alternative pathway in the absence of preformed antibody *(54–56)*. However, in what is considered the most clinically relevant model, pig to primate, complement is activated through the classical pathway after binding of natural antibody and formation of antigen–antibody complex *(57,58)*. In either case, the terminal event in the complement cascade is the formation of the membrane attack complex (MAC), which mediates cytolysis by forming pores in cell membranes *(59–61)*. However, the MAC is probably not the only complement component implicated in hyperacute rejection. Inflammatory mediators such as C3b and terminal complement proteins undoubtedly contribute to the process *(62,63)*.

In humans, the vigor of the complement cascade is regulated by a number of endothelial proteins, including decay-activating factor (DAF or CD55), membrane cofactor protein (MCP or CD46), and CD59. These complement regulatory proteins are membrane glycoproteins that act as inhibitors at several key points in the cascade at which the activation of both pathways may be halted. Of major importance in discordant xenotransplantation is the fact that these regulatory proteins are effective only with complement proteins of their own species *(64)*. Indeed, part of the reason why the hyperacute rejection response is so intense and universal in pig-to-human transplantation is that the species-specific pig complement regulatory proteins in the xenograft are unable to control human complement proteins, resulting in uncontrolled activation of the host's complement system. This concept is the basis for the creation of transgenic animals expressing human complement regulatory proteins, with the hope that organs from such animals would resist injury by human complement (*see* Genetic Engineering section).

Type I Endothelial Cell Activation

Resting endothelium and the molecules expressed on the surface of quiescent endothelial cells perform several important functions, including prevention of intravascular coagulation and platelet aggregation. The binding of xenoreactive antibodies and activation of complement on the endothelial surface stimulates the resting endothelium to initiate

a rapid, protein-synthesis-independent response referred to as *type I endothelial cell activation (65)*. This response is manifested by (1) a change in endothelial cell shape *(66)*, (2) the loss of heparan sulfate from the cell surface *(67)*, and (3) the elaboration of proinflammatory cytokines, chemokines, and adhesion molecules *(68)*.

Reconfiguration of endothelial cell shape causes the cells to separate from one another, forming gaps that allow intravascular fluid to extravasate and platelets to be activated through contact with matrix. The loss of heparan sulfate increases sensitivity to oxidant-mediated injury and gives rise to procoagulant changes on the endothelial surfaces. The elaboration of inflammatory mediators also contributes to vasoconstriction and to direct injury by polymorphonuclear leukocytes. The attachment and activation of platelets leads to the release of a variety of vasoactive substances, such as thromboxane A_2, that constrict vascular smooth muscle and alter regional blood flow. Together, these changes account for the early intravascular thrombosis and extravascular hemorrhage observed in hyperacute rejection.

Prevention of Hyperacute Rejection

The pharmacological immunosuppressive agents currently used to treat allogeneic rejection have no effect in the prevention of hyperacute rejection. Therefore, new and different approaches have been devised to overcome early xenogeneic rejection. Because the two principal factors that precipitate hyperacute rejection are xenogeneic antibodies and complement, these circulating plasma constituents and their receptors have been targeted for elimination or inhibition in attempts to prevent this process.

Depletion or Inhibition of Anti-αGal Antibody

Four primary methods of depleting or inhibiting anti-αGal antibody and prolonging experimental xenograft survival have been described. They include (1) plasmapheresis *(69–71)*, (2) donor organ perfusion *(57,72)*, (3) extracorporeal immunoadsorption *(73)*, and (4) oligosaccharide infusion *(74)*. Although effective to varying degrees at removing or inactivating natural xenogeneic antibodies, none of these techniques has proven successful in preventing their return. Xenoreactive antibodies usually return within 24 to 48 hours in untreated recipients and between 5 and 7 days in immunosuppressed hosts.

Plasmapheresis represents an effective, albeit nonspecific, method of removing xenogeneic antibody. Plasmapheresis can effectively remove IgM antibodies and, when combined with other therapies such as splenectomy, T-cell depletion, and pharmacological immunosuppres-

sion, has resulted in prolongation of pig kidney or heterotopic heart grafts up to 23 days in baboons *(75)*. However, in addition to preformed anti-αGal antibodies, plasmapheresis also eliminates useful proteins that contribute to hemostasis and antimicrobial defense. Furthermore, plasma exchange can cause paradoxical thrombosis secondary to an increase in the synthesis of acute phase-reactant proteins *(76)*. For these reasons, methods have been developed that selectively target xenogeneic antibodies for removal or inactivation.

Donor organ perfusion is more selective than plasmapheresis in removing natural antibodies directed against αGal. This technique involves connecting a vascularized organ from the prospective donor (e.g., a swine liver) to the recipient's (e.g., baboon) circulatory system through catheter connections and then perfusing the organ with three or more of the recipient's circulating blood volumes. During this process, the recipient's xenogeneic antibodies are adsorbed out of the recipient's circulation and onto the vascular endothelium of the donor organ, which is then discarded. A second organ from the donor swine (e.g., a heart) is then transplanted into the antibody-depleted recipient baboon. Cooper et al. *(72)* used porcine kidneys to absorb out natural antibody in baboon recipients that subsequently received pig hearts. Survival of the cardiac xenografts was prolonged from 3 hours in untreated controls to 4–5 days in the group treated with donor organ perfusion.

Although donor organ perfusion is effective in depleting natural antibody, its clinical utility has been reduced by the development of immunoaffinity columns that are more specific, efficient, and safe. Extracorporeal immunoadsorption uses synthetic immunoaffinity columns containing αGal oligosaccharides (Fig. 5). When placed in-line with the recipient's circulation, these highly specific immunoaffinity columns deplete only those antiswine antibodies detrimental to the transplant *(73,77)*. More than 99% of anti-αGal IgM and 97% of anti-αGal IgG can be depleted by this technique *(75)*. Unfortunately, like donor organ perfusion, extracorporeal immunoadsorption is unable to prevent the return of the anti-αGal antibodies. Indeed, even with adjunctive therapy (i.e., pharmacological immunosuppression and splenectomy), the reduction in natural antibody is always transient and is sometimes followed by a rebound within several days to levels of antibody higher than that observed at baseline *(62,63)*.

Another experimental approach involves treating the recipient with continuous intravenous infusion of synthetic or natural αGal oligosaccharides to inhibit natural antibody *(78)*. The infused oligosaccharides are bound by circulating anti-αGal antibodies that are no longer free to attack a subsequently transplanted organ. The infused sugar, however,

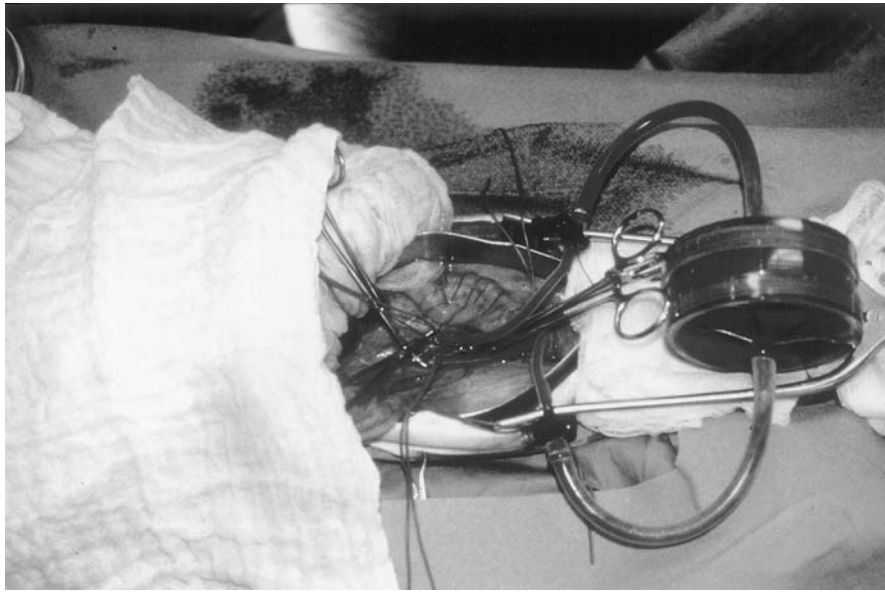


Fig. 5. Perfusion of an αGal oligosaccharide immunoaffinity column with baboon blood. Blood enters the column via a cannula connected to the aorta, and it is returned to the animal by way of a cannula connected to the inferior vena cava. This technique has supplanted liver perfusion for adsorption of natural antibody in nonhuman primates.

is rapidly excreted, making this tactic limited by the difficulty and expense of synthesizing large quantities of oligosaccharides. This problem may be solved by new enzymatic methods to produce the relevant oligosaccharides *(78)*. An alternative to the use of αGal oligosaccharides, either in immunoaffinity columns or as intravenous infusions, is murine-derived antiidiotypic antibodies. Initial studies with these murine antibodies directed against human antipig antibodies have shown them to be effective in temporarily inhibiting circulating anti-αGal antibodies in baboons *(79,80)*. Better results have been obtained using bovine serum albumin conjugated to Gal oligosaccharides *(81)* or multiple Gal molecules conjugated to a poly-L-lysine backbone (GAS914) (D. K. C. Cooper, personal communication, June 2001).

In summary, the ideal technique to remove or inactivate preformed natural xenogeneic antibodies and prevent their return without jeopardizing the baseline immunological properties of circulating nonxenogenic antibodies has not been achieved. More recent efforts to have an impact on natural antibody have concentrated on attempts to eliminate or toler-

ize the B cells that produce the αGal antibodies by genetic engineering *(82–84)* (*see* Genetic Engineering section).

Suppressing Complement Activation

Attempts to control complement activation in the host have made use of systemic treatment with either purified cobra venom factor or soluble complement receptor type 1 (sCR1). By activating C3b, purified cobra venom factor is very effective in depleting complement and temporarily protecting a discordant xenograft from hyperacute rejection *(85,86)*. However, even with the addition of concomitant pharmacological immunosuppression, treatment with cobra venom factor typically delays rejection by only a matter of days. Within 1 week, xenografts usually develop the histopathological features of acute vascular rejection and fail. The longest survival of a pig organ in a nonhuman primate treated with cobra venom factor has been 27 days *(87)*.

The sCR1is also effective in suppressing complement activation and prolonging the survival of discordant xenografts *(88,89)*. The sCR1 molecule is a soluble form of the human complement receptor 1*(90)*, which is found on most lymphohematopoietic cells. By competitively binding to complement receptor 1, sCR1 inhibits both the classic and alternative pathways of complement activation. Discordant xenografts have survived for more than 3 weeks in recipients treated with sCR1 *(88)*. However, like purified cobra venom factor, the protection afforded the xenograft by sCR1 is temporary.

Genetic Engineering

Perhaps the most significant advance in providing long-term suppression of complement activation has been achieved using genetically engineered swine. Using microinjection techniques, transgenic swine have been created that express human complement regulatory proteins on their vascular endothelium *(91,92)* (Fig. 6). Because these regulatory proteins are species specific, functioning effectively only with the complement proteins of their own species, it was hypothesized that organs from swine that express human regulatory proteins would successfully inhibit the activation of human complement.

The concept of expressing human inhibitors of complement in the pig originated with Dalmasso and colleagues *(64)* and was based on earlier work by Medof et al. *(93)*. When human decay accelerating factor (hDAF or CD55) was incorporated into porcine endothelial cells in vitro, it rendered the pig endothelial cells resistant to cytotoxicity mediated by human complement in a dose-dependent fashion. Of note, the level of functional hDAF expressed on pig endothelial cells that

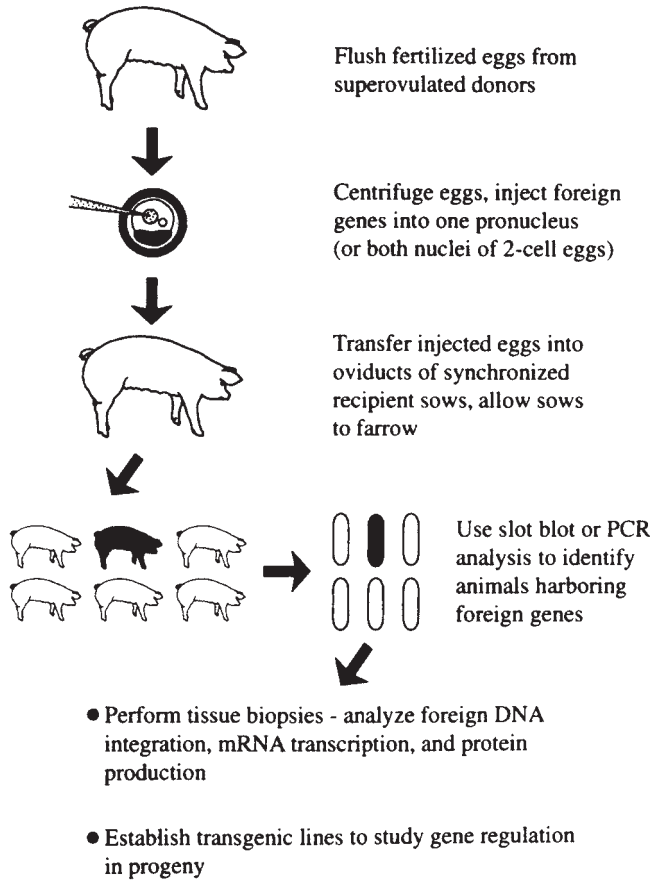


Fig. 6. Creation of transgenic swine. mRNA, messenger ribonucleic acid. (Courtesy of Stem Cell Sciences, Melbourne, Australia.)

was required to abrogate hyperacute rejection was much higher than that normally present on human endothelial cells *(94,95)*. However, exactly how much higher the levels of hDAF must be to prevent hyperacute rejection is unclear.

White and colleagues *(91,96)* have successfully bred transgenic swine that express hDAF on their vascular endothelium. When hearts from these hDAF pigs were heterotopically transplanted into nonimmunosuppressed cynomolgus monkeys, hyperacute rejection was successfully avoided. The hDAF hearts survived for up to 5 days (range 97–126 hours); control hearts from nontransgenic pigs survived for an average of 1.6 days (range 0.4–101 hours) *(97)*. Adding pharmaco-

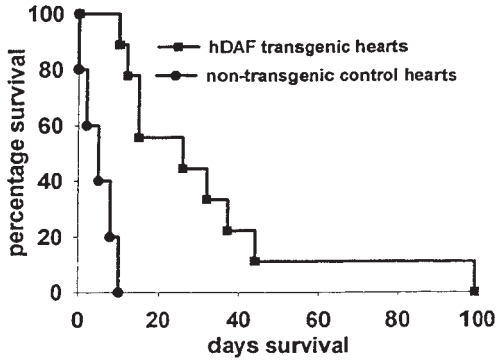


Fig. 7. Survival of hearts from hDAF transgenic swine (n = 9; median survival 26 days) and normal controls (n = 5; median survival 5 days) transplanted heterotopically into immunosuppressed cynomolgus monkeys. (Reproduced with permission from ref. *98*.)

logical immunosuppression (cyclosporine, cyclophosphamide, and methlyprednisolone) extended hDAF heterotopic cardiac xenograft survival to a median of 40 days *(97)*, with one hDAF heart surviving for 99 days *(98)* (Fig. 7).

Kuwaki and colleagues further intensified the immunosuppressive regimen by adding pretransplant T-cell depletion with low CD2, the costimulation inhibitor anti-CD154, and continuous anticoagulation with heparin. Using this regimen, heterotopic hDAF heart grafts survived in baboons for up to 139 days, which is the longest survival of a non-life-supporting, pig-to-primate organ to date *(99)*. White and colleagues demonstrated that hearts from hDAF transgenic pigs transplanted orthotopically into immunosuppressed baboons were not hyperacutely rejected and were capable of maintaining an adequate cardiac output for up to 39 days *(12,100)*.

Transgenic swine have also been created which express CD59 *(101)*. When hearts from CD59 transgenic pigs were transplanted into baboons, there was diminished complement activation, as demonstrated by the markedly reduced deposition of the MAC *(101)*. Orthotopic transplantation of CD59-expressing pig hearts into baboons treated with plasmapheresis, steroids, and cyclosporine resulted in up to 2-week survival compared to the 24- to 30-hour survival of nonengineered control hearts *(102)*.

Transgenic swine have been produced that express both hDAF and human CD59 proteins on their vascular endothelium. Early results suggested that the survival times of hearts from these double-transgenic

swine do not exceed the survival times of hDAF-expressing hearts *(103)*. However, organ-specific expression of the transgenes in the double-transgenic animals was less than that observed in human tissue; therefore, improved results might be observed with better expression of the two transgenes *(104)*.

A second approach to genetic engineering donor swine is competitive glycosylation, which involves inserting a gene that competes with or masks the αGal epitope with an overabundance of another oligosaccharide epitope *(105,106)*. For instance, the α1,2-fucosyltransferase (or H-transferase) gene, which humans use to form the blood group O antigen, has been transferred into mice *(107)* and swine *(108)*. In vitro experiments confirmed that, by competing successfully for substrate with the galactosyltransferase enzyme, transfer of the H-transferase gene reduced the expression of αGal to a remarkable degree (<5% of its original expression) *(107,108)*. However, it is unclear at present what percentage of αGal expression must be eliminated before hyperacute rejection is completely prevented.

Nuclear Transfer (Cloning). Another exciting approach is to eliminate or knock out the gene that codes for the αGT enzyme in the porcine donor. That would eliminate the αGal epitopes and theoretically leave no target for human anti-αGal antibodies *(109)*. Reports have shown that knocking out the α1,3GT gene in the pig is feasible. Using nuclear transfer technique, two groups have produced piglets in which one copy of the α1,3GT gene was disrupted *(110,111)*. They isolated somatic cells from porcine fetuses for production of donor cell lines and replaced the endogenous allele for α1,3GT with a targeting vector. Successful knockout at the α1,3GT locus was confirmed by reverse transcription polymerase chain reaction (RT-PCR) and Southern blot analyses *(110)*. Several lines of cells with the desired knockout were produced, and subsequently the deoxyribonucleic acid (DNA) content of the prepared cells was transferred into in vitro-matured oocytes. The nuclear transfer embryos were finally transferred to the oviducts of the recipient female pig. α1,3GT-null pigs with both α1,3GT-alleles inactivated (homozygotes) have been created through natural breeding of male and female heterozygous knockout animals and by targeted disruption of both alleles of the α1,3GT gene in cloned pigs *(112)*.

Initial studies using the first three homozygous (double α1,3GT knockout) donors available (provided by R. Prather, Missouri, and Infigen, Wisconsin) were performed in the laboratory of David H. Sachs. Baboons received hearts, kidneys, thymokidneys, or kidneys plus vascularized thymic lobes *(113)* from homozygous α1,3GT-

knockout pigs. The recipients received either standard immunosuppression or a tolerance induction protocol (*see* Mixed Chimerism). Standard immunosuppression consisted of anticoagulants, steroids, T-cell depletion, mycophenolate mofetil, and anti-CD154 monoclonal antibody with or without cobra venom factor during the first 2 weeks. The tolerance protocol included thymectomy and transplantation of vascularized xenogeneic thymic tissue, either as a vascularized thymic lobe transplant or as part of a composite thymokidney, in which autologous donor thymic tissue had been implanted 6 to 12 weeks prior to transplantation.

These preliminary studies produced two exciting findings. First, even with no antibody or complement depletion, organs from homozygous α1,3GT-knockout donor suffered no hyperacute rejection and survived for over 81 days *(99)*. Second, when immunosuppression was weaned off recipients undergoing the tolerance protocol, excellent organ function was maintained for more than 81 days *(113)*. The success of these pioneering experiments represents a quantum leap forward in bringing xenotransplantation to the clinic.

B-Cell Tolerance. A genetic engineering approach to eliminating natural antibodies can also be aimed at inducing tolerance to αGal antibody-producing B cells in the recipient. This approach involves introducing a functional αGT gene into host autologous bone marrow-derived cells by retroviral gene transfer, resulting in the expression of αGal epitopes at the cell surface. Because it is presumably the absence of the αGT gene in Old World primates and humans that permits the production of αGal antibodies, introduction of the αGT gene into the bone marrow of these animals should inhibit their production *(114)*.

To test this hypothesis, Iacomini and colleagues *(83)* used αGT knockout mice, which, like humans, make αGal antibody *(115)*. Bone marrow from αGT knockout mice was transduced with the gene encoding pig αGT. This transduced marrow, which now expressed αGal epitopes, was then used to reconstitute lethally irradiated syngeneic αGT knockout mice. In contrast to unmodified αGT knockout mice, the αGT knockout mice reconstituted with αGT-transduced marrow failed to produce anti-αGal antibodies and showed no return of these antibodies *(83)*. Furthermore, they made no anti-αGal antibody in response to a subsequent challenge with pig cells *(116)*. This represents the first demonstration that production of preexisting natural antibodies can be inhibited by a gene therapy approach *(114)*.

In summary, creation of a pig lacking both α1,3GT alleles has brought xenotransplantation much further toward clinical applicability.

The α1,3GT knockout donor organs appear resistant to hyperacute rejection without the need for removal or inhibition of natural antibodies or complement. This opens the field for further exploration of other ill-defined barriers to xenotransplantation, namely, acute vascular rejection and cellular rejection.

Acute Vascular Rejection

Even when hyperacute rejection is prevented in discordant species combinations using one or more of the methods described above, vigorous rejection still develops days to weeks following transplantation. This delayed rejection response is characterized by the same diffuse intravascular coagulation and lack of cellular infiltrate seen in hyperacute rejection. The timing and histology of this process is suggestive of an induced humoral response that, like hyperacute rejection, targets the vascular endothelium. Indeed, there is an emerging consensus that acute vascular rejection is initiated by returning or residual anti-αGal antibodies in addition to xenoreactive antibodies induced to other swine cell surface molecules, such as donor MHC antigens *(53,117,118)*.

Type II Endothelial Cell Activation

Like hyperacute rejection, the primary component in the pathophysiology of acute vascular rejection is endothelial activation. However, unlike hyperacute rejection, endothelial activation occurs more slowly, allowing time for new gene transcription and protein synthesis by the endothelium. Furthermore, it is controversial whether this activation requires complement *(53)*. This delayed endothelial activation is sometimes referred to as type II activation because it represents a different process from the type I endothelial activation associated with hyperacute rejection.

The exact sequence of events that leads to acute vascular rejection remains unclear. Xenogeneic antibodies appear to play a predominant role *(53)*. In addition to antibody, there are cellular elements that can initiate type II endothelial cell activation through the elaboration of cytokines *(119)*. Most notable are monocytes and natural killer cells, which activate endothelial cells through the production of tumor necrosis factor-α and interferon-γ, respectively *(83,120)*.

There are two predominant physiological consequences of type II endothelial activation. One is the generation of a procoagulant state caused by the loss of thrombomodulin and other regulators of thrombosis, such as heparan sulfate *(121–123)*. Thrombomodulin normally binds thrombin and leads to the activation of protein C, which has anti-

coagulant effects *(124)*. Downregulation of endothelial thrombomodulin results in loss of these anticoagulant mechanisms. Heparan sulfate produces its antithrombotic effect by binding or complexing to antithrombin III, thereby interfering with thrombin activity. Loss of heparan sulfate from the endothelial cell surface results in the loss of anticoagulant activity via antithrombin III inhibition of blood coagulation proteases and the induction of tissue factor activity *(67,124–127)*.

The other physiological consequence of type II endothelial activation is the upregulation of a large number of proinflammatory genes encoding molecules such as interleukin (IL)-1, E-selectin, P-selectin, intercellular adhesion molecule I, and vascular cell adhesion molecule 1. In addition, the activated endothelial cells secrete IL-1, IL-6, and IL-8 as well as platelet-activating factor and plasminogen activator inhibitor. IL-l is stimulatory to the endothelium and functions to activate monocytes. IL-8 is a chemoattractant for leukocytes, and it mimics some of the functions of C5a. Platelet-activating factor serves to activate neutrophils and platelets. Secretion of plasminogen activator inhibitor inhibits the naturally occurring action of tissue plasminogen activator and results in a decrease in the fibrinolytic activity on the endothelial cell surface. This provides the physiological basis for the pathological findings of platelet aggregation and clot formation in acute vascular rejection. Of note, these events are thought to be in part the consequence of an increase in transcriptional activity mediated by nuclear factor-κB (NF-κB) *(128–131)*.

Prevention of Acute Vascular Rejection

Because of the importance of antibody in acute vascular rejection, current therapies to control this immune response have been primarily directed against B cells. Treatment protocols have included cyclophosphamide, leflunomide, brequinar, 15-deoxyspergualin, and methotrexate *(62)*. However, these regimens are not without substantial toxicity and mortality. Based on current knowledge, inducing robust tolerance to αGal *(83)* or even eliminating the αGal saccharide on donor endothelium (αGT knockout) may still not prevent acute vascular rejection because antibodies other than those directed against αGal are contributory *(132)*.

NF-κB and Protective Genes

Given the large number of proinflammatory genes that are upregulated in type II endothelial activation as a consequence of the tran-

scriptional factor NF-κB *(128–130,133,134)*, Bach *(65)* suggested that targeting NF-κB for inhibition would be an ideal way to prevent acute vascular rejection. NF-κB is present in the cytoplasm of quiescent endothelial cells and is associated with an inhibitory protein, IkBα *(134–136)*. On type II endothelial activation, IkBα is degraded, which releases and activates NF-κB *(137–139)*. NF-κB is then translocated to the nucleus, where it binds to the targeted DNA sequence and activates transcription of various proinflammatory and prothombotic genes.

In studying ways of inhibiting NF-κB, Cooper and colleagues *(140)* investigated the role of antiapoptotic genes in endothelial cells. Their in vitro findings demonstrated that three genes, *A20*, *bcl-2*, and *bcl-xl*, not only prevented apoptosis, but also were effective at blocking the upregulation of NF-κB. The expression of these "protective" genes in endothelial cells blocked the upregulation of the proinflammatory genes in vitro *(65)*. Further evidence that these particular genes exert a protective influence comes from studies in a hamster-to-rat cardiac xenograft model in which recipients were treated with daily cobra venom factor and cyclosporine. All the surviving xenografts expressed the antiapoptotic genes in their endothelium, whereas the endothelium from hearts that were rejected did not *(141)*.

Based on these results, Bach and colleagues argued that acute vascular rejection could be prevented by the expression of protective genes *(141)*, including the stress-response gene *HO-1 (142)*, on the graft vasculature. This is illustrated by the observation that hearts from *HO-1*-deficient ($HO\text{-}1^{(/(}$) mice transplanted into rats treated with cobra venom factor and cyclosporine underwent acute vascular rejection, whereas hearts from wild-type ($HO\text{-}1^{+/+}$) mice transplanted under the same regimen survived long term *(142)*. The exact molecular mechanism responsible for the cytoprotective effects of *HO-1* remains unclear. However, recent studies have suggested that carbon monoxide contributes in a critical manner to the overall antiinflammatory actions of *HO-1 (143)*.

Goodman and colleagues suggested that genetic modifications of donor animals by the transgenic expression of protective genes that inhibit NF-κB and prevent apoptosis might be used to prevent acute vascular rejection *(144)*. Another genetic engineering approach to the prevention of acute vascular rejection would be overexpression of antithrombotic molecules on the surface of resting endothelium (i.e., thrombomodulin) of the donor so that these antithrombotic molecules would not be lost during the initial phase of endothelial cell activation *(65,68,123)*.

Cellular Rejection

Accumulating evidence indicates that T cells can reject a xenograft with equal or even greater vigor than they reject an allograft *(145,146)*. This may be caused in part by a more diverse array of T-cell receptors capable of recognizing xenoantigens than alloantigens *(63)*. As in allotransplantation, T cells are able to respond both to direct presentation of xenogeneic antigens *(147)* and to xenogeneic peptides indirectly presented by self-antigen-presenting cells *(148)*. Furthermore, porcine endothelial cells are capable of directly presenting xenogeneic MHC antigens to human T cells and elicit a markedly stronger response than the allogeneic antiendothelial response *(149)*. In addition to T cells, NK cells, macrophages, and neutrophils have all been shown to play an active role in xenograft rejection (reviewed in refs. *53* and *63*).

Prevention of Cellular Rejection

It is clear that controlling T-cell-mediated rejection will be essential in bringing xenotransplantation to the clinic. Some of the nonspecific immunosuppressive agents that have been developed to suppress cellular immunity to allografts are likely to have a suppressive effect on the cellular response to discordant xenografts. However, the intensity of immunosuppression that would be required to prevent the rejection of a xenograft would be so great it would make the associated complications of infection, neoplasm, and drug-related side effects intolerable. Indeed, in pig-to-primate xenograft recipients, the high level of immunosuppression required to achieve even moderate survival has resulted in numerous deaths because of infection and drug-specific complications *(100,150)*.

Many scientists and transplant physicians feel that the success of clinical xenotransplantation will likely depend on developing ways to induce immunological tolerance in the human recipient to pig antigens *(145)*. Thus far, three experimental approaches to inducing T-cell tolerance across a xenograft barrier have been attempted: mixed chimerism, molecular chimerism, and thymic transplantation.

Mixed Chimerism

A promising way to induce tolerance across a xenogeneic barrier is by establishing mixed hematopoietic chimerism in the host through infusion of donor bone marrow at the time of organ transplantation. *Mixed chimerism* refers to a state in which both donor and host bone marrow progenitor cells coexist and populate the peripheral circulation

with hematopoietic cells of multiple lineages *(10,151)*. By way of comparison, *full chimerism* refers to a state in which all hematopoietic elements are derived from the donor. Full chimerism is achieved by ablating the host's hematopoietic system, usually through lethal irradiation, then reconstituting the host with allogeneic bone marrow. This strategy is useful for the treatment of some hematopoietic malignancies. However, full chimerism is neither necessary nor desirable for solid organ transplantation tolerance, partly because it requires a highly toxic myeloablative conditioning regimen.

Mixed chimerism can be achieved with much less toxicity and will still induce a state of donor-specific tolerance, as demonstrated by the pioneering work of Owen, Medawar, and others (reviewed in refs. *10* and *152*). Also, mixed chimerism is associated with the presence of residual host antigen-presenting cells, which is essential to ensure immunocompetence in the recipient because mature T-cell populations of both host and donor origin are restricted to the recognition of foreign antigens in the context of host MHC antigens *(153)*.

The establishment of mixed chimerism induces central deletional tolerance by actively "tricking" the recipient's immune system into treating donor antigens as self-antigens *(154)*. To achieve this goal, the host, until recently, has received some form of whole body irradiation to make "space" for a subsequent donor bone marrow transfusion. Once hematopoietic stem cells contained in the donor bone marrow engraft, they coexist with recipient stem cells and give rise to cells of all hematopoietic lineages. In addition, hematopoietic progenitor cells seed the thymus, giving rise to both T cells and dendritic cells *(155)*. Because hematopoietic cells from both the recipient and the donor collocate to the thymus, both self-reactive and donor-reactive T cells are eliminated by negative selection (the process that defines the phrase "central deletional tolerance") *(156)*. Consequently, the newly developing T-cell repertoire in mixed chimeras is tolerant toward the donor and remains so as long as chimerism persists *(157)*.

Based on the strategy of mixed chimerism developed in mouse models of xenotransplantation and successfully applied to large animal models of concordant xenotransplantation, Sachs and colleagues have investigated this strategy in the pig-to-nonhuman primate model (reviewed in refs. *10* and *63* and illustrated in Fig. 8). The early preparative regimen of lethal irradiation used to make space for the donor marrow has been supplanted by less-toxic nonmyeloablative methods. One such regimen involves depleting mature host T cells using antithymocyte globulin, anti-CD154 monoclonal antibody, cyclosporine, and

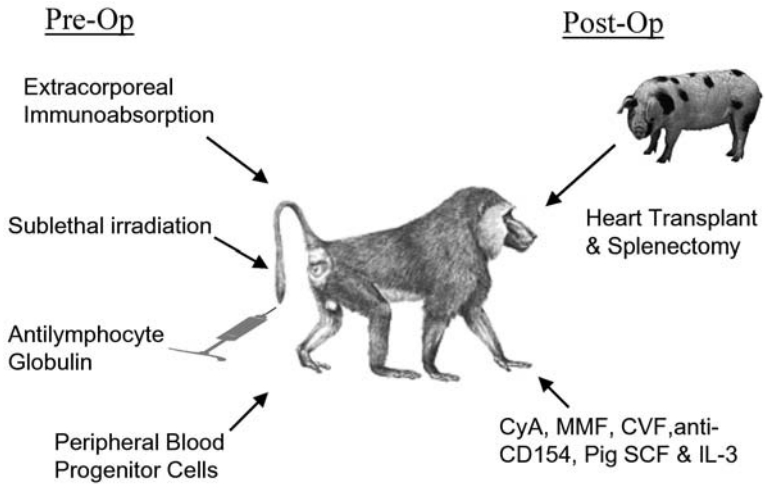


Fig. 8. A protocol for xenogeneic tolerance induction through mixed chimerism. Natural antibody is depleted through the extracorporeal immunoabsorption of the anti-αGal antibody on a solid matrix column that bears the α1,3Gal sugar moiety. Low-toxicity nonmyeloablative whole body radiation. Antithymocyte globulin and/or anti-T-cell monoclonal antibodies are used to remove mature T cells from the recipient. Cyclosporine (CyA) is added to immunosuppress any residual T cells in the posttransplant period. On day 0, the recipient receives high-dose cytokine-mobilized peripheral blood progenitor cells and a heart transplant from the same donor miniature swine. Splenectomy is performed and cobra venom factor (CVF) is added to diminish natural antibody effects. Recombinant cytokines (stem cell factor [SCF] and IL-3) are administered for 2 weeks after the preparative regimen to aid engraftment of the pig progenitor cells. (Modified from ref. *63* with permission.)

mycophenolate mofetil. Large numbers of cytokine-mobilized miniature swine peripheral blood progenitor cells (3×10^{10}/kg) are infused at the time of organ transplantation *(132)*, along with species-specific growth factors (pig recombinant stem cell factor and IL-3) to promote the survival of the pig cells *(83,158,159)*. To prevent antibody-mediated rejection of the porcine hematopoietic cells, extracorporeal immunoadsorption of anti-Gal antibodies *(57,160–162)*, in addition to cobra venom factor and host splenectomy, have been employed *(163,164)*.

Using this regimen, porcine cells have been detectable in conditioned baboons on occasion for more than 20 days by flow cytometry and for at least 1 month by PCR *(165,166)*. Invariably, however, there was return of anti-αGal antibodies, which coincided with loss of the pig cells. This precluded subsequent organ transplantation. Current efforts are therefore focusing on attempts to increase the engraftment of

porcine hematopoietic progenitor cells in primate recipients using bone marrow from αGal knockout animals *(167)*.

Molecular Chimerism

Successful engraftment of allogeneic or xenogeneic bone marrow cells carries with it the induction of tolerance to any other tissues or organs from the bone marrow donor. However, because of the difficulty encountered in inducing porcine cells to engraft in nonhuman primates, an alternative approach to tolerance has been developed that utilizes gene therapy techniques. Genes from the donor, coding for donor MHC antigens, are inserted into bone marrow cells of the host to induce T-cell unresponsiveness to those immunogenic molecules *(168)*. This strategy, termed *molecular chimerism*, is similar in concept to attempts at achieving B-cell tolerance by transducing autologous bone marrow cells with the αGT gene (discussed in the Hyperacute Rejection section). It is so named because molecular rather than cellular chimerism is established *(114)*.

This approach has induced prolonged acceptance of allogeneic skin grafts transplanted across an isolated MHC class I barrier in mice *(169,170)*. Furthermore, reconstitution of porcine recipients with autologous bone marrow transduced with an allogeneic MHC class II gene permitted successful renal transplantation in a fully mismatched miniature swine treated with a short course of cyclosporine *(11,27)*.

Based on these encouraging results, primates were reconstituted with autologous bone marrow transduced with porcine class II genes *(171)*. The transgene was detected for more than 12 weeks by PCR in most animals. When kidney xenografts were transplanted from pigs expressing the same MHC class II as the transgene, they succumbed to antibody-mediated rejection. However, late T-cell-dependent responses to the porcine xenografts were prevented, suggesting that the gene transfer led to diminution or possibly tolerance to some T-cell responses *(171)*.

Thymic Transplantation

The difficulty in coercing xenogeneic hematopoietic cells to migrate to the recipient thymus and induce deletional tolerance through a strategy of mixed chimerism might be overcome by replacing the recipient thymus with the thymus from the xenogeneic organ donor after host T-cell depletion and thymectomy. Support for this notion comes from studies in which thymectomized, T-cell-depleted mice transplanted with discordant pig thymic grafts not only demonstrated functional recovery of murine CD4 T cells in the pig thymic grafts *(172,173)*, but also became tolerant to donor xenogeneic skin grafts *(174)*.

In summary, the benefits of achieving immunological tolerance to xenografts have far-reaching implications. One of the major advantages of successful application of this strategy would be the avoidance of long-term immunosuppression, which has been implicated in the appearance of posttransplantation lymphoproliferative disease and other malignancies. Loss of transplanted organs from chronic rejection may not be a significant factor because the grafted organ presumably would escape the persistent immunological bombardment implicated in chronic rejection *(175)*. For further reading on this subject, excellent reviews are given in refs. *53, 63, 176,* and *177*.

INFECTIOUS DISEASE OBSTACLES

The possibility that an animal organ donor will pass an infectious agent (xenozoonoses) to a human xenograft recipient and that the infection may be passed to the human population in general has been the center of much debate *(6,178)*. On the one hand, transplanting a pig organ into a human patient bypasses many natural defenses or barriers to infection. Furthermore, the immunosuppression required to prevent xenograft rejection may result in a further reduction in the host's resistance to infections. Most concern has revolved around the transfer of porcine endogenous retroviruses (PERVs) *(179,180)*. These retroviruses are similar to human endogenous retroviruses, which are present in all human cells. Data have shown that PERVs are able to infect human cells in vitro *(181)*.

On the other hand, no known passage of PERVs to humans has ever occurred in vivo, and no human disease associated with PERVs (or for that matter human endogenous retroviruses) has ever been observed *(182)*. Also, using gnotobiotic techniques of delivering piglets, early weaning from the sow, and pathogen-free housing facilities may result in pigs actually representing less of an infectious threat than the current human donor pool for hearts, which frequently carries cytomegalovirus and Epstein-Barr virus, as well as hepatitis and human immunodeficiency virus *(2,176,183)*.

It is generally felt that the potential infection risk associated with successful discordant xenotransplantation remains uncertain, and that knowledge regarding both known and novel xenozoonoses must be expanded before progressing to major clinical trials of pig-to-human heart transplantation. For further reading, excellent reviews are given in refs. *2* and *184*.

SUMMARY

Within a relatively short time, a significant number of barriers to xenotransplantation have been identified and potential solutions generated. However, the survival rates for pig-to-primate heart transplantation remain modest at best, with the longest functioning heterotopic heart transplant surviving only 139 days *(99)*, and the longest functioning orthotopic heart transplant surviving only 39 days *(12,100)*. The most significant recent development has been the generation of α1,3GT double-knockout cloned pigs, which appears to have solved the problem of hyperacute rejection. Although prevention of hyperacute rejection will not, in and of itself, induce long-term acceptance of xenografts, it represents a major achievement and allows for further exploration of acute vascular rejection and cellular rejection. It is anticipated that refined tolerance induction strategies will be able to mitigate the problems of acute vascular rejection and cellular rejection. Taken together, these advances give hope that xenotransplantation will fulfill its promise of alleviating the suffering of the thousands of patients now on transplant waiting lists around the world.

ACKNOWLEDGMENTS

We thank Dr. David K. C. Cooper for his constructive critique of the manuscript. This work was supported in part by grants from the National Heart, Lung, and Blood Institute (R01 HL67110, R01 HL54211, RO1 HL71932, P01 HL18646) and the National Institute of Allergy and Infectious Disease (P01 AI50157) of the National Institutes of Health.

REFERENCES

1. United Network for Organ Sharing. Waiting List Data. 2001. United Network for Organ Sharing, Washington DC, 2001.
2. Cooper DKC, Keogh AM, Brink J, et al. Report of the Xenotransplantation Advisory Committee of the International Society for Heart and Lung Transplantation: the present status of xenotransplantation and its potential role in the treatment of end-stage cardiac and pulmonary diseases. J Heart Lung Transplant 2000;19: 1125–1165.
3. Vanderpool HY. Critical ethical issues in clinical trials with xenotransplants. Lancet 1998;351:1347–1350.
4. Pierson RN III, White DJ, Wallwork J. Ethical considerations in clinical cardiac xenografting. J Heart Lung Transplant 1993;12:876–878.
5. Cooper DKC, Lanza RP. Xeno—The Promise of Transplanting Animal Organs Into Humans, 1st ed. Oxford University Press, New York: 2000.

6. Sachs DH, Colvin RB, Cosimi AB, et al. Xenotransplantation—caution, but no moratorium. Nat Med 1998;4:372–373.
7. Pratschke J, Wilhelm MJ, Kusaka M, et al. Brain death and its influence on donor organ quality and outcome after transplantation. Transplantation 1999;67:343–348.
8. Laskowski I, Pratschke J, Wilhelm MJ, Gasser M, Tilney NL. Molecular and cellular events associated with ischemia/reperfusion injury. Ann Transplant 2000;5:29–35.
9. Terasaki PI. The HLA-matching effect in different cohorts of kidney transplant recipients. Clin Transpl 2000;497–514.
10. Sykes M, Sachs DH. Mixed chimerism. Philos Trans R Soc Lond B Biol Sci 2001;356:707–726.
11. Sonntag KC, Emery DW, Yasumoto A, et al. Tolerance to solid organ transplants through transfer of MHC class II genes. J Clin Invest 2001;107:65–71.
12. Vial CM, Ostlie DJ, Bhatti FN, et al. Life supporting function for over 1 month of a transgenic porcine heart in a baboon. J Heart Lung Transplant 2000;19: 224–229.
13. Salama AD, Delikouras A, Pusey CD, et al. Transplant accommodation in highly sensitized patients: a potential role of Bcl-xL and alloantibody. Am J Transplant 2001;1:260–269.
14. Polejaeva IA, Chen SH, Vaught TD, et al. Cloned pigs produced by nuclear transfer from adult somatic cells. Nature 2000;407:86–90.
15. Hajjar RJ, del Monte F, Matsui T, Rosenzweig A. Prospects for gene therapy for heart failure. Circ Res 2000;86:616–621.
16. Jonas RA, Giglia TM, Sanders SP, et al. Rapid, two-stage arterial switch for transposition of the great arteries and intact ventricular septum beyond the neonatal period. Circulation 1989;80:I203–I208.
17. Bonhoeffer P, Carminati M, Parenzan L, Tynan M. Non-surgical left ventricular preparation for arterial switch in transposition of the great arteries. Lancet 1992; 340:549–550.
18. Anversa P, Ricci R, Olivetti G. Quantitative structural analysis of the myocardium during physiologic growth and induced cardiac hypertrophy: a review. J Am Coll Cardiol 1986;7:1140–1149.
19. Calne RY. Organ transplantation between widely disparate species. Transplant Proc 1970;2:550.
20. US Department of Health and Human Services Public Health Service. Guidance for industry: public health issues posed by the use of nonhuman primate xenografts in humans. Federal Regulations 64, 16743–16744 (1999).
21. Sachs DH. MHC homozygous miniature swine. In: Swindle MM, Moody DC, Phillips LD, eds. Swine as Models in Biomedical Research. Iowa State University Press, Ames: 1992, pp. 3–15.
22. Sachs DH. The pig as a potential xenograft donor. Pathol Biol 1994;42:217–228.
23. Allan JS, Rose GA, Choo JK, et al. Morphometric analysis of miniature swine hearts as potential human xenografts. Xenotransplantation 2001;8:90–93.
24. Sullivan JA, Oettinger HF, Sachs DH, Edge AS. Analysis of polymorphism in porcine MHC class I genes: alterations in signals recognized by human cytotoxic lymphocytes. J Immunol 1997;159:2318–2326.
25. Gustafsson K, Leguern C, Hirsch F, Germana S, Pratt K, Sachs DH. Class II genes of miniature swine. IV. Characterization and expression of two allelic class II DQB cDNA clones. J Immunol 1990;145:1946–1951.
26. Gustafsson K, Germana S, Hirsch F, Pratt K, Leguern C, Sachs DH. Structure of miniature swine class II DRB genes: conservation of hypervariable amino acid

residues between distantly related mammalian species. Proc Natl Acad Sci USA 1990;87:9798–9802.
27. Emery DW, Sablinski T, Shimada H, et al. Expression of an allogeneic MHC DRB transgene, through retroviral transduction of bone marrow, induces specific reduction of alloreactivity. Transplantation 1997;64:1414–1423.
28. Fishman JA. Infection and xenotransplantation. Developing strategies to minimize risk. Ann NY Acad Sci 1998;862:52–66.
29. Reemtsma K, McCracken BH, Schlegel JV, Pearl M. Heterotransplantation of the kidney: two clinical experiences. Science 1964;143:700–702.
30. Hardy JD, Chavez CM, Kurrus FD, et al. Heart transplantation in man. Developmental studies and report of a case. JAMA 1964;188:1132–1140.
31. Taniguchi S, Cooper DK. Clinical xenotransplantation: past, present and future. Ann R Coll Surg Engl 1997;79:13–19.
32. Beecher HK, Adams RD, Barger AC, et al.. A definition of reversible coma. JAMA 1968;205:85–88.
33. Bailey LL, Nehlsen-Cannarella WSL, Concepcion W, Jolley WB. Baboon-to-human cardiac xenotransplantation in a neonate. JAMA 1985;254:3321–3329.
34. Makowka L, Cramer DV, Hoffman A, et al. The use of a pig liver xenograft for temporary support of a patient with fulminant hepatic failure. Transplantation 1995;59:1654–1659.
35. Groth CG, Korsgren O, Wennberg L, et al. Xenoislet rejection following pig-to-rat, pig-to-primate, and pig-to-man transplantation. Transplant Proc 1996;28: 538–539.
36. Ildstad ST. Xenotransplantation for AIDS. Lancet 1996;347:761–766.
37. Brevig T, Holgersson J, Widner H. Xenotransplantation for CNS repair: immunological barriers and strategies to overcome them. Trends Neurosci 2000;23: 337–344.
38. Subramanian T. Cell transplantation for the treatment of Parkinson's disease. Semin Neurol 2001;21:103–115.
39. Deacon T, Schumacher J, Dinsmore J, et al. Histological evidence of fetal pig neural cell survival after transplantation into a patient with Parkinson's disease. Nat Med 1997;3:350–353.
40. Perper RJ, Najarian JS. Experimental renal heterotransplantation. III. Passive transfer of transplantation immunity. Transplantation 1967;5:514–533.
41. Hoffmann MW, Heath WR, Ruschmeyer D, Miller JFAP. Deletion of high-avidity T cells by thymic epithelium. Proc Natl Acad Sci U S A 1995;92:9851–9855.
42. Bravery CA, Batten P, Yacoub MH, Rose ML. Direct recognition of SLA- and HLA-like class II antigens on porcine endothelium by human T cells results in T cell activation and release of interleukin-2. Transplantation 1995;60:1024–1033.
43. Cooper DKC, Good AH, Koren E, et al. Identification of alpha-galactosyl and other carbohydrate epitopes that are bound by human anti-pig antibodies: relevance to discordant xenografting in man. Transplant Immunol 1993;1: 198–205.
44. Galili U, Macher BA, Buehler J, Shohet SB. Human natural anti-α-galactosyl IgG. II. The specific recognition of $\alpha(1\text{-}_3)$ linked galactose residues. J Exp Med 1985;162:573–582.
45. Galili U, Rachmilewitz EA, Peleg A, Flechner I. A unique natural human IgG antibody with anti-alpha-galactosyl specificity. J Exp Med 1984;160:1519–1531.
46. Minanov OP, Itescu S, Neethling FA, et al. Anti-Gal IgG antibodies in sera of newborn humans and baboons and its significance in pig xenotransplantation. Transplantation 1997;63:182–186.

47. Galili U, Mandrell RE, Hamadeh RM, Shohet SB, Griffiss JM. The interaction between the human natural anti-α?galactosyl IgG (anti-Gal) and bacteria of the human flora. Infect Immunol 1988;57:1730–1737.
48. Rother RP, Fodor WL, Springhorn JP, et al. A novel mechanism of retrovirus inactivation in human serum mediated by anti-alpha-galactosyl natural antibody. J Exp Med 1995;182:1345–1355.
49. Parker W, Bruno D, Holzknecht ZE, Platt JL. Characterization and affinity isolation of xenoreactive human natural antibodies. J Immunol 1994;153:3791–3803.
50. Sandrin MS, Vaughan HA, Dabkowski PL, McKenzie IF. Anti-pig IgM antibodies in human serum react predominantly with Gal(alpha 1-3)Gal epitopes. Proc Natl Acad Sci U S A 1993;90:11,391–11,395.
51. Galili U, Tibell A, Samuelsson B, Rydberg L, Groth CG. Increased anti-Gal activity in diabetic patients transplanted with porcine islet cells. Transplant Proc 1996; 28:564–566.
52. Bartholomew A, Latinne D, Sachs DH, et al. Utility of xenografts: lack of correlation between PRA and natural antibodies to swine. Xenotransplantation 1997;4: 34–39.
53. Cascalho M, Platt JL. The immunological barrier to xenotransplantation. Immunity 2001;14:437–446.
54. Miyagawa S, Hirose H, Shirakura R, et al. The mechanism of discordant xenograft rejection. Transplantation 1988;46:825–829.
55. Gambiez L, Weill BJ, Chereau C, Calmus Y, Houssin D. The hyperacute rejection of guinea pig to rat heart xenografts is mediated by preformed IgM. Transplant Proc 1990;22:1058.
56. Johnston PS, Wang MW, Lim SML, Wright LJ, White DJG. Discordant xenograft rejection in an antibody-free model. Transplantation 1992;54:573–577.
57. Sablinski T, Latinne D, Bailin M, et al. Xenotransplantation of pig kidneys to nonhuman primates: I. Development of the model. Xenotransplantation 1995;2: 264–270.
58. Dalmasso AP, Vercelolotti GM, Fischel RJ, Bolman RM, Bach FH, Platt JL. Mechanism of complement activation in the hyperacute rejection of porcine organs transplanted into primate recipients. Am J Pathol 1992;140:1157–1166.
59. Müller-Eberhard HJ. Complement: chemistry and pathways. In: Gallin JI, Goldstein IM, Snyderman R, eds. Inflammation. Basic Principles and Clinical Correlates. Raven Press, New York: 1992, pp. 33–61.
60. Frank MM. Complement system. In: Frank MM, Austen KF, Claman HN, Unanue ER, eds. Samter's Immunological Diseases. Little, Brown and Company, Boston: 1995, pp. 331–352.
61. Abbas AK, Lichtman AH, Pober JS. The complement system. In: Abbas AK, Lichtman AH, Pober JS, eds. Cellular and Molecular Immunology, 2nd ed. WB Saunders, Philadelphia, PA: 1994, pp. 225–315.
62. Auchincloss H, Sachs DH. Xenogeneic transplantation. Annu Rev Immunol 1998; 16:433–470.
63. Sachs DH, Sykes M, Robson SC, Cooper DKC. Xenotransplantation. In: Dixon FJ, ed. Advances in Immunology. Academic Press, San Diego, CA: 2001, pp. 129–233.
64. Dalmasso AP, Vercelolotti GM, Platt JL, Bach FH. Inhibition of complement-mediated endothelial cell cytotoxicity by decay-accelerating factor: potential for prevention of xenograft hyperacute rejection. Transplantation 1991;52: 530–533.

65. Bach FH. Xenotransplantation: problems and prospects. Annu Rev Med 1998;49: 301–310.
66. Saadi S, Platt JL. Transient perturbation of endothelial integrity induced by natural antibodies and complement. J Exp Med 1995;181:21–31.
67. Platt JL, Vercelolotti GM, Lindman BJ, Oegema TR Jr, Bach FH, Dalmasso AP. Release of heparan sulphate from endothelial cells: Implications for pathogenesis of hyperacute rejection. J Exp Med 1990;171:1363–1368.
68. Parker W, Saadi S, Lin SS, Holzknecht ZE, Bustos M, Platt JL. Transplantation of discordant xenografts: a challenge revisited. Immunol Today 1996;17:373–378.
69. Alexandre GPJ, Latinne D, Carlier M, et al. Plasmapheresis and splenectomy in experimental renal xenotransplantation. In: Hardy MA, ed. Xenograft 25, 1st ed. Excerpta Medica, New York: 1989, p. 259.
70. Rydberg L, Hallberg E, Samuelsson B, et al. Studies on the removal of anti-pig xenoantibodies in the human by plasmapheresis/immunoadsorption. Xenotransplantation 1995;2:253–263.
71. Gannedahl G, Tufveson G, Sundberg B, Groth CG. The effect of plasmapheresis and deoxyspergualin or cyclophosphamide treatment on an anti-porcine Gal-α(1-3)-Gal antibody levels in humans. Xenotransplantation 1996;3:166–170.
72. Cooper DKC, Human PA, Lexer G, et al. Effects of cyclosporine and antibody adsorption on pig cardiac xenograft survival in the baboon. J Heart Transplant 1988;7:238–246.
73. Taniguchi S, Neethling FA, Korchagina EY, et al. In vivo immunoadsorption of anti-pig antibodies in baboons using a specific Galα1-3Gal column. Transplantation 1996;62:1379–1384.
74. Ye Y, Neethling FA, Niekrasz M, et al. Evidence that intravenously administered alpha-galactosyl carbohydrates reduce baboon serum cytotoxicity to pig kidney cells (PK15) and transplanted pig hearts. Transplantation 1994;58:330–337.
75. Sablinski T, Cooper DKC, Sachs DH. Xenotransplantation. In: Austen KF, Burakoff SJ, Rosen FS, Strom TB, eds. Therapeutic Immunology, 2nd ed. Blackwell Science, Malden, MA: 2001, pp. 535–549.
76. Platt JL. Therapeutic strategies for hyperacute xenograft rejection. In: Platt JL, ed. Hyperacute Xenograft Rejection. RJ Landes, Austin, TX: 1995, pp. 161–187.
77. Cooper DKC, Cairns TDH, Taube DH. Extracorporeal immunoadsorption of anti-pig antibody in baboons using αGal oligosaccharide immunoaffinity columns. Xeno 1996;4:27–29.
78. Simon PM, Neethling FA, Taniguchi S, et al. Intravenous infusion of Galα1–3Gal oligosaccharides in baboons delays hyperacute rejection of porcine heart xenografts. Transplantation 1998;65:346–353.
79. Koren E, Milotic F, Neethling FA, et al. Monoclonal antiidiotypic antibodies neutralize cytotoxic effects of anti-alphaGal antibodies. Transplantation 1996;62:837–843.
80. Koren E, Milotic F, Neethling FA, et al. Murine monoclonal anti-idiotypic antibodies directed against human anti-alpha Gal antibodies prevent rejection of pig cells in culture: implications for pig-to-human organ xenotransplantation. Transplant Proc 1996;28:559.
81. Teranishi K, Gollackner B, Buhler L, et al. Depletion of anti-Gal antibodies in baboons by intravenous therapy with bovine serum albumin conjugated to Gal oligosaccharides. Transplantation 2002;73:129–139.
82. Yang YG, deGoma E, Ohdan H, et al. Tolerization of anti-Galalpha1-3Gal natural antibody-forming B cells by induction of mixed chimerism. J Exp Med 1998;187: 1335–1342.

83. Bracy JL, Sachs DH, Iacomini J. Inhibition of xenoreactive natural antibody production by retroviral gene therapy. Science 1998;281:1845–1847.
84. Ohdan H, Yang YG, Shimizu A, Swenson KG, Sykes M. Mixed chimerism induced without lethal conditioning prevents T cell- and anti-Gal alpha 1,3Gal-mediated graft rejection. J Clin Invest 1999;104:281–290.
85. Leventhal JR, Dalmasso AP, Cromwell JW, et al. Prolongation of cardiac xenograft survival by depletion of complement. Transplantation 1993;55: 857–865.
86. Candinas D, Lesnikoski BA, Robson SC, et al. Effect of repetitive high-dose treatment with soluble complement receptor type 1 and cobra venom factor on discordant xenograft survival. Transplantation 1996;62:336–342.
87. Kobayashi T, Taniguchi S, Ye Y, et al. Delayed xenograft rejection in C3-depleted discordant (pig-to-baboon) cardiac xenografts treated with cobra venom factor. Transplant Proc 1996;28:560.
88. Pruitt SK, Baldwin WD, Marsh HC Jr, Linn SS, Yeh CG, Bollinger RR. The effect of soluble complement receptor type 1 on hyperacute xenograft rejection. Transplantation 1991;52:868–873.
89. Pruitt SK, Kirk AD, Bollinger RR, et al. The effect of soluble complement receptor type 1 on hyperacute rejection of porcine xenografts. Transplantation 1994;57: 363–370.
90. Weisman HF, Bartow T, Leppo MK, et al. Soluble human complement receptor type 1: in vivo inhibitor of complement suppressing post-ischemic myocardial inflammation and necrosis. Science 1990;249:146–151.
91. Cozzi E, White DJG. The generation of transgenic pigs as potential organs donors for humans. Nat Med 1995;1:964–966.
92. McCurry KR, Kooyman DL, Alvarado CG, et al. Human complement regulatory proteins protect swine-to-primate cardiac xenografts from humoral injury. Nat Med 1995;1:423–427.
93. Medof ME, Kinoshita T, Nussenzweig V. Inhibition of complement activation on the surface of cells after incorporation of decay-accelerating factor (DAF) into their membranes. J Exp Med 1984;160:1558–1578.
94. Rosengard AM, Cary NRB, Langford GA, Tucker AW, Wallwork J, White DJG. Tissue expression of human complement inhibitor, decay-accelerating factor, in transgenic pigs. Transplantation 1995;59:1325–1333.
95. Cozzi E, Tucker AW, Langford GA, et al. Characterization of pigs transgenic for human decay-accelerating factor. Transplantation 1997;64:1383–1392.
96. Schmoeckel M, Nollert G, Shahmohammadi M, et al. Prevention of hyperacute rejection by human decay accelerating factor in xenogeneic perfused working hearts. Transplantation 1996;62:729–734.
97. Cozzi E, Yannoutsos N, Langford GA, Pinto-Chavez G, Wallwork J, White DJG. Effect of transgenic expression of human decay-accelerating factor on the inhibition of hyperacute rejection of pig organs. In: Cooper DKC, Kemp E, Platt JL, White DJG, eds. Xenotransplantation. Springer-Verlag, Heidelberg, Germany: 1997, pp. 665–682.
98. Bhatti FN, Schmoeckel M, Zaidi A, et al. Three-month survival of HDAFF transgenic pig hearts transplanted into primates. Transplant Proc 1999;31:958.
99. Kuwaki K, Knosalla C, Dor FJMF, et al. Gal-conjugate anti-CD154 monoclonal antibody, and anticoagulation improve graft survival in pig-to-baboon heart transplantation. Xenotransplantation 2003;10:489.
100. Schmoeckel M, Bhatti FNK, Zaidi A, et al. Orthotopic heart transplantation in a transgenic pig-to-primate model. Transplantation 1998;65:1570–1577.

101. Diamond LE, McCurry KR, Martin MJ, et al. Characterization of transgenic pigs expressing functionally active human CD59 on cardiac endothelium. Transplantation 1996;61:1241–1249.
102. Squinto SP. Genetically modified animal organs for human transplantation. World J Surg 1997;21:939–942.
103. Byrne GW, McCurry KR, Martin MJ, McClellan SM, Platt JL, Logan JS. Transgenic pigs expressing human CD59 and decay-accelerating factor produce an intrinsic barrier to complement-mediated damage. Transplantation 1997;63: 149–155.
104. Chen RH, Naficy S, Logan JS, Diamond LE, Adams DH. Hearts from transgenic pigs constructed with CD59/DAF genomic clones demonstrate improved survival in primates. Xenotransplantation 1999;6:194–200.
105. Sandrin MS, Fodor WL, Mouhtouris E, et al. Enzymatic remodeling of the carbohydrate surface of a xenogeneic cell substantially reduces human antibody binding and complement-mediated cytolysis. Nat Med 1995;1:1261–1267.
106. Sandrin MS, Fodor WL, Cohney S, et al. Reduction of the major porcine xenoantigen Galα(1,3)Gal by expression of α(1,2) fucosyltransferase. Xenotransplantation 1996;3:134–140.
107. Chen C, Fisicaro N, Shinkel TA, et al. Reduction in Gal-α1,3-Gal epitope expression in transgenic mice expressing human H-transferase. Xenotransplantation 1996;3:69–75.
108. Koike C, Kannagi R, Takuma Y, et al. Introduction of α(1,2)-fucosyltransferase and its effect on α-Gal epitopes in transgenic pig. Xenotransplantation 1996;3: 81–86.
109. Cooper DKC, Koren E, Oriol R. Genetically-engineered pigs. Lancet 1993, 342: 682–683.
110. Dai Y, Vaught TD, Boone J, et al. Targeted disruption of the alpha1,3-galactosyltransferase gene in cloned pigs. Nat Biotechnol 2002;20:251–255.
111. Lai L, Kolber-Simonds D, Park KW, et al. Production of alpha-1,3-galactosyltransferase knockout pigs by nuclear transfer cloning. Science 2002;295: 1089–1092.
112. Phelps CJ, Koike C, Vaught TD, et al. Production of alpha 1,3-galactosyltransferase-deficient pigs. Science 2003;299:411–414.
113. Yamada K, Yazawa K, Kamono C, et al. An initial report of alpha-Gal deficient pig-to-baboon renal xenotransplantation: evidence for the benefit of co-transplanting vascularized donor thymic tissue. Xenotransplantation 2003;10:480.
114. Bracy JL, Cretin N, Cooper DK, Iacomini J. Xenoreactive natural antibodies. Cell Mol Life Sci 1999;56:1001–1007.
115. Tearle RG, Tange MJ, Zanettino ZL, et al. The α1,3-galactosyltransferase knockout mouse. Implications for xenotransplantation. Transplantation 1996;61:13–19.
116. Bracy JL, Iacomini J. Induction of B-cell tolerance by retroviral gene therapy. Blood 2000;96:3008–3015.
117. Lin SS, Weidner BC, Byrne GW, et al. The role of antibodies in acute vascular rejection of pig-to-baboon cardiac transplants. J Clin Invest 1998;101:1745–1756.
118. Lin SS, Hanaway MJ, Gonzalez-Stawinski GV, et al. The role of anti-Galalpha1-3Gal antibodies in acute vascular rejection and accommodation of xenografts. Transplantation 2000;70:1667–1674.
119. Goodman DJ, Millan M, Ferran C, Bach FH. Mechanism of delayed xenograft rejection. In: Cooper DKC, Kemp E, Platt JL, White DJG, eds. Xenotransplantation: The Transplantation of Organs and Tissues Between Species. Springer, Heidelberg, Germany: 1997, pp. 77–94.

120. Blakely ML, Van der Werf WJ, Berndt MC, Dalmasso AP, Bach FH, Hancock WW. Activation of intragraft endothelial and mononuclear cells during discordant xenograft rejection. Transplantation 1994;58:1059–1066.
121. Robson SC, Siegel JB, Lesnikoski BA, et al. Aggregation of human platelets induced by porcine endothelial cells is dependent upon both activation of complement and thrombin generation. Xenotransplantation 1996;3:24–34.
122. Robson SC, Kaczmarek E, Siegel JB, et al. Loss of ATP diphosphohydrolase activity with endothelial cell activation. J Exp Med 1997;185:153–163.
123. Bach FH. Genetic engineering as an approach to xenotransplantation. World J Surg 1997;21:913–916.
124. Esmon CT. Cell mediated events that control blood coagulation and vascular injury. Annu Rev Cell Biol 1993;9:1–26.
125. Balla G, Jacob HS, Balla J, et al. Ferritin: a cytoprotective antioxidant stratagem of endothelium. J Biol Chem 1992;267:18,148–18,153.
126. Dong VM, Womer KL, Sayegh MH. Transplantation tolerance: the concept and its applicability. Pediatr Transplant 1999;3:181–192.
127. Platt JL, Dalmasso AP, Lindman BJ, Ihrcke NS, Bach FH. The role of C5a and antibody in the release of heparan sulfate from endothelial cells. Eur J Immunol 1991;21:2287–2890.
128. Whelan J, Ghersa P, van Huijsduijnen RH, et al. An NFκB-like factor is essential but not sufficient for cytokine induction of endothelial leukocyte adhesion molecule 1 (ELAM-1) gene transcription. Nucleic Acids Res 1991;19:2645–2653.
129. deMartin R, Vanhove B, Cheng Q, et al. Cytokine-inducible expression in endothelial cells of an IκBα–like gene is regulated by NFκB. EMBO J 1993;12: 2773–2779.
130. Cogswell JP, Godlevski MM, Wisely GB, et al. NF-κB regulates IL-1B transcription through a consensus NF-κB binding site and a nonconsensus CRE-like site. J Immunol 1994;153:712–723.
131. Millan MT, Geczy C, Stuhlmeier KM, Goodman DJ, Ferran C, Bach FH. Human monocytes activate porcine endothelial cells, resulting in increased E-selectin, interleukin-8, monocyte chemotactic protein-1, and plasminogen activator inhibitor-type-1 expression. Transplantation 1997;63:421–429.
132. Buhler L, Awwad M, Basker M, et al. High-dose porcine hematopoietic cell transplantation combined with CD40 ligand blockade in baboons prevents an induced anti-pig humoral response. Transplantation 2000;69:2296–2304.
133. Voraberger G, Schäfer R, Stratowa C. Cloning of the human gene for intercellular adhesion molecule 1 and analysis of its 5′-regulatory region. J Immunol 1991; 147:2777–2786.
134. Pescovitz MD, Sakopoulos AG, Gaddy JA, Husmann RJ, Zuckermann FA. Porcine peripheral blood $CD4^+/CD8^+$ dual expressing T-cells. Vet Immunol Immunopathol 1994;43:53–62.
135. Siebenlist U, Franzoso G, Brown K. Structure, regulation and function of NF-κB. Annu Rev Cell Biol 1994;10:405–455.
136. Finco TS, Baldwin AS Jr. Mechanistic aspects of NF-κB regulation: the emerging role of phosphorylation and proteolysis. Immunity 1995;3:263–272.
137. DiDonato J, Mercurio F, Rosette C, et al. Mapping of the inducible IκB phosphorylation sites that signal its ubiquitination and degradation. Mol Cell Biol 1996;16:1295–1304.
138. Beg AA, Finco TS, Nantermet PV, Baldwin AS Jr. Tumor necrosis factor and interleukin-1 lead to phosphorylation and loss of IκBα: a mechanism for NF-κB activation. Mol Cell Biol 1993;13:3301–3310.

139. Henkle T, Machieldt T, Alkalay I, Krönke M, Ben-Nerial Y, Baeuerie PA. Rapid proteolysis of IκB-α is necessary for activation of transcription factor NF-κB. Nature 1993;365:182–185.
140. Cooper JT, Stroka DM, Brostjian C, Palmetshofer A, Bach FH, Ferran C. A20 blocks endothelial cell activation through a NF-kappaB-dependent mechanism. J Biol Chem 1996;271:18,068–18,073.
141. Bach FH, Ferran C, Hechenleitner P, et al. Accommodation of vascularized xenografts: expression of "protective genes" by donor endothelial cells in a host Th2 cytokine environment. Nat Med 1997;3:196–204.
142. Soares MP, Lin Y, Anrather J, et al. Expression of heme oxygenase-1 can determine cardiac xenograft survival. Nat Med 1998;4:1073–1077.
143. Sato K, Balla J, Otterbein L, et al. Carbon monoxide generated by heme oxygenase-1 suppresses the rejection of mouse-to-rat cardiac transplants. J Immunol 2001;166:4185–4194.
144. Goodman DJ, von Albertini MA, McShea A, Wrighton CJ, Bach FH. Adenoviral-mediated overexpression of IκBα in endothelial cells inhibits natural killer cell-mediated endothelial cell activation. Transplantation 1996;62:967–972.
145. Dorling A, Lechler RI. T cell-mediated xenograft rejection: specific tolerance is probably required for long term xenograft survival. Xenotransplantation 1998;5: 234–245.
146. Chitilian HV, Laufer TM, Stenger K, Shea S, Auchincloss H Jr. The strength of cell-mediated xenograft rejection in the mouse is due to the $CD4^+$ indirect response. Xenotransplantation 1998;5:93–98.
147. Rollins SA, Kennedy SP, Chodera AJ, Elliott EA, Zavoico GB, Matis LA. Evidence that activation of human T cells by porcine endothelium involves direct recognition of porcine SLA and costimulation by porcine ligands for LFA-1 and CD2. Transplantation 1994;57:1709–1716.
148. Dorling A, Lombardi G, Binns R, Lechler RI. Detection of primary direct and indirect human anti-porcine T cell responses using a porcine dendritic cell population. Eur J Immunol 1996;26:1378–1387.
149. Murray AG, Khodadoust MM, Pober JS, Bothwell ALM. Porcine aortic endothelial cells activate human T cells: direct presentation of MHC antigens and costimulation by ligands for human CD2 and CD28. Immunity 1994;1:57–63.
150. Zaidi A, Schmoeckel M, Bhatti F, et al. Life-supporting pig-to-primate renal xenotransplantation using genetically modified donors. Transplantation 1998;65: 1584–1590.
151. Ildstad ST, Bluestone JA, Barbieri SA, Sachs DH. Characterization of mixed allogeneic chimeras. Immunocompetence, in vitro reactivity, and genetic specificity of tolerance. J Exp Med 1985;162:231.
152. Charlton B, Auchincloss H Jr, Fathman CG. Mechanisms of transplantation tolerance. Annu Rev Immunol 1994;12:707–734.
153. Zinkernagel RM, Althage A, Callahan G, Welsh RM Jr. On the immunocompetence of H-2 incompatible irradiation bone marrow chimeras. J Immunol 1980; 124:2356–2365.
154. Wekerle T, Sykes M. Mixed chimerism as an approach for the induction of transplantation tolerance. Transplantation 1999;68:459–467.
155. Ardavin C, Wu L, Li C-L, Shortman K. Thymic dendritic cells and T cells develop simultaneously in the thymus from a common precursor population. Nature 1993;362:761–763.
156. Nikolic B, Sykes M. Clonal deletion as a mechanism of transplantation tolerance. J Heart Lung Transplant 1996;15:1171–1178.

157. Sykes M. Mixed chimerism and transplant tolerance. Immunity 2001;14: 417–424.
158. Alexandre GPJ, Squifflet JP, deBruyere M, et al. Present experiences in a series of 26 ABO-incompatible living donor renal allografts. Transplant Proc 1987;19: 4538.
159. Sachs DH, Sablinski T. Tolerance across discordant xenogeneic barriers. Xeno 1995;2:234–239.
160. Latinne D, Smith CV, Nickeleit V, et al. Xenotransplantation from pig to cynomolgus monkey: approach toward tolerance induction. Transplant Proc 1993; 25:336.
161. Tanaka M, Latinne D, Sablinski T, et al. Xenotransplantation from pig to cynomolgus monkey: the potential for overcoming xenograft rejection through induction of chimerism. Transplant Proc 1994;26:1326.
162. Sachs DH, Sykes M, Greenstein J, Cosimi AB. Tolerance and xenograft survival. Nat Med 1995;1:969.
163. Xu Y, Lorf T, Sablinski T, et al. Removal of anti-porcine natural antibodies from human and nonhuman primate plasma in vitro and in vivo by a Galα1-3Galβ1-4βGlc-X immunoaffinity column. Transplantation 1998;65:172–179.
164. Kozlowski T, Fuchimoto Y, Monroy R, et al. Apheresis and column absorption for specific removal of Gal-alpha-1,3 Gal natural antibodies in a pig-to-baboon model. Transplant Proc 1997;29:961.
165. Buhler L, Awwad M, Treter S, et al. Induction of mixed hematopoietic chimerism in the pig-to-baboon model. Transplant Proc 2000;32:1101.
166. Buhler L, Basker M, Alwayn IP, et al. Coagulation and thrombotic disorders associated with pig organ and hematopoietic cell transplantation in nonhuman primates. Transplantation 2000;70:1323–1331.
167. Tseng YL, Dor FJMF, Kuwaki K, et al. Preliminary results of Gal-knockout porcine bone marrow xenotransplantation in nonhuman primates. Xenotransplantation 2003;10:486.
168. Sachs DH, Smith CV, Emery DW, et al. Induction of specific tolerance to MHC-disparate allografts through genetic engineering. Exp Nephrol 1993;1:128–133.
169. Sykes M, Sachs DH, Nienhuis AW, Pearson DA, Moulton AD, Bodine DM. Specific prolongation of skin graft survival following retroviral transduction of bone marrow with an allogeneic major histocompatibility complex gene. Transplantation 1993;55:197–202.
170. Bagley J, Wu Y, Sachs DH, Iacomini J. Defining the requirements for peptide recognition in gene therapy-induced T cell tolerance. J Immunol 2000;165: 4842–4847.
171. Ierino FL, Gojo S, Banerjee PT, et al. Transfer of swine major histocompatibility complex class II genes into autologous bone marrow cells of baboons for the induction of tolerance across xenogeneic barriers. Transplantation 1999;67: 1119–1128.
172. Lee AL, Gritsch HA, Sergio JJ, et al. Specific tolerance across a discordant xenogeneic transplantation barrier. Proc Natl Acad Sci U S A 1994;91:10,864–10,867.
173. Zhao Y, Fishman JA, Sergio JJ, et al. Immune restoration by fetal pig thymus grafts in T cell-depleted, thymectomized mice. J Immunol 1997;158:1641–1649.
174. Zhao Y, Swenson K, Sergio JJ, Arn JS, Sachs DH, Sykes M. Skin graft tolerance across a discordant xenogeneic barrier. Nat Med 1996;2:1211–1216.
175. Madsen JC, Yamada K, Allan JS, et al. Transplantation tolerance prevents cardiac allograft vasculopathy in major histocompatibility complex class I-disparate miniature swine. Transplantation 1998;65:304–313.

176. Cooper DK, Keogh AM, Brink J, et al. Report of the Xenotransplantation Advisory Committee of the International Society for Heart and Lung Transplantation: the present status of xenotransplantation and its potential role in the treatment of end-stage cardiac and pulmonary diseases. J Heart Lung Transplant 2000;19: 1125–1165.
177. Cooper DK. Xenotransplantation: How far have we come? Graft 2001;4:6–86.
178. Bach FH, Fineberg HV. Call for moratorium on xenotransplants. Nature 1998; 391:326.
179. Stoye JP, Coffin JM. The dangers of xenotransplantation. Nat Med 1995;1:1100.
180. Patience C, Takeuchi Y, Weiss RA. Zoonosis in xenotransplantation. Curr Opin Immunol 1998;10:539–542.
181. Patience C, Takeuchi Y, Weiss RA. Infection of human cells by an endogenous retrovirus of pigs. Nat Med 1997;3:282–286.
182. Paradis K, Langford G, Long Z, et al. Search for cross-species transmission of porcine endogenous retrovirus in patients treated with living pig tissue. The XEN 111 Study Group. Science 1999;285:1236–1241.
183. Onions D, Cooper DK, Alexander TJ, et al. An approach to the control of disease transmission in pig-to-human xenotransplantation. Xenotransplantation 2000;7: 143–155.
184. Fishman JA. Xenosis and xenotransplantation: addressing the infectious risks posed by an emerging technology. Kidney Int Suppl 1997;58:S41–S45.
185. Logan JS. Prospects for xenotransplantation. Curr Opin Immunol 2000;12:563.

12 Left Ventricular Reconstruction for Ischemic Heart Failure

Vincent Dor, MD

CONTENTS

INTRODUCTION

Postinfarct ischemic cardiomyopathy is characterized by a variable degree of left ventricular (LV) dyssynergy secondary to dyskinetic and/or akinetic walls. Since 1984, we have surgically repaired such ventricles by inserting a patch inside the ventricle to exclude the nonresectable akinetic/dyskinetic segments and reestablishing the preinfarct ventricular geometry. Left ventricular reconstruction (LVR) using an endoventricular patch is an accepted and efficient technique to treat the dilated, hypocontractile ventricle of ischemic heart disease as both diastolic and systolic function are improved.

From: *Contemporary Cardiology: Surgical Management of Congestive Heart Failure*
Edited by: J. C. Fang and G. S. Couper © Humana Press Inc., Totowa, NJ

THE VENTRICULAR WALL AFTER INFARCTION

In the classic transmural infarct without reperfusion, the infarcted area undergoes necrosis, fibrosis, and sometimes calcification. Although the remaining uninfarcted myocardium is initially normal, the transmural infarction produces increases in load and activates neurohormonal mechanisms that lead to eccentric myocardial hypertrophy and ventricular dilation (i.e., ventricular remodeling) of the myocardium remote to the original infarct. This course of events is most commonly seen in occlusion of the left anterior descending artery (LAD), leading to an antero-apical-septal scar.

However, in the modern era of early reperfusion therapy (i.e., angioplasty and thrombolysis) for myocardial infarction (MI), the classical process of transmural infarction has been modified into nontransmural infarction with necrosis of the subendocardial muscle and sparing of the subepicardial muscle *(1)*. In this situation, the nontransmurally infarcted myocardial wall appears nonviable by echocardiography or ventriculography because of akinesia. Although thallium nuclear imaging may suggest viability, intraoperative findings usually demonstrate a thin rim of subepicardial myocardium of little functional importance, primarily because of the dominant underlying scar. Cardiac magnetic resonance imaging is able to detect these differences between transmural and nontransmural infarction *(2,3)*. Subendocardial scar can induce immediately or progressively an asynergic LV wall.

Pathophysiology

Klein et al. demonstrated in 1967 *(4)* that if more than 20% of the left ventricle is infarcted, the Starling and Laplace laws will lead to progressive global ventricular hypokinesia. Gaudron et al. *(5)* showed that 20% of all MIs follow this evolution. The undamaged area is normal at first, then hypertrophied to compensate the lack of contractility of the necrotic wall, and is finally dilated by physical mechanical forces. The dilatation increases the stroke volume and temporarily improves the cardiac index (Starling law), but the increased wall tension has a detrimental effect on the myocardial contractility (Laplace law). This physical and mechanical explanation of the progressive dilatation of the heart—LV remodeling—is based on a complex inflammatory and neurohormonal process, which, in reality, is the result of the reaction of the "organism" against the lack of contractility of a large scar when the remaining nonischemic area is not able to assume and maintain a normal cardiac output. This reaction explains the progressive dilatation (remodeling), but is more a consequence than a cause of it. The

real cause of remodeling is anatomical: the extension of the asynergic scarred area of LV wall. Therefore, it is important to detect it early and assess its size precisely. The aim for cardiology would be to analyze the percentage of LV wall circumference, which can be considered a critical trigger of the progressive remodeling. The LV volume is a sensitive marker of ventricular dysfunction, and LV end-systolic volume is an important predictor of prognosis after myocardial infarction *(10)*. If 25 to 30 mL/m^2 for end-systolic volume index (ESVI) and 50 to 60 mL/m^2 for end-diastolic volume index (EDVI) are considered as normal values, doubling these indices can be considered as severe dilatation.

Assessing precisely and regularly the evolving process of remodeling by objective paramaters (LV volumes and performances) by echo or cardiac magnetic resonance (CMR) is mandatory.

The Role of Revascularization

Is the recanalization of the occluded coronary artery able to prevent this process? Immediately after coronary artery occlusion, irreversible cell necrosis can occur within minutes. Prompt reperfusion, when myocytes are in a state of critical ischemia, can reduce cell death, limit infarct size, and thereby increase survival. However, nuclear assessment (sestamibi) after successful recandalization of the culprit artery shows that in more than 80% of cases, a necrotic area exists *(11)*.

Coronary revascularization by percutaneous or surgical techniques during the acute phase of infarct has greatly changed the prognosis of MI and is an essential treatment but, not always sufficient, and the percentage of scarred LV wall must be checked in all cases after MI to avoid or to follow the LV remodeling.

CONVENTIONAL SURGICAL TECHNIQUES

Since Likoff and Bailey's and Cooley et al.'s descriptions in 1955 *(12)* and 1958 *(13)*, respectively, surgery for the LV aneurysm has been well known *(14)*. The classic operation involves resection and exteriorization of scar tissue by a long linear suture on either a beating or an arrested heart. Although this conventional operation is both easy and safe, the classic work of Froelich et al. *(15)* and Cohen et al. *(16)* suggested that the conventional procedure led to disappointing hemodynamics and poor ventricular geometry as a result of resection of only a small part of the dyskinesia. Techniques to improve on the classic linear suture repair of the scarred ventricle are currently referred to as LV "reconstruction"

rather than "remodeling" because this term is traditionally reserved for the spontaneous reshaping of the infarcted ventricle.

LVR: CIRCULAR REORGANIZATION OF LEFT VENTRICLE

A more physiological reconstruction of the left ventricle was described in a large study by Jatene in 1985 *(17)*, who used a technique of external circular reconstruction of the LV wall. The akinetic septum is let inside the ventricular cavity and plicated, and either a linear suture or a patch (in 6% of cases) was used to close the reorganized circular defect in the ventricular wall. Coronary revascularization being performed in 20% of cases.

In 1984, we used a patch inserted inside the ventricle on contractile muscle to exclude all akinetic nonresectable areas, to reconstruct the ventricular cavity as it was before the infarct, and to allow for eventual revascularization of all diseased coronary arteries. Our first series of 25 patients using this technique, endoventricular circular patch plasty (EVCPP), was presented in 1985 *(18)*. Following these two pioneering series, other similar techniques were described: the endoaneurysmorrhaphy by Cooley in 1989 *(19)* and a tailored scar incision by Mickleborough et al. in 1994 *(20)*.

Endoventricular Circular Patch Plasty

In EVCPP (Fig. 1), the mitral valve is first examined by transesophageal echocardiography. Surgery is then performed on a totally arrested heart. Coronary revascularization is accomplished first. The left ventricle is then opened at the center of the depression in the myocardium. Thrombi are removed, and the endocardial scar is resected, especially if the scar is calcified or if spontaneous or inducible ventricular tachycardia (VT) exists. In such circumstances, cryoablation is employed at the edges of the resection. If mitral insufficiency is present, the valve is examined by both atrial and ventricular approaches to plan the specific mitral reconstruction (posterior annuloplasty, Goretex neochordae, an Alfieri E-to-E suture, or mitral valve replacement if the posterior papillary muscle is totally diseased).

The rebuilding of the left ventricular cavity is initiated by a continuous 2.0 monofilament suture that follows the border between the fibrous scar and normal muscle (Fig 1B). Tightening of this suture restores the curvature of the LV wall (Fig. 2C), as it was before the

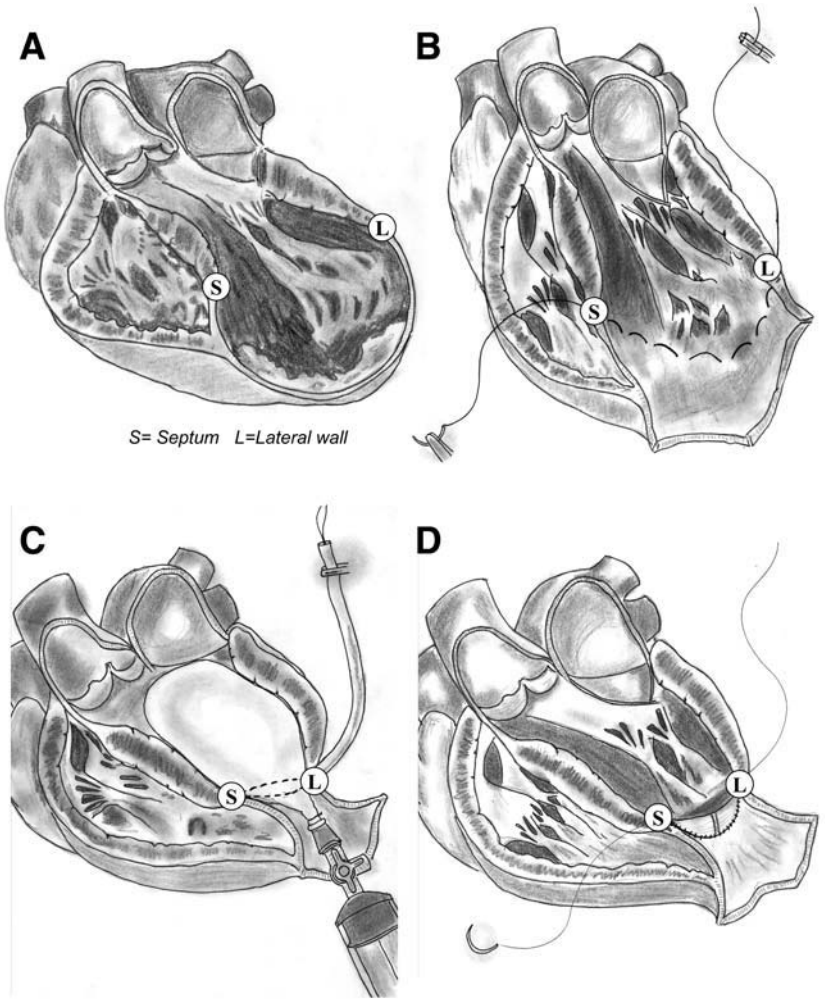


Fig. 1. Left ventricular reconstruction. **(A)** Antero-septoapical aneurysm. **(B)** Endoventricular purse-string suture. **(C)** Curvature restoration and balloon sizing. **(D)** Endoventricular patch reconstruction. S, septum; L, lateral wall.

infarct. To avoid an excessive reduction of volume, with risk of immediate or delayed diastolic incompliance, this suture must be tied with a soft, rubber balloon inside the LV inflated at the patient's theoretical diastolic capacity (i.e., 50 mL/m^2 of body surface area). This maneuver, in addition, gives shape and size of the patch which is anchored on this clothesline inside the LV.

In antero-septo-apical aneurysm, as the septum and apex are more involved than the lateral wall, the patch roughly approximates the direction of the septum (Fig 1D).

Alternatives

Autologous tissue can be used instead of a synthetic patch: Either a semicircle of the fibrous endocardial scar can be mobilized using a septal hinge (if the scar is without calcification or thrombus) or autologous pericardium can be used (autologous tissue patches represent 30% of the cases in our series).

In the case of a posterior or posterolateral infarct (Fig. 2), a triangular patch is used by attaching its base to the posterior or posterolateral mitral annulus and its apex to the base of the posterior or anterolateral papillary muscle. This patch repair reconstructs the normal mitral geometry and a normal posterior wall after large endocardectomy. If resected scar involves the posterior papillary muscle, the mitral valve has to be replaced by a prosthesis, and this can be easily accomplished through a transventricular approach.

If necrotic tissues are encountered during the repair of an acute mechanical complication of a MI (i.e., ventricular septal or free-wall rupture), the patch has to be inserted at the border between viable and necrotic tissue by transmural U stitches reinforced with Teflon pledgets. The patch is anchored above the septal rupture, excluding it from the ventricular cavity.

Concomitant Surgical Problems

Revascularization of all diseased coronary arteries of the contractile area is mandatory. Revascularization of the infarcted area is almost always possible with the left internal mammary artery, even when the left anterior descending artery is thrombosed, and the distal artery is not visualized by collaterals on the preoperative coronary angiogram. In our experience, 97% of our patients underwent coronary revascularization (90% with the internal mammary artery), and at 1 year, more than 80% of these bypassed arteries were patent.

Mitral insufficiency is a common part of the disease and must be looked for carefully both before and during surgery by transesophageal echocardiography. If there is more than grade 2 mitral regurgitation or the mitral annulus is greater 35 mm, a posterior annuloplasty is mandatory. Personally, we prefer the atrial approach with posterior annulus reduction with a Goretex strip, but a transventricular approach is possible *(21)*. Patients with associated degenerative mitral valve disease may require a more complete repair.

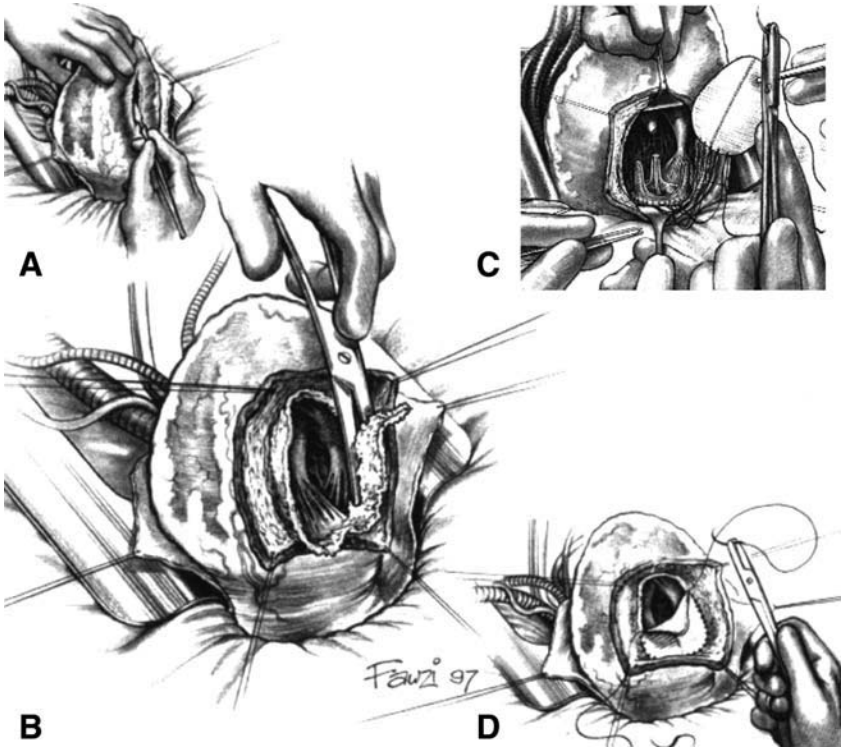


Fig. 2. Technique for posterior and posterolateral localization. **(A)** Primary incision. **(B)** Endocardial resection. **(C)** Mitral valve replacement (as needed). **(D)** Triangular patch repair.

Spontaneous or inducible VT is frequent (13–25% of our patients). In such circumstances, a subtotal nonguided endocardectomy is performed on the endoventricular scar. Cryoablation at the border of this resection completes the surgical excision.

Large Asynergic Ventricles

Large akinetic segments are typically characterized by a congestive heart failure with elevated mean pulmonary artery pressures (>25 mmHg), low ejection fractions (EFs) (<30%), and dilated ventricles (EDVI >150 cc and ESVI >100 cc).

In such cases, the surgery is accomplished with some modifications (Fig. 3). If all of the scarred areas are excluded, an inappropriately small ventricular cavity may result, with a high subsequent risk of immediate or delayed diastolic dysfunction. To avoid this complication, the continuous suture is placed above the limit of the sound muscle in the "transitional" fibrous border zone. The balloon, inside the ventricle inflated to

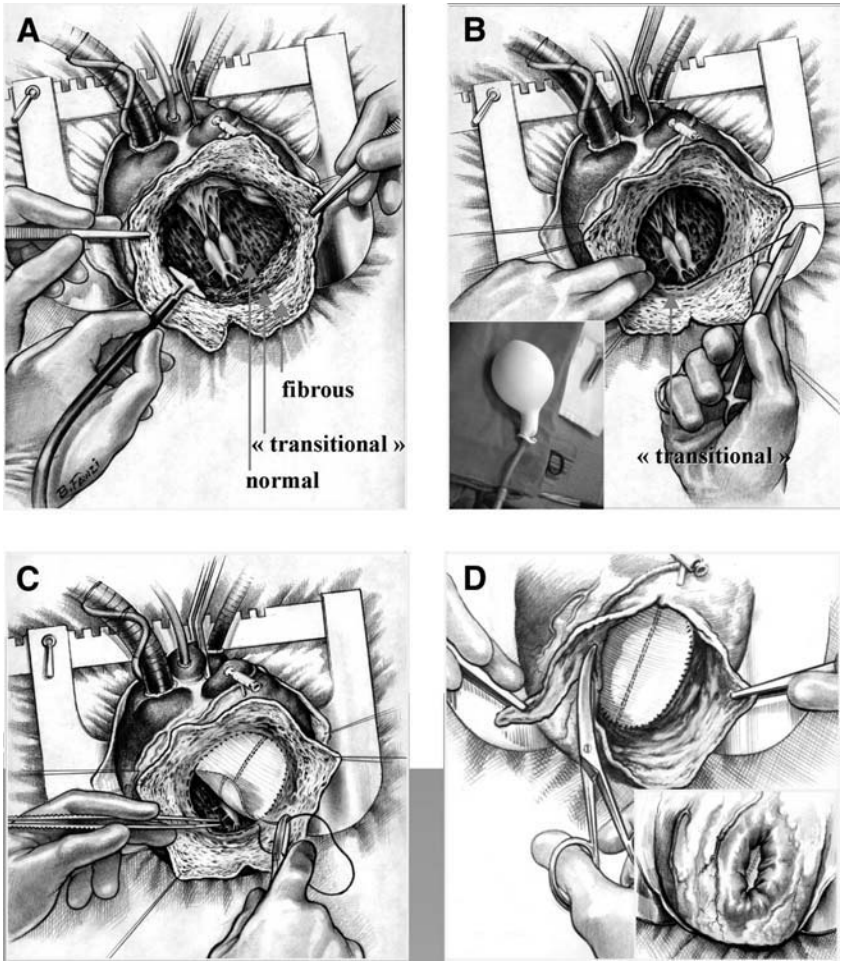


Fig. 3. Technique of left ventricular reconstruction for large akinetic segments. **(A)** Cryoablation at the limit of endocardial resection. **(B)** Endoventricular suture and the balloon to check the diastolic volume. **(C)** Patch anchoring. **(D)** Resection and folding of excluded areas.

the theoretical end diastolic volume, is mandatory before tightening of the circumferential suture. For these reasons, the patch is often larger (3 to 4 cm diameter) than in the usual technique. The excluded septum often cannot be sutured with lateral wall because of potential damage to the revascularized LAD and inappropriate restraint of the right ventricle. In this case, the fibrous tissue is simply folded onto the patch with surgical glue. VT and mitral insufficiences are common in these large asynergia and require attention.

In summary, LVR with EVCPP in combination with coronary revascularization and mitral repair (when needed), improves ventricular performance for several reasons: (1) exclusion of the septal scar promotes more normal ventricular geometry; (2) reconstruction of the ventricular cavity prevents ventricular distortion, decreases wall tension on myocardial segments remote to the area of infarction, and improves regional contractility (demonstrable by pressure volume relationships); and (3) in contrast to a linear repair, the endoaneurysmorrhaphy (patch repair) allows maintenance of reasonably physiological diastolic volume and geometry.

RESULTS

Based on our personal experience of more than 1000 cases and on other published series *(23–26)*, LVR using an endoventricular circular patch works to restore a more normal morphology and physiology to the left ventricle *(27,28)*. This improvement is even apparent by postoperative ventriculography, which demonstrates a return to a normal ventricular cavity, particularly in relationship to the septal exclusion (Fig. 4).

There are also measurable hemodynamic benefits. There is a significant improvement in EF, with a mean increase of 10–15%. In addition, this improvement of EF is apparent whether the abnormal myocardial segment was initially dyskinetic or akinetic (Fig. 5).

Diastolic function is also improved (Fig. 6). The peak filling rate increases from a preoperative baseline of less than 1.8 EDV per second to 3/s EDV/second at 1 month and remains at 2.5/s EDV/second after 1 year, when the time-to-peak-filling rate decreases from 190 ms to respectively 110 ms and 90 ms after 1 year. There is also a shift of the pressure–volume relationship to the left. Finally, ventricular arrhythmias (spontaneous or inducible) are successfully controlled in 90% of cases *(29)*.

Surgical LVR is feasible with acceptable risk. From 1984 to 2001, in our series of 1011 patients (all indications included), there were 76 in-hospital deaths (7.5% operative mortality). With increasing surgical experience, improvements in the management of severely ill patients, larger indication for mitral repair, and greater attention to the remaining postoperative diastolic volume by balloon sizing. The operative mortality in our most recent series since 1998 (more than 400 cases) improved, with an overall mortality of 4.8 and less than 8% in the subgroup with large akinetic segments.

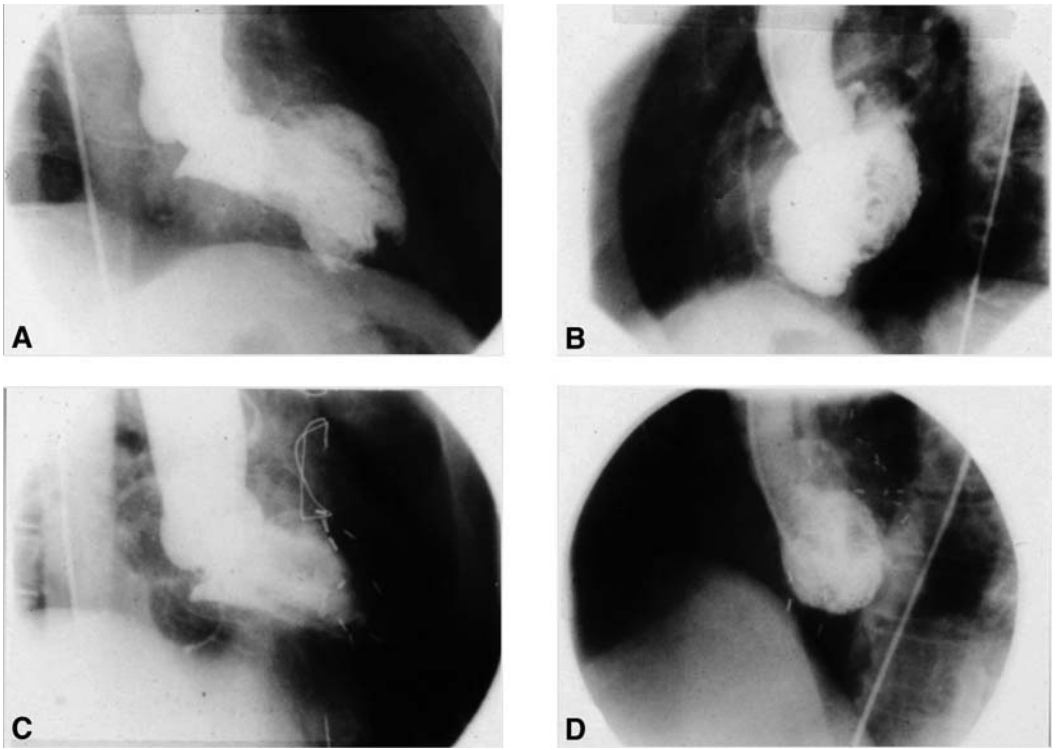


Fig. 4. Ventriculography after EVCPP of antero-septo-apical infarct. **(A)** Preoperative ventriculogram (right anterior oblique). **(B)** Preoperative ventriculogram (left anterior oblique). **(C)** Postoperative ventriculogram (right anterior oblique). **(D)** Postoperative ventriculogram (left anterior oblique). Note: the total disappearance of septal bulging.

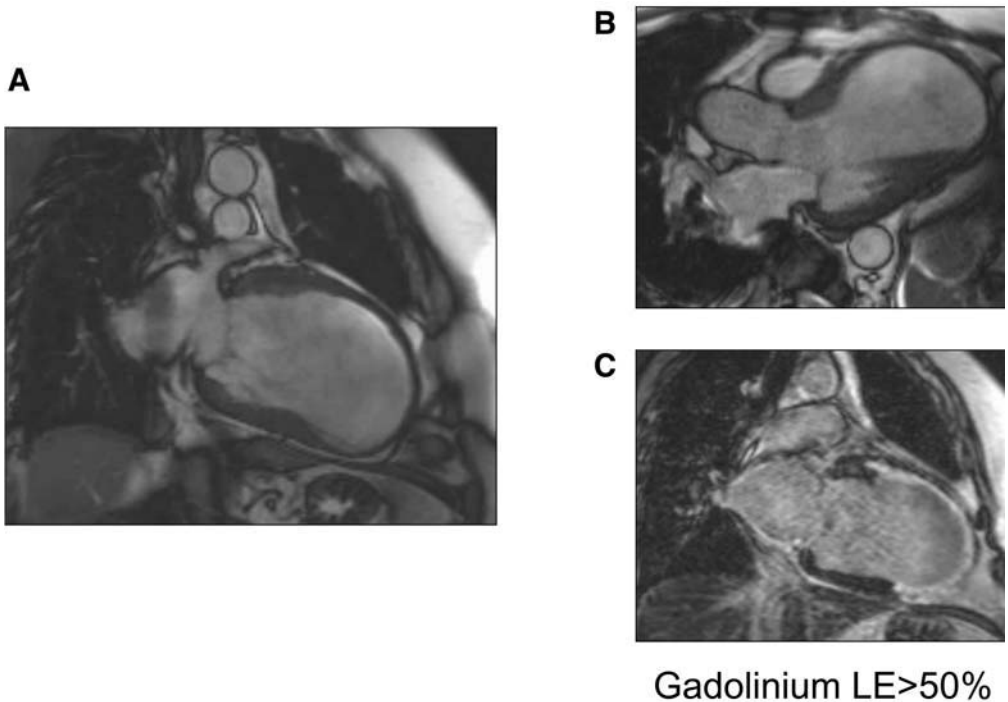


Fig. 5. CMR assessment of an antero-septo-apical aneurysm 4 years after successful stenting of a thrombosed LAD artery **(A,B)** Four chambers and two chambers preoperative view of a large antero-septal dyskinesia LVEF : 23%, EDVI: 180 mL/m^2, ESVI: 138 mL/m^2. **(C)** Gadolinium late enhancement shows a transmural apical necrosis and subendocardial necrosis.

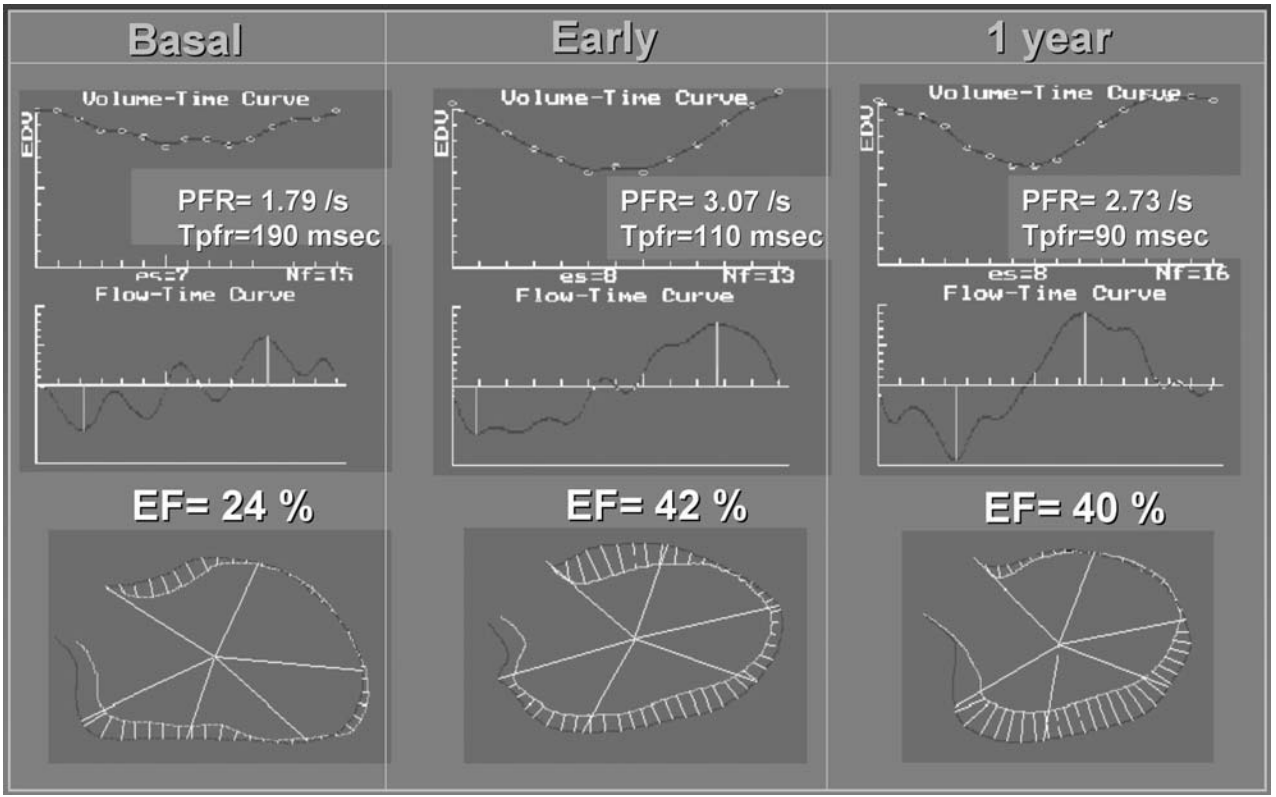


Fig. 6. Diastolic improvements after left ventricular reconstruction.

Table 1
Patients With Preoperative CI <2.0 L/min/m^2 and EF <30% (*N* = 40)

	Preoperative	*Postoperative*	*1 year postoperative*	*p*
CI (L/min/m^2)	1.7 ± 0.2	2.2 ± 0.5	2.5 ± 1.5	<0.001
EF (%)	22 ± 6	40 ± 7	38 ± 7	<0.001

CI, cardiac index; EF, ejection fraction.

Table 2
Akinetic vs Dyskinetic Postinfarction Segments (*N* = 245)

	Small dyskinetic (n = 4)	*Large dyskinetic (n = 41)*	*Small akinetic (n = 72)*	*Large akinetic (n = 48)*
Preoperative ejection fraction (EF)	42 ± 11	26 ± 7	41 ± 10	25 ± 9
Postoperative EF	53 ± 11	45 ± 11	49 ± 13	41 ± 12
Hospital death	4.8%	12.2%	0%	12.5%

DISAPPOINTING RESULTS

Some patients with large akinetic ventricular segments and global dilatation who underwent this procedure, developed recurrent mitral insufficiency and secondary pulmonary hypertension months and years after the LVR *(30)*. The mechanism of this process is not clear; continued ventricular remodeling may not be avoidable, especially when the interval between the sentinel infarct and the surgical reconstruction is long (i.e., >40 months) *(31)*. However, since 1998 with "balloon sizing" of the diastolic volume and more liberal use of mitral annuloplasty to keep the annulus smaller than 30 mm became routine, the delayed occurrence of mitral insufficiency and pulmonary hypertension decreased from 25 to 10%. Continued ventricular remodeling also occurs for other reasons than simple mechanical ones (i.e., neurohormonal processes); therefore, patients should be treated medically with β-blockers and angiotensin-converting enzyme inhibitors during the first preoperative year. When delayed hemodynamic control (i.e., essentially CMR) shows stability in terms of ejection fraction and volume, this medical therapy can be discontinued.

Late Survival

Late survival was analyzed in a surgical cohort of 245 consecutive patients operated on between December 1991 and December 1996 *(32)*. There were 20 hospital deaths (8.2%). Eighteen additional patients were lost to follow-up (8% of survivors), 207 patients represented the study cohort. There were no significant differences in baseline characteristics between the excluded patients and the study group. The clinical characteristics of the group are shown in Table 3. There were 163 patients with anterior dyskinesis, 30 with anterior akinesis, and 14 with both anterior abnormalities and severe remote hypokinesis.

During a mean follow-up period of 39 ± 19 months (12–72 months), there were 27 deaths and 3 heart transplants. Event-free survival was 98 ± 1% at 1 year, 95.8 ± 1.4% at 2 years, and 82.1 ± 3.3% at 5 years. Figure 6 shows the Kaplan–Meyer event-free survival curve for the overall population. Late deaths included 16 caused by progressive heart failure, 8 caused by sudden death, and 3 caused by noncardiac causes (2 from strokes and 1 from lung cancer).

Preoperative functional class, EF, and end-systolic volume appeared to predict poor long-term survival. The study population included a significant number of these patients: 57% were New York Heart Association (NYHA) class III–IV; 39% had an EF of 30% or less, and 35% had an ESVI above 120 mL/m^2. For these patient subgroups, the mortality rates were 21, 26, and 28%, respectively. However, it should be noted that these mortality rates are lower than previously reported in patients with reduced LV systolic dysfunction and advanced functional class *(33)*.

The presence of akinesis remote to the anterior wall scar (primarily inferior wall) also identified a high-risk subgroup of patients. Despite surgery, these patients had the worst prognosis, primarily from progressive heart failure. Although the great majority of patients in the study population showed improved regional inferior wall function following LVR, these patients did not. It is reasonable to hypothesize that the lack of recovery in function of these remote inferior segments was related to preoperative nonviability, as reported by Pagley et al. *(34)*. Cardiac transplantation may be more suitable for this patient subgroup.

The postoperative late incidence of malignant arrhythmias was reduced from 46 to 7.1% ($p < 0.0001$; Table 4). Sudden death was the cause of death in 8 of 27 patients. In summary, global life expectancy at 5 years is about 82%. This percentage is above 90% for patients with preoperative ESVI less than 120 mL/m^2 and at 70% for those with ESVI greater than120 mL/m^2. At 10 years, in this last category of very large dilated failing ventricle, the percentage of survival is 50%, whereas it is 80% for patients with ESVI less than 90 mL/m2.

Other clinical, operative, and hemodynamic univariate predictors of survival are reported in Table 5. Patients who died had a worse preoperative functional class (NYHA class 3.4 ± 0.9 vs 2.5 ± 0.9, $p < 0.0001$) and had more clinical signs of heart failure before surgery than did survivors (90 vs 56.5%). Cox regression analysis confirmed preoperative NYHA functional class, EF, ESVI, and remote asynergy were independent predictors of mortality. Actuarial survival curves were also created according to ESVI, EDVI, EF, and NYHA classification (Fig. 7). Although other studies have found the ESVI was the strongest predictor of future cardiac events and mortality in postinfarction patients before or after revascularization *(35–38)*, we found that the preoperative clinical status measured by the NYHA functional class had more predictive power.

In summary, EVCPP improves late survival in postinfarction patients with anterior wall scars, ventricular systolic dysfunction, ventricular dilatation, and significant functional limitation. Survival in this patient population is comparable to cardiac transplantation and much higher than reported in the literature for medical therapy or coronary artery bypass graft alone *(33,39)*.

THE FUTURE

Patient selection remains a critical issue for the success of surgical LVR. Although the clinical assessment of ventricular function is rather sophisticated today, cardiac magnetic resonance imaging may provide a more detailed assessment of viability, ventricular geometry, and hemodynamic performance *(40)*. Such information would allow more precise patient selection and more detailed operative planning.

Other surgical therapies could also be combined with LVR. For example, by combining a ventricular assist device with surgical LVR, the now mechanically unloaded uninfarcted myocardium might "recover" more quickly or more completely and allow for more aggressive pharmacological neurohormonal antagonism, all in the hope of increasing the chances for myocardial recovery. Preliminary data from the Berlin Heart Center *(41)* and Yacoub et al. (personal communication, 2001) suggest that such a strategy may be possible. In their experience with idiopathic dilated cardiomyopathies, months of ventricular assistance improved ventricular function and morphology to an extent that weaning was possible, a so-called bridge to recovery. In the case of ischemic cardiomyopathies, this type of long-term chronic ventricular unloading may provide similar improvements to the viable but hypocontractile myocardium remote to the areas of infarction. Therefore,

Table 3
Clinical Characteristics

Men/women	183/24
Age (years)	58–8
Time from myocardial infarction (months)	42–52
Urgent operation (%)	20 (9.7)
NYHA I–II (%)	90 (43.4)
NYHA III (%)	69 (33.3)
NYHA IV (%)	48 (23.2)
Angina (%)	133 (64.3)
Congestive heart failure (%)	127 (61.4)
Spontaneous ventricular tachycardia (%)	44 (21.3)
Coronary disease:	
1 vessel (%)	69 (34.8)
2 vessel (%)	73 (35.3)
3 vessel (%)	59 (28.5)
Wall motion	
Dyskinetic (%)	163 (79)
Akinetic (%)	30 (14.5)
Anterior scar and remote asynergy (%)	14 (6.5)

left ventricular surgical reconstruction would improve ventricular geometry by the exclusion of akinetic or dyskinetic segments, and the ventricular assist device would provide mechanical unloading of the viable but hypokinetic segments remote to the area of infarction in those patients suffering from advanced ischemic congestive heart failure. Finally, trials currently in process will inform later if cell transplantation could also be added to the procedure.

SUMMARY

LVR by EVCPP appears useful for pure ventricular dyskinesia (true aneurysm) or akinesia. LVR is performed on the totally arrested heart. Coronary revascularization is completed first. The mitral valve is inspected by transesophageal echocardiography and repaired if necessary. Endocardectomy and cryotherapy can be employed at this time in cases of ventricular tachycardia. At the border between scarred and normal tissue, a continuous suture is placed and tied on a rubber balloon inflated at the patient's theoretical volume in order to avoid diastolic incompliance and to select size and shape of the patch that is anchored on this endoventricular suture. Autologous tissue can also be used. Geometry and performance of the ventricle are improved,

Table 4
Hemodynamic Data for Entire Cohort

	Preoperative	*Postoperative*
CI (L/min/m^2)	2.7–0.6	2.7–0.6
EF (%)	35–13	48–12*
CWP (mmHg)	14–7	12–7
Mean PAP (mmHg)	21–10	18–8
EDVI (mL/m^2)	166–77	86–34*
ESVI (mL/m^2)	112–64	46–26*
Inducible VT (%)	75/163 (46)	13/182 (7.1)*

EDVI, end-diastolic volume index; ESVI, end systolic volume index; EF, ejection fraction; PAP, pulmonary artery pressure; CWP, capillary wedge pressure; CI, cardiac index; VT, ventricular tachycardia.

*$p < 0.0001$.

Table 5
Clinical, Operative, and Hemodynamic Parameters Associated With Major Events During Follow-Up

	Patients with events (n = 30)	*Patients without events (n = 177)*	*p*
Preoperative*			
NYHA class	3.4–0.9	2.5–0.9	0.0001
EF (%)	27–9	36–13	0.0001
EDVI (mL/m^2)	203–75	159–76	0.006
ESVI (mL/m^2)	150–60	105–63	0.001
Postoperative*			
EF (%)	38–9	50–11	0.0001
EDVI (mL/m^2)	106–42	82–32	0.001
ESVI (mL/m^2)	66–32	42–23	0.0001
Chi-square tests	*N* (%)	*N* (%)	
Preoperative signs of CHF,	27 (90)	96 (57)	0.001
Remote asynergy, *N* (%)	6 (20)	8 (4.8)	.009

Means and standard deviations used.

with a mean increase in the EF between 10 and 15%. The operative mortality on the global series over 1100 cases from 1984 is below 8%. Continued ventricular remodeling, lack of diastolic capacity, or absence of mitral repair may prevent postsurgical improvement.

After myocardial infarction resulting in a large akinetic scar (i.e., >50% of LV circumference), LVR should be considered to prevent pro-

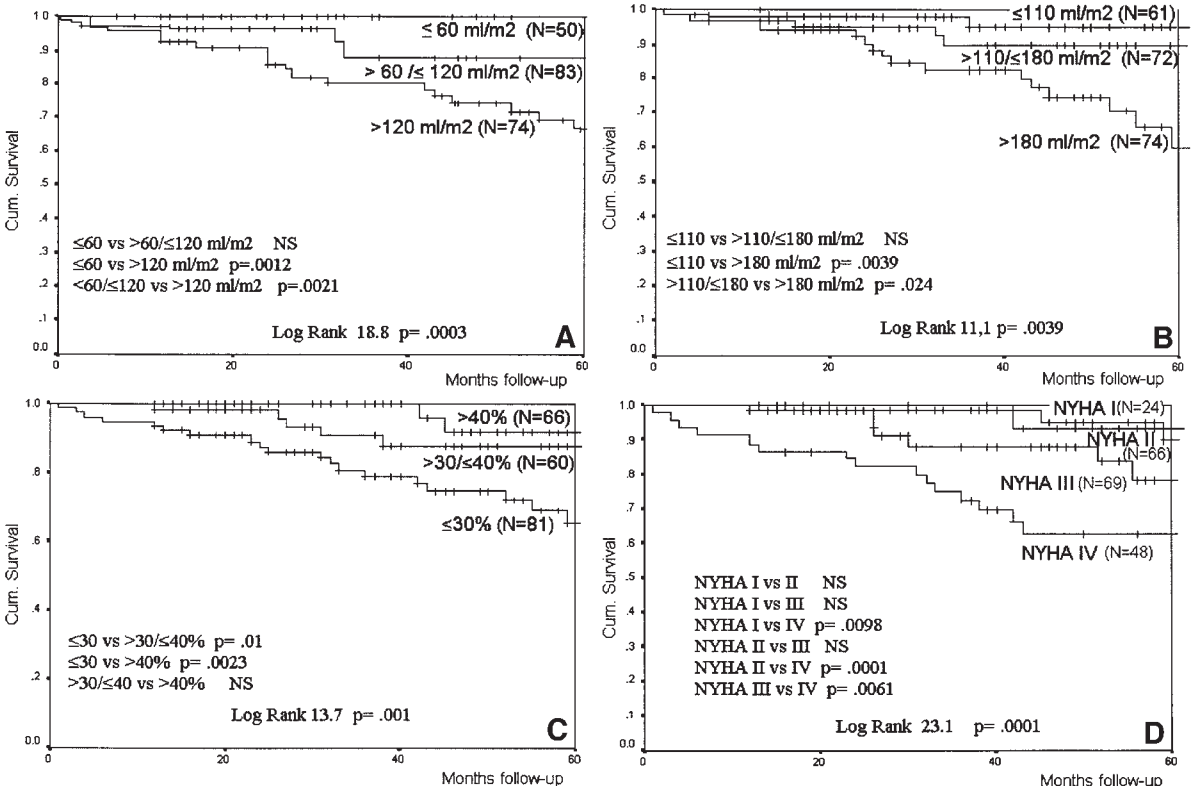


Fig. 7. Actuarial survival curves. **(A)** End-systolic volume index (ESVI). **(B)** End-diastolic volume index (EDVI). **(C)** Left ventricular ejection fraction (LVEF). **(D)** NYHA class.

gressive ventricular dilatation and clinical heart failure. In medically refractory ischemic heart failure, LVR may slow ventricular remodeling and delay the need for heart transplantation. Seventeen years after it was first conceived, LVR is now a good technique to rebuild a scarred and dilated left ventricle after MI. This procedure is easily reproducible, efficient, and safe. It must be considered as one of the major surgical treatments for ischemic cardiomyopathy.

REFERENCES

1. Bogaert J, Maes A, Van de Werf F, et al. Functional recovery of subepicardial myocardial tissue in transmural myocardial infarction after successful reperfusion. Circulation 1999;99:36–43.
2. Fieno DS, Kim RJ, Chen EL, Lomasney JW, Klocke FJ, Judd RM. Contrast-enhanced magnetic resonance imaging of myocardium at risk. Distinction between reversible and irreversible injury throughout infarct healing. J Am Coll Cardiol 2000;36:1985–1991.
3. Rehwald WG, Fieno DS, Chen EL, Kim RJ, Judd RM. Myocardial magnetic resonance imaging contrast agent concentrations after reversible and irreversible ischemic injury. Circulation 2002;105:224–229.
4. Klein MD, Herman MV, Gorlin R. A hemodynamic study of left ventricular aneurysm. Circulation 1967;35:614–630.
5. Gaudron P, Eilles C, Kugler I, et al. Progressive left ventricular dysfunction after myocardial infarction. Circulation 1993;87:755–762.
6. Yousef ZR, Redwood SR, Marber MS. Postinfarction left ventricular remodeling: where are the theories and trials leading us? Heart 2000;83:76–80.
7. Braunwald E, Pfeffer MA. Ventricular enlargement and remodeling following acute myocardial infarction: mechanisms and management. Am J Cardiol 1991; 68(suppl D):1D–6D.
8. McAlpine HM, Morton JJ, Leckie B, et al. Neuroendocrine activation after acute myocardial infarction. Br Heart J 1988;60:117–124.
9. Packer M. The neurohormonal hypothesis: a theory to explain the mechanism of disease progression in heart failure. J Am Coll Cardiol 1992;20:248–254.
10. White HD, Norris RM, Brown MA, et al. Left ventricular end-systolic volume as the major determinant of survival after recovery from myocardial infarction. Circulation 1987;76:44–51.
11. Marber MS, Brown DL, Kloner RA, et al. The open artery hypothesis: to open, or not to open, that is the question. Eur Heart J 1996;17:505–509.
12. Likoff W, Bailey CP. Ventriculoplasty: excision of myocardial aneurysm. JAMA 1955;158:915.
13. Cooley DA, Collins HA, Morris GC, et al. Ventricular aneurysm after myocardial infarction: surgical excision with use of temporary cardiopulmonary bypass. JAMA 1958;167:557.
14. Mills NL, Everson CT, Hockmuth D, et al. Technical advances in the treatment of left ventricular aneurysm. Ann Thorac Surg 1993;55:792–800.
15. Froehlich RT, Falsetti HL, Doty DB, et al. Prospective study of surgery for left ventricular aneurysm. Am J Cardiol 1980;45:923.
16. Cohen M, Packer M, Gorlin R. Indications for left ventricular aneurysmectomy. Circulation 1983;67:717.

17. Jatene AD. Left ventricular aneurysmectomy resection or reconstruction. J Thorac Cardiovasc Surg 1985;89:321–331.
18. Dor V, Kreitmann P, Jourdan J, Acar C, Saab M, Coste P. Interest of "physiological closure (circumferential plasty on contractile areas) of left ventricle after resection and endocardectomy for aneurysm of akinetic zone comparison with classical technique about a series of 209 left ventricular resections [abstract]. J Cardiovasc Surg 1985;26:73.
19. Cooley D. Ventricular endoaneurysmorrhaphy: a simplified repair for extensive postinfarction aneurysm. J Card Surg 1989;4:200–205.
20. Mickleborough L, Maruyama H, Liu P, et al. Results of left ventricular aneurysmectomy with a tailored scar excision and primary closure technique. J Thorac Cardiovasc Surg 1994;107:690–698.
21. Menicanti L, Frigiola A, Buckberg G, et al. Ischemic mitral regurgitation; intraventricular papillary muscle imbrication without mitral ring. Paper presented at: 81st Annual Meeting, American Association for Thoracic Surgery, May 6–9, 2001; San Diego, CA.
22. Di Donato M, Sabatier M, Toso A. Regional myocardial performance of non-ischaemic zones remote form anterior wall left ventricular aneurysm. Effects of aneurysmectomy. Eur Heart J 1995;16:1285–1292.
23. Jakob H, Z^lch B, Schuster S, et al. Endoventricular patch plasty improves results of LV aneurysmectomy. Eur J Cardiothorac Surg 1993;7:428–436.
24. Grossi E, Chimitz L, Galloway A, et al. Endoventricular remodeling of left ventricular aneurysm: functional, clinical and electrophysiological results. Circulation 1995;92(suppl II):98–100.
25. Shapira O, Davudoff R, Hilkert R, et al. Repair of left ventricular aneurysm: long-term results of linear repair vs endoaneurysmectomorrhaphy. Ann Thorac Surg 1997;63:401–405.
26. Athanasuleas C, Stanley A, Buckberg G, et al. Surgical Anterior Ventricular Endocardial Restoration (SAVER) in the dilated remodeled ventricle after anterior myocardial infarction. J Am Coll Cardiol 2001;37:5.
27. Dor V, Sabatier M, Di Donato, et al. Late hemodynamic results after left ventricular patch repair associated with coronary grafting in patients with postinfarction akinetic or dyskinetic aneurysm of the left ventricle. J Thorac Cardiovasc Surg 1995;110:1291–1301.
28. Di Donato M, Barletta G, Maioli M. Early hemodynamic results of left ventricular reconstructive surgery for anterior wall left ventricular aneurysm. Am J Cardiol 1992;69:886–890.
29. Dor V, Sabatier M, Montiglio F, et al. Results of nonguided subtotal endocardiectomy associated with left ventricular reconstruction in patients with ischemic ventricular arrhythmias. J Thorac Cardiovasc Surg 1994;107:1301–1308.
30. Di Donato M, Sabatier M, Dor V, et al. Effects of the Dor procedure on left ventricular dimension and shape and geometric correlates of mitral regurgitation 1 year after surgery. J Thorac Cardiovasc Surg 2001;121:91–96.
31. Louagie Y, Alouini T, Lesperence J, et al. Left ventricular aneurysm complicated by congestive heart failure: analysis of long term results and risk factors of surgical treatment. J Cardiovasc Surg 1989;30:648–655.
32. Di Donato M, et al. Efficacy of Dor procedure on late survival in patients with post-infarction akinetic or dyskinetic scar and predictors of outcome. Am Coll Cardiol Suppl A 2001:370A.
33. Emond M, Mock MB, Davis KB. Long term survival of medically treated patients in the Coronary Artery Surgery Study (CASS). Circulation 1994;90:2645–2657.

34. Pagley PR, Beller GA, Watson DD, Gimple LW, Ragosta M. Improved outcome after coronary bypass surgery in ischemic cardiomyopathy and residual myocardial viability. Circulation 1997;96:793–800.
35. White HD, Norris RM, Brown MA, Brandt PWT, Whitlock RML, Wild C. Left ventricular end systolic volume as the major determinant of survival after recovery of myocardial infarction. Circulation 1987;76:44–51.
36. Migrino RQ, Young JB, Ellis SG, et al. End-systolic volume index at 90 to 180 minutes into reperfusion therapy for acute myocardial infarction is a strong predictor of early and late mortality. The Global Utilization for Streptokinase and t-PA for Occluded Coronary Arteries (GUSTO)-I Angiographic Investigators. Circulation 1997;96:116–121.
37. Hamer AW, Takaiama M, Abraham RA, et al. End systolic volume and long term survival after coronary artery by pass surgery in patients with impaired left ventricular function. Circulation 1994;90:2899–2904.
38. Yamaguchi A, Ino T, Adachi H, et al. Left ventricular volume predicts postoperative course in patients with ischemic cardiomyopathy. Ann Thorac Surg 1998;65: 434–438.
39. Dor V. The endoventricular circular patch plasty ("Dor procedure") in ischemic akinetic dilated ventricles. Heart Failure Rev 2001;6:187–193.
40. Young A, Dougherty A, Bogen D, et al. Validation of tagging with MR imaging to estimate material deformation. Radiology 1993;188:101–108.
41. Hetzer R, Müller J, Weng Y, et al. Midterm follow-up of patients who underwent removal of a left ventricular assist device after cardiac recovery from end-stage dilated cardiomyopathy. AATS April 1999.

13 The Total Artificial Heart in the Surgical Management of Congestive Heart Failure

Jack G. Copeland, MD,
Francisco A. Arabia, MD,
and Richard G. Smith, MSEE, CEE

CONTENTS

INTRODUCTION

The idea of completely replacing both ventricles of the heart with an orthotopic mechanical substitute for the treatment of severe heat failure is probably as old as the first understanding of cardiac anatomy and function. However, the first clinical use of such a device dates back less than half a century. In 1969, after considerable animal experimentation, Cooley implanted the Liotta heart (Table 1). Twelve years later, he implanted another total artificial heart (TAH), designed by Akutsu *(1)*. Neither of these desperately ill patients survived for more than a

From: *Contemporary Cardiology: Surgical Management of Congestive Heart Failure*
Edited by: J. C. Fang and G. S. Couper © Humana Press Inc., Totowa, NJ

Table 1
World Experience With TAHs as of September 1, 2001

Device	*Time frame*	*Centers*	*Implants*	*Transplants*	*Discharged*
Liotta	1969	1	1	1	0
Akutsu	1981	1	1	1	0
Jarvik 7-100	1982–1992	10	44	26	16
Phoenix	1985	1	1	1	0
Penn State	1985–1989	1	4	1	0
Jarvik 7-70	1985–1992	30	159	120	69
Berlin	1986–1990	1	7	2	0
Unger	1986–1990	3	4	2	0
Vienna	1989	1	2	1	1
Brno	1988–1990	3	6	3	0
Poisk	1987–1990	3	16	3	2
CardioWest	1993–2001	10	203	131	115
Phoenix-7	1998	1	2	1	1
Abiomed	2001	1	2	N/A	N/A
Total			452	293	204

N/A, not applicable.

few days. One year later, in 1982, DeVries and his team implanted the Jarvik-100 TAH. This experience with four "permanent" implants demonstrated surprisingly long survivals *(2)*, but was complicated by device endocarditis and subsequent strokes.

Since that experience, 452 TAHs with 11 different names have been implanted. Of the 452 TAHs, 406 have been the basic device that came from Dr. Kolff's laboratory in Salt Lake City, Utah: the Jarvik-7, now renamed the CardioWest TAH. In August 1985, at the University of Arizona, we had the first survival of a bridge-to-transplant patient with a TAH, using this device to support a patient for 9 days prior to cardiac transplantation. He lived for 4.5 years after heart transplantation *(3)*. More than 44 patient-years of implantation have been accumulated with this TAH, 27 with the CardioWest TAH (Tables 2 and 3).

There are currently two types of TAH implanted: the CardioWest TAH and the AbioCor TAH. The CardioWest TAH, a pneumatic device that discussed in detail in this chapter, is approved for commercial distribution in Europe and Canada and is on the verge of such approval in the United States. Marketing of this device has been on hold pending US Food and Drug Administration (FDA) approval. In the interim, experience with this device has been confined to a few centers, which have now accumulated more than 10,000 patient implant days (Tables 2 and 3). In contrast, the AbioCor device, a

Table 2
World Experience With Total Artifical Hearts by Device

Device type	*Implants*[1]	*Days*[2]	*Years*[3]
CardioWest C-70	203	>10,000	27
Symbion J 7-70	159	4000	11
Symbion J 7-100	44	2000	6
Penn State	4	400	1
Poisk	16	100	0.3
AbioCor	2	60	0.2
Berlin	7	60	0.2
Unger	6	50	0.1
Total	441	>16,000	>45

[1]Total number of human implants.
[2]Total duration of implantation in days.
[3]Number of patient-years accumulated.

Table 3
CardioWest Implantation Experience by Center

Center	*Implants (on)*[1]	*Transplants*	*Discharged*[2]	*Alive*[3]	*Average (Range)*[4]
Arizona	60 (3)	42 (75%)	38 (91%)	33 (87%)	90 (0–413)
LaPitie	72 (1)	40 (56%)	30 (75%)	26 (87%)	29 (0–268)
Loyola	17	12 (71%)	11 (92%)	9 (82%)	28 (0–123)
Nantes	19 (1)	11 (61%)	11 (100%)	11 (100%)	74 (1–224)
Ottawa	14	14 (100%)	14 (100%)	13 (93%)	16 (1–37)
All centers	203 (7)	131 (67%)	115 (88%)	102 (89%)	47 (0–413)

[1]Number of patients on device support in parentheses.
[2]Discharged to home after transplantation.
[3]Number of patients currently alive.
[4]Average length of implantation in days and range of implant time in days.

totally implantable electrohydraulic TAH, has been implanted in only 10 patients in four centers (Jewish Hospital of Louisville, Kentucky; Texas Heart Institute, Houston; Hahnemann University Hospital, Philadelphia; University of California at Los Angeles).

The extensive experience with the CardioWest TAH provides information on the indications, usefulness, complications, quality of life, and survival that may be helpful in determining the role of a TAH in patients with congestive heart failure (CHF). These data also form the basis for comparison to other circulatory support devices, such as the

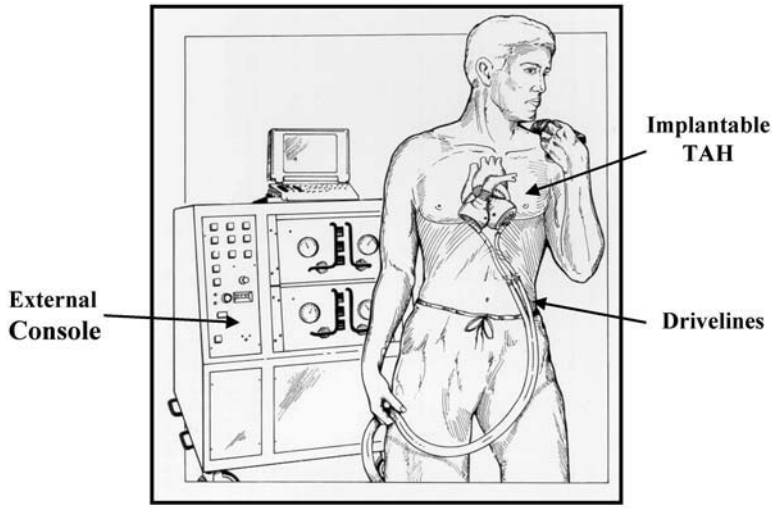


Fig. 1. Drawing to scale of the CardioWest TAH and console.

extracorporeal pulsatile, implantable pulsatile, and continuous flow ventricular assist devices. The remainder of this chapter therefore addresses the use of the CardioWest TAH in CHF.

DEVICE DESCRIPTION

The CardioWest TAH is an orthotopic, biventricular, pneumatic, pulsatile blood pump *(4)*. As shown in Fig. 1, it replaces the native ventricles. It is attached to the left and right atrial cuffs with individual "quick connectors" (elastic polyurethane couplers over rigid ventricular valve mounts) that couple to their respective ventricles. Blood passes through this almost imperceptible junction from the atrium, across a 27-mm Medtronic-Hall valve, to the ventricular chamber. The spherical chamber is lined with segmented polyurethane. The outer chamber is a semirigid polyurethane-lined housing that does not move. The inner chamber contains a four-layer polyurethane diaphragm driven by air pressure. The diaphragm moves toward a rigid plastic wall as the ventricle fills with blood in diastole and toward a 25-mm Medtronic-Hall outflow valve in systole, ejecting about 55 to 60 cc per beat. Blood flows through the outflow valves into woven Dacron conduits to the respective great vessels.

Dacron-covered drivelines exit through tunnels in the left epigastrium and connect to a driver console. This console contains a backup driver,

multiple alarms, an internal compressed air supply, and a laptop monitor. The monitor provides beat-to-beat monitoring of ventricular filling, ejection pressure, heart rate, cardiac output on both the left and right sides, and trend monitoring of cardiac output (Fig. 2). The console is mobile within the hospital, allowing patients to attend daily cardiac rehabilitation classes and to ambulate outside. There are at least two portable consoles under development that are compatible with out-of-hospital life. The company plans to use these consoles once commercial approval for the device and large console have been obtained in the United States.

INDICATIONS

Indications that clearly favor the use of an orthotopic TAH in patients with end-stage CHF include incessant malignant arrhythmias, thrombus in the left ventricle, impaired right ventricular (RF) function, acquired ventricular septal defect, the "stone heart," severe rejection of a transplanted heart, diseases of the right ventricle (i.e., arrhythmogenic RF dysplasia), aortic insufficiency, mitral stenosis, and tricuspid stenosis. The TAH has been called the ultimate solution to arrhythmias because both native ventricles are removed and replaced. Situations that result in virtual nonfunction of both ventricles, such as profound rejection and the stone heart, have no better mechanical solution. The niche for TAH use in end-stage heart failure may be quite broad.

Oz and colleagues *(5)* at Columbia University in New York City have reported the influence of preoperative risk factors on postoperative survival in patients with left ventricular assist device (LVAD; HeartMate). They found significantly increased risk in those patients with central venous pressure (CVP) above 16 mmHg, urine output less than 30 cc per hour, elevated serum creatinine, and elevated Acute Physiology and Chronic Health Evaluation (APACHE) II scores.

Our own univariate and multivariate stepwise logistic regression analyses of preimplant risk factors comparing the TAH, LVAD, and biventricular assist device supported these findings. In the LVAD group, the predictors of poor outcome were CVP above 20 mmHg, serum creatinine above 2.0 mg/dL, and an APACHE II score of above 28. None of these variables was significant in the TAH group *(6,7)*. CVP in these very sick inotrope-supported heart failure patients seems to be a reasonable way to select those with "right heart failure" (RHF). In addition to the data from Columbia, there seems to be a general consensus among LVAD users that RHF occurs in up to 25% of LVAD cases, and it is associated with a very high mortality rate if present after LVAD implantation.

When we retrospectively compared our LVAD and TAH results *(8)*, we found the mean preimplant CVP for the CardioWest patients was 20 mmHg vs 14 mmHg in the LVAD patients. Thus, the CardioWest recipients had evidence of preimplant RHF, but the LVAD preimplant patients did not; yet, the survival rate was higher in the TAH patients. This observation fits with the experience we have had with LVADs vs TAHs in critically ill patients and the reason that we implant the TAH in all of those with RHF. We reserve LVADs for patients who are "more stable" and lack evidence of RHF *(8)*. Our recommended indications for the TAH in severe congestive heart failure include unstable hemodynamics (rapid decline), failure to wean from cardiopulmonary bypass, cardiac arrest, RHF, pulmonary edema, CVP above16 mmHg, creatinine above 2.0 mg/dL, as well as those conditions mentioned at the beginning of this section. The only qualification is that the TAH must fit in the patient's mediastinum.

Size criteria for the CardioWest TAH include one or more of the following: 70 mm or larger LV end-diastolic dimension by echo, a cardiothoracic ratio above 0.5, a computerized tomographic scan anterior–posterior dimension at T-10 from posterior sternum to anterior vertebral column of 10 cm or more, and a body surface area (BSA) of 1.7 m^2. In general, a combination of BSA over 1.7 m^2 and a "large heart" by one other criterion from this list was a reliable predictor of a "good fit."

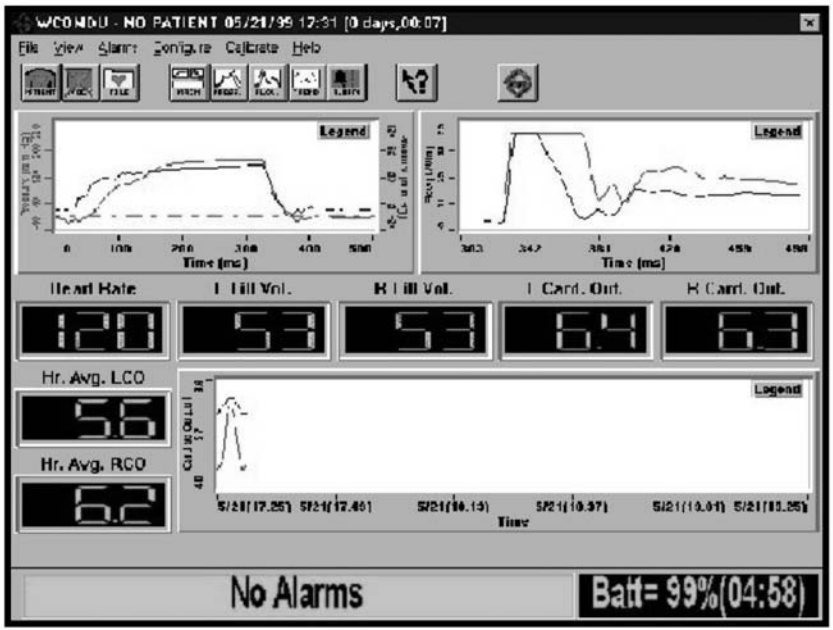
Data from the ongoing FDA study of the CardioWest TAH demonstrate that the typical patient has a BSA of 2.0 m^2, a cardiac index of 1.6 L/min/m^2, and a CVP of 19 mmHg. The patient is generally on multiple inotropes (often more than 10 μg/kg/min of dobutamine and/or 3 μg/kg/min dopamine), including milrinone, epinephrine, and/or norepinephrine. Such patients are critically ill and demonstrate high-dose diuretic resistance and hemodynamic instability with minimal patient movement despite escalating degrees of hemodynamic and medical support.

IMPLANTATION

The implantation technique has been previously described in detail *(9)*. Primary considerations include achieving excellent hemostasis,

Fig. 2. *(see facing page)* The console and the laptop screen, which displays driveline pressure (upper left), ventricular filling rate with respect to time (upper right), and, in the second row, heart rate, left fill volume, right fill volume, left cardiac output, and right cardiac output. On the left bottom are average left cardiac output; on the bottom is the average right cardiac output. To the right of these is a trend display of left- and right-sided outputs.


CARDIOWEST
EXTERNAL
CONSOLE
PRIMARY
CONTROLLER
BACKUP
CONTROLLER


WCOMDU - NO PATIENT 05/21/99 12:31 [0 days,00:07]
File View Alarm Configure Calibrate Help
Legend
Time (ms)
Legend
Time (ms)
Heart Rate
L Fill Vol.
R Fill Vol.
L Card. Out.
R Card. Out.
120
53
53
6.4
6.3
Hr. Avg. LCO
5.6
Hr. Avg. RCO
6.2
Legend
Time
No Alarms
Batt= 99%(04:58)

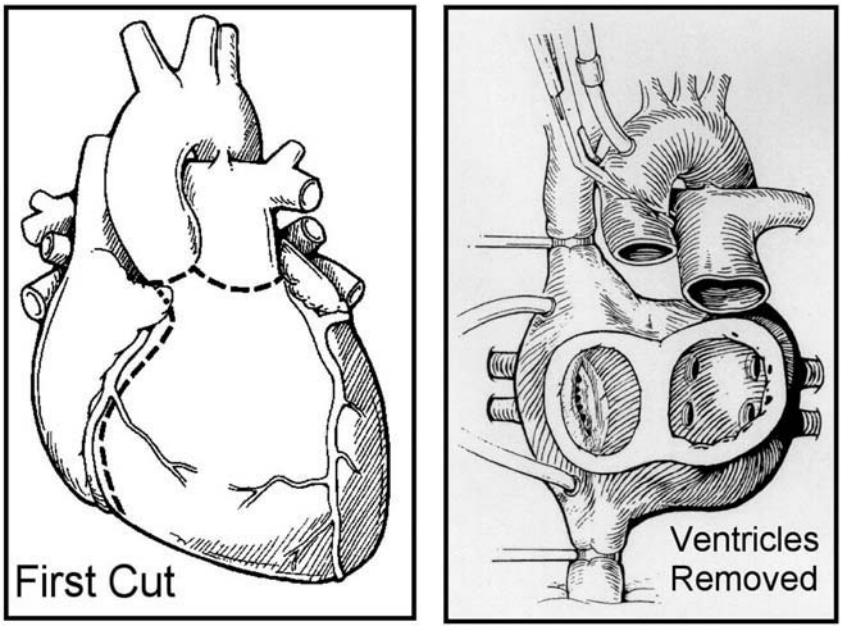


Fig. 3. Lines of resection of the native heart and appearance after ventriculectomy.

good fitting and positioning of the two ventricles, and preparing for explantation.

Briefly, the cardiectomy is made on the ventricular side of the atrioventricular (AV) groove. The great vessels are transected at the sinotubular junctions (Fig. 3). The atrial cuffs are buttressed with an 8-mm Teflon felt band sewn to the free walls (Fig. 4). The gathering stitch includes the Teflon felt, all cut edges that might otherwise bleed, and the endocardium/AV valve remnant on the atrial side. The atrial quick connectors (flanges trimmed to 6 mm) are then sewn to the respective cuffs.

We begin with the elastic connector inverted and then evert them after completing both suture lines. We next anastomose the great vessel conduits. The lengths of the great vessel conduits beyond the connectors are usually 2 to 3 cm for the aorta and 5 to 6 cm for the pulmonary artery. Finally, we check the suture lines for leaks with saline under pressure and then connect the ventricles (Fig. 5). One recent change in

Fig. 4. *(see facing page)* Left: The Teflon felt buttress is sewn in place. Middle: **(A)** The inverted atrial connectors are sewn to the atrial cuffs; **(B)** appearance of the everted connectors after the anastomoses. Right: Appearance of the aortic outflow conduit with proximal connector sewn to the aorta.

Atrial
Suture
Atrial
Cuff
Outflow
Suture
A
B

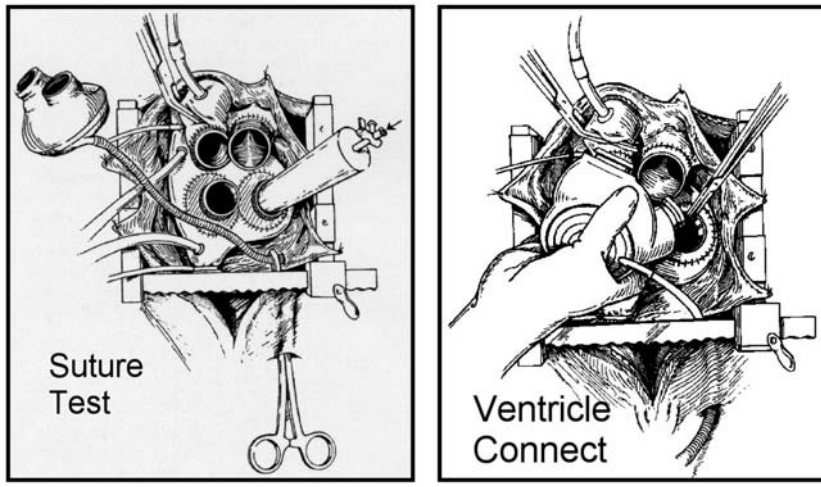


Fig. 5. Left: Testing the suture lines for leaks. Right: connecting the left ventricle.

our technique has been to cover the device, native atrial cuffs, and aorta with 0.1-mm thick extended polytetrafluoroethylene material *(10)*. This creation of a synthetic membrane neopericardium has facilitated explantation and has not, in our early experience with 16 patients, caused clinical infection.

Before cardiopulmonary bypass is discontinued, deairing of the left side is done with a vent in the aorta and the patient in steep Trendelenburg position. After discontinuation of cardiopulmonary bypass, outputs are generally high. Vacuum is not used to facilitate ventricular filling until the chest is closed and chest tubes are placed on suction. As the chest is closed, we look very carefully at the cardiac output and trans-esophageal echocardiography. The most common problems arise in patients who are too small for the device. Chest closure in this group may cause the right ventricular atrial connector to compress the inferior vena cava and/or the LV atrial connector to compress the left-sided pulmonary veins. Sudden drop in cardiac output and the appearance of flow turbulence by trans-esophageal echo in the inferior vena cava or the left pulmonary veins would indicate the need for device repositioning.

DEVICE MANAGEMENT, PATIENT CONDITION

Most patients have a cardiac output of 6 to 7 L per minutes at the end of the implant procedure, with a CVP in the range of 12 to 15 mmHg.

The systemic vascular resistance is maintained with intravenous vasoactive agents in the range of 700 to 1000 dyne-s-cm^{-5} (e.g., nitroglycerin or nitroprusside for vasodilation and norepinephrine for vasoconstriction). Usually, the vasoactive support is discontinued within 48 hours. Cardiac outputs rise and stay at 7 to 8 L per minute (mean cardiac index of 3.0 L/min/m^2).

Patients are extubated within 3 days, out of bed walking within 3.5 days, able to walk more than 100 feet within 11 days, and discharged from intensive care in 11 days. Within the first week, arterial and central venous lines are removed. Patients participate in cardiac rehabilitation three to five times per week; this includes treadmill walking, use of a stationary bicycle, and upper extremity exercises. They do not have RHF or problems with arrhythmias. They also do not experience symptomatic orthostatic changes in pressure or low output alarms, which are common with LVADs. Finally, they do not have nutritional problems from the presence of a large LVAD compressing the stomach.

In the more than 80 FDA CardioWest study patients, the blood urea nitrogen and creatinine returned to normal and remained normal after postimplant day 25. Total bilirubin fell to normal levels by day 20. Plasma free hemoglobin stayed constant at 8 mg/dL, and the hematocrit was constant over time at 26%. The mean body weight fell by 6 kg in the first 3 weeks, but rose by 4 kg by week 7.

Standard settings on the controller are 200 mmHg LV pressure, 60 mmHg RV pressure, 10 cm H_2O vacuum pressure, 50% systole, and beat rate of 120 beats per minute (bpm). Early on, these settings are rarely changed, and after the first week, almost never are changed. The laptop monitor provides continuous assessment of driveline pressure and ventricular diastolic volume (fill volume) as well as cardiac output (the product of the fill volume and the bpm rate).

We try to maintain maximal cardiac outputs based on the concept that high flows discourage thrombus formation. The driveline (ventricular) pressures are set high enough to accommodate sudden rises in peripheral pressures (left driveline pressure is set 60 mmHg higher than the patient's blood pressure; right driveline pressure is set 30 mmHg higher than estimated pulmonary artery pressure). When the ventricular diaphragm has a full excursion (full eject), a small isovolumic pressure rise appears at the end of the pressure curve, indicating full ejection. Vacuum, percentage systole (the percentage of the cardiac cycle taken by systole), and beat rate are set so that ventricular filling is about 85% of the maximal of 70 cc. This allows the device to have reserve to accommodate increased venous return and to exhibit a Star-

ling principle in response to increased filling. In summary, the device is set to provide 85% filling and to eject fully with each beat.

Anticoagulation is based on the prothrombin time, international normalized ratio, partial thromboplastin time, platelet count, hematocrit, platelet activation studies, bleeding time, and thromboelastogram. The anticoagulants used are heparin (generally for the first 1–2 weeks), warfarin (begun just before heparin discontinuation), aspirin, dipyridamole, and pentoxifylline. This strategy has been discussed elsewhere *(4)*. Anticoagulation guidelines include normal coagulability assessed by thromboelastogram, normal reactivity to collagen in platelet aggregometry, and a bleeding time of 17 to 23 min. In 56 patients from September 1994 to September 2001, the incidence of stroke not associated with implant or explant was 1 case (0.08 events/patient-year or 0.007 events/patient-month). There were three additional strokes related to implantation (0.33 events per patient-year). Thus, thromboembolism during device support was extremely rare.

Bleeding, defined as requiring reoperation or requiring 8 or more units of blood within 48 hours, has been almost completely confined to the first postimplant week. The incidence has been 33%. This incidence is attributable to a number of factors. Many of the implant recipients have some element of synthetic liver dysfunction. Many patients have also been anticoagulated as part of their chronic preimplant therapy or for recent operations. Furthermore, balancing heparin therapy early postimplant in the face of ongoing coagulopathies can occasionally lead to excessive bleeding and complications such as atrial tamponade.

Perioperative antibiotic management is the same prophylactic routine as we use in all open heart cases. We do not routinely use any other regimen. As of mid-September 2001, we had seen two clinical infections of the mediastinum (on the basis of positive blood cultures), one bacterial (*Staphylococcus aureus*) and one fungal (*Candida* species). Both infections were treated with continuous intravenous therapy until the time of transplant. Both patients are long-term survivors.

Another theoretical issue is the percutaneous driveline potential for infection. Our experience and those of other investigators suggest that the Dacron covering of the drivelines stimulates marked tissue ingrowth. We have found driveline removal at explant/transplant to be very difficult because of an abundance of healthy adhesions around the Dacron. We have never seen an ascending infection along a driveline. We have seen only superficial infections at the skin level, which are treated topically with antiseptic and cleansing. We do use systemic antibiotics if we find a persistent pathogen.

SURVIVAL, QUALITY OF LIFE, FUTURE USES

The picture of a patient transformed from dying with end-stage CHF to a stable, well-fed individual on the CardioWest TAH who exercises daily and interacts with family and friends within the confines of the hospital and immediate surroundings is at once dramatic and limited. It is a miraculous transition. These patients can reach an oxygen consumption of 12–14 cc/kg per minute on treadmill testing. Renal and hepatic functions return to normal. Pulmonary edema disappears. Serum albumin returns to normal, and the patients start gaining lean body mass. On the other hand, they are bound to a large console and cannot be discharged to home. They await a transplant that represents another brutal hurdle toward a more normal life.

With the CardioWest, 61 to 75% of implanted patients (131 of 203 = 64.5%) have survived for an average of 47 days (range 16 to 90) on device support to receive a transplant (Table 3). Of those who were transplanted, 115 (88%) survived to discharge, and 102 are currently alive. In our national trial, 89% of the bridge-to-transplant patients with CardioWest survived long term compared to 33% ($p < 0.00001$) of matched historical controls transplanted without a mechanical circulatory support device *(11)*. Other subsequent studies have also demonstrated that the TAH as a bridge-to-transplant device prolongs life in very sick patients and is comparable to LVADs and paracorporeal biventricular assist devices in this role. In our own retrospective comparison of these three types of devices, it was clear that the TAH was more effective in sicker patients than the other two devices *(8)*.

What are the prospects for the CardioWest in the future? A portable system (Fig. 6) has been developed and may be used clinically in the near future. A wearable system is also under development. This portability should allow out-of-hospital living, improve the quality of life substantially, and open the possibility for "permanent" implantation. The longest survivor on a TAH (Symbion) lived 603 days, dying in 1988 of a ruptured cerebral aneurysm. There have been 10 other implants of 225 days or longer, 9 of whom survived to transplant. The longest implant time preceding successful heart transplantation was 414 days. These figures suggest that permanent implantation may be reasonable, especially when considering the technical difficulty, morbidity, and mortality (12%) of an explant/transplant operation. This concept is particularly robust in view of the low incidence of stroke (0.08 per year) with the use of multidrug anticoagulation therapy.

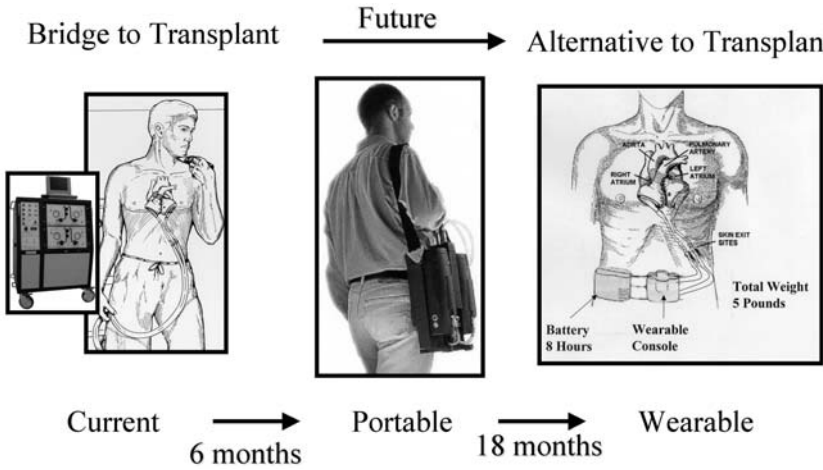


Fig. 6. Consoles for the CardioWest. Current console is on the left. A portable console of the type currently available is in the middle. On the right is a wearable console currently under development.

In summary, the past experience with the TAH has been promising. We have found the implantation of a CardioWest TAH, by providing high cardiac outputs in acutely and chronically ill patients, has led to recovery of vital organs and an improved nutritional status. Simultaneous mechanical support of the left- and right-sided circulations allows for optimal outputs free from the influences encountered with LVADs, such as RHF, low outputs, and recurrent arrhythmias. It also permits optimal transcapillary perfusion pressure (mean systemic pressure, CVP), facilitating vital organ perfusion and recovery. Bridge to transplantation with the TAH has proved effective and reasonably safe in an extremely sick group of patients. Future commercialization, portability, and permanent implantation should provide for extension of life of a good quality in properly selected patients.

REFERENCES

1. Cooley DA, Liotta D, Hallman GL, Bloodwell RD, Leachman RD, Milam JD. Orthotopic cardiac prosthesis for two-staged cardiac replacement. Am J Cardiol 1969;24:723–730.
2. DeVries WC, Anderson JL, Joyce LD, et al. Clinical use of the total artificial heart. N Engl J Med 1984;310:273–278.
3. Copeland JG, Levinson MM, Smith R, et al. The total artificial heart as a bridge to transplantation. JAMA 1986;256:2991–2995.

4. Copeland J, Arabia F, Smith R, Nolan P. Intracorporeal support: the CardioWest total artificial heart. In: Goldstein DJ, Oz MC, eds. Cardiac Assist Devices. Futura, Armonk, NY: 2000, pp. 341–355.
5. Oz MC, Goldstein DJ, Pepino P, et al. Screening scale predicts patients successfully receiving long-term implantable left ventricular assist devices. Circulation 1995;92(9 suppl):II169–II173.
6. Mehta VK, Copeland JG, Arabia FA, Smith RG, Banchy M. Analysis of preoperative comorbid factors associated with biventricular assist device and total artificial heart: a single center experience. J Heart Lung Transplant 2000;19:65.
7. Mehta VK, Copeland JG, Arabia FA, Banchy ME, Smith RG. Mechanical ventricular support as bridge to transplant: risk factor and selection. ASAIO J 2000; 46:192.
8. Copeland JG, Smith RG, Arabia FA, et al. Comparison of the CardioWest total artificial heart, the Novacor left ventricular assist system and the Thoratec ventricular assist system in bridge to transplantation. Ann Thorac Surg 2001;71 (3 suppl):S92–S97.
9. Arabia FA, Copeland JG, Pavie A, Smith RG. Implantation technique for the CardioWest total artificial heart. Ann Thorac Surg 1999;68:698–704.
10. Copeland JG, Arabia FA, Smith RG, Covington D. Synthetic membrane neopericardium facilitates total artificial heart explantation. J Heart Lung Transplant 2001;20:654–656.
11. Copeland JG, Arabia FA, Banchy ME, et al. The CardioWest total artificial heart bridge to transplantation: 1993 to 1996 national trial. Ann Thorac Surg 1998;66: 1662–1669.

INDEX

M