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Pathophysiology, Evaluation and Management of Valvular Heart Diseases

Volume 2

Editors
J.S. Borer
O.W. Isom

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Pathophysiology, Evaluation and Management of Valvular Heart Diseases, Volume 2

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Pathophysiology, Evaluation and Management of Valvular Heart Diseases, Volume 2

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Volume Editors

Jeffrey S. Borer *New York, N.Y.*
O. Wayne Isom *New York, N.Y.*

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Introduction

The first volume in the series, *Pathophysiology, Evaluation and Management of Valvular Heart Diseases*, was produced in 2002. The stimulus to undertaking the work was the growing realization that valvular diseases, now understood as progressive concomitants of aging, are increasing in prevalence throughout our society and, indeed, have reached the point at which they must be considered, as a group, to be an important public health problem. Data about valvular diseases emerge frequently in the medical literature and, thus, approaches to patient care in this area must be re-examined regularly. Therefore, our hope in publishing the first volume was to highlight the most up-to-date understanding of maximally effective approaches to evaluation and management of these diseases. Simultaneously, we aimed to review recent developments elucidating pathophysiology at the organ, cellular and molecular levels that will serve as the basis for improvement in evaluation and management strategies in the near future and the longer term.

We chose to produce the book by requesting articles from the faculty members of the symposium, '*Valves in the Heart of the Big Apple: Evaluation and Management of Valvular Heart Diseases*', which we produced for the first time in May, 2001, in New York City. Since the three-day symposium could not cover all areas of valvular diseases, we knew that the resulting volume would be a selective rather than a comprehensive review of the field. We knew, also, that we planned to continue the symposium on a regular basis, and that subsequent programs would fill the gaps in the first iteration while providing timely updates, when appropriate, of areas already presented. The second edition of '*Valves in the Heart of the Big Apple*' was held in New York on May 2–3, 2002.

The program was developed specifically to cover areas not discussed in 2001, as well as to present updates in the key areas relating to timing of surgery in asymptomatic patients. The result was a program in which more than three-fourths of the presentations focused on topics not discussed formally in the initial symposium. Several months following the symposium, we again requested articles from the faculty on the areas they had covered, appropriately updated for the lag between presentation and book production. The faculty comprised individuals whose research has shaped the concepts and practice of all physicians who deal with patients afflicted with valvular diseases. Therefore, the written reviews produced by this faculty are of particular value. Contributions covered many areas, including molecular, cellular and hemodynamic pathophysiology, prognostication strategies and results, technical approaches to measuring disease characteristics, pharmacological and surgical therapy, etc.

The product of these contributions is *Pathophysiology, Evaluation and Management of Valvular Heart Diseases, Volume 2*. It is intended to complement and supplement Volume 1 (and to be followed in 2004 by Volume 3). Together, we hope these books will provide a relatively comprehensive overview of contemporary thinking about valvular heart diseases and will be useful both to the clinician and the researcher.

This effort has required considerable support. The symposium from which it was generated was organized by The Howard Gilman Institute for Valvular Heart Diseases of Weill Medical College of Cornell University. As we noted in our introduction to Volume 1, we formed this institute to focus and facilitate our ongoing joint efforts to explore new and novel concepts in the field of valvular heart diseases and to apply them in evaluating and treating patients afflicted with these diseases. The Institute was enabled by the generosity of the late Howard Gilman and the ongoing support of The Howard Gilman Foundation, as well as by the kind and generous support of many other foundations and individual contributors, most prominently including The Gladys and Roland Harriman Foundation, The Schiavone Family Foundation, The Charles and Jean Brunie Foundation, The David Margolis Foundation, The Mary A. H. Rumsey Foundation, The Irving A Hansen Foundation, The Daniel and Elaine Sargent Charitable Trust, The Messinger Family Foundation, The Howard L. and Judie Ganek Philanthropic Fund of the Jewish Communal Fund, and individual support from Donna and William Acquavella, Gerald Tannenbaum, Stephen and Suzanne Weiss and John and Susan Zuccotti. The second edition of the symposium, itself, received direct support in the form of much appreciated educational grants to Cornell from our major benefactor, Johnson & Johnson, as well as from Edwards Lifesciences, Corp., Medtronic, St. Jude Medical, American Home Products, AstraZeneca Pharmaceuticals, ATS Medical, Inc., GlaxoSmithKline, Pfizer, Inc., Sankyo Pharma, and Sulzer Carbomedics/Scanlon Cardiopulmonary.

Finally, this book could not have been produced without the editorial assistance of Joseph Franciosa, MD, Adjunct Professor of Medicine in the Division of Cardiovascular Pathophysiology at Weill Medical College and a member of The Howard Gilman Institute. A world-renowned expert in heart failure who, more than 30 years ago, authored (with Jay Cohn) the seminal article on vasodilation with nitroprusside for patients hospitalized with this disorder, ushering a new era in heart failure therapy, Joe helped to shape the symposium and personally reviewed all written submissions, markedly alleviating our own responsibilities in completing this task.

We very much appreciate the participation of our colleagues, respected experts, all, in the field of valvular heart diseases, and the industrial supporters of '*Valves in the Heart of the Big Apple*' who enabled the creation of the substrate for Volume 2. We hope readers will find the result useful.

Jeffrey S. Borer, MD
O. Wayne Isom, MD

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The Howard Gilman Foundation Lecture

Where Have We Come From and Where Are We Going? Valve Management Past, Present and Future

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Where Have We Come From?

The term *valve* is derived from the Latin *valvae*, which was used in the plural by the Romans for a pair of folding double doors that permitted traffic in only one direction. Cardiac valves and venous valves open to allow flow in one direction, then close to prevent flow in the opposite direction. William Harvey, as a student, had witnessed the experiments of Hildanus Fabricious of Padua and demonstrated that veins always swelled *below* a ligature (fig. 1), i.e., away from the heart, which was characterized as a pump that functioned by muscular force. Harvey inferred from the position of valves that these delicate structures served to counteract the effect of gravity in the veins and to prevent reflux of blood from the heart. The observations served as the basis for one of the most famous books in medical history, Exercitatio Anatomica de Motu Cordis et Sanguinis in Animalibus (1628), which was dedicated to his *Most Illustrious and Invincible Monarch, Charls*, and in which Harvey set forth a singular concept of the circulation.

Italian anatomists of the Renaissance called the left atrioventricular valve *mitral* because the two leaflets resembled a bishop's *mitre* or headdress. Tricuspid referred to the right atrioventricular valve because of three pointed leaflets (tri + Latin *cuspis*, 'pointed end,' as of a spear). *Aorta* was derived from the Greek *aorte*, which Aristotle used to refer to the main arterial channel issuing from the heart. *Pulmonary* originated from the Latin *pulmo* (genitive *pulmonis*) 'the lung'.

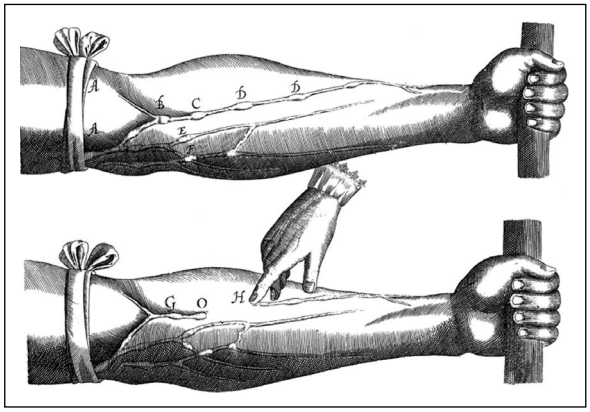

Fig. 1. William Harvey's original demonstration of the direction of blood flow in veins (De Motu Cordis et Sanguinis, 1628, with permission from Gryphon Editions LLC, publishers of The Classics of Medicine Library).

The anatomical drawings of Leonardo da Vinci (1452–1519) included aortic valves that were quadricuspid, trileaflet, and bicuspid (fig. 2a–d). Leonardo provided evidence that three equal aortic leaflets were hydraulically optimal. Over 300 years elapsed before Thomas Peacock (1858) characterized the congenital bicuspid aortic valve (fig. 2e).

The *audible language of the heart* was described in De Mortu Cordis: 'With each movement of the heart, when there is the delivery of a quantity of blood from the veins to the arteries, a pulse takes place and can be heard within the chest.' In 1832, Joseph Rouanet of Paris devoted his MD thesis to '*An Analysis of Heart Sounds*', stating that his objective was to 'show that action of the heart valves is accompanied by sound' and 'that these sounds coincide with those of the heart' [1].

My interest in cardiac valves began about 50 years ago, inspired by Paul Wood's seminal article, *An Appreciation of Mitral Stenosis* published in 1954 in the *British Medical Journal* [2]. The article remains a model of scientific writing that is superb in content and explication and that deals comprehensively with a single lesion of a single cardiac valve. My first publication on cardiac valves was *The Clinical Recognition of Tricuspid Stenosis* (1960) that used intracardiac phonocardiography to define the mechanism of the distinctive inspiratory increase in the presystolic murmur [3]. *The Effect of Nitroglycerine on Left Ventricular Wall Tension in Fixed Orifice Aortic Stenosis* appeared in 1963 [4]. Carl Wiggers' remarkable *Cardiodynamics of Mitral Insufficiency* (1922) [5] prompted *The Mitral Apparatus: The Functional Anatomy of Mitral Regurgitation* (1972) that defined the left atrioventricular orifice as a complex

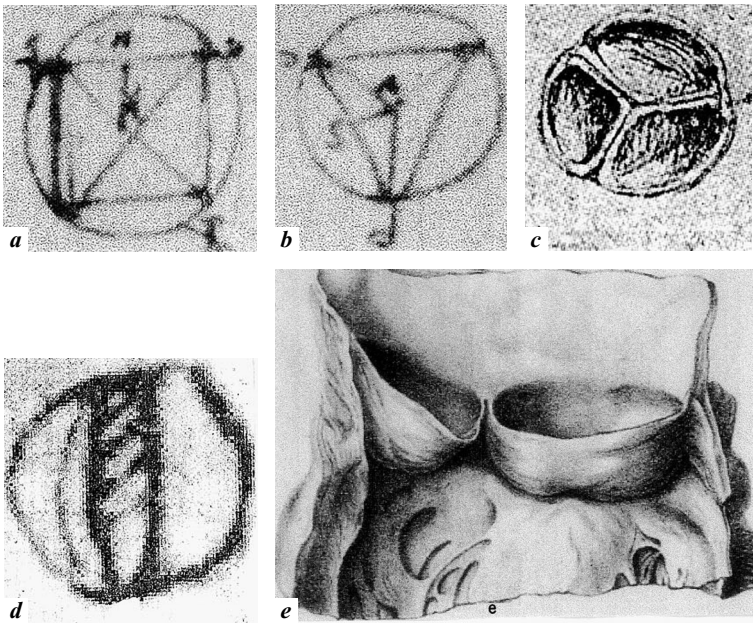

Fig. 2. Illustrations from Leonardo da Vinci's anatomical drawings showing three types of aortic valves: ***a*** quadricuspid, ***b*** tricuspid with equality of the three cusps, ***c*** tricuspid with inequality of the three cusps, and ***d*** bicuspid with inequality of the two cusps. ***e*** Illustration of a congenitally bicuspid aortic valve from Thomas Peacock (1858) (with permission from Gryphon Editions LLC, publishers of The Classics of Medicine Library).

mechanism consisting of the left atrial wall, the annulus, the leaflets, the chordae tendineae, the papillary muscles, and the left ventricular wall [6].

Where Are We Going?

Valve Management Past

In 1923, Elliott Carr Cutler, with the moral support of Samuel A. Levine, inserted a valvulotome into the apex of the left ventricle of a young woman with mitral stenosis. Although initially praised in the *British Medical Journal* as a surgical landmark, the operation was abandoned a few years later. In 1925, Sir Henry Souttar at the Peter Bent Brigham Hospital performed the first digital dilatation of a stenotic mitral valve and went on to describe operation: 'The information given by the finger is exceedingly clear, and personally I felt an appreciation of the mechanical reality of stenosis and regurgitation which I never

before possessed. To hear a murmur is a very different matter from feeling the blood itself pouring back over one's finger. I could not help but be impressed by the mechanical nature of these lesions and by the practicability of their surgical relief.' Even though Souttar's patient recovered uneventfully, he performed the operation only once because '… the physicians declared that it was all nonsense and in fact that the operation was unjustifiable. … it is of no use to be ahead of ones time.' The operation remained dormant for over two decades until Dwight Harken (1948) and Charles Bailey (1949) digitally separated the fused commissures of rheumatic mitral stenosis. Interestingly, the indirect Bland-Sweet approach to mitral stenosis (1949) was based on the physiology of Lutembacher syndrome in which the left atrium in rheumatic mitral stenosis was effectively decompressed by a congenital defect in the atrial septum. Blind transventricular pulmonary valvotomy was performed in France by Jean-Marie Doyen (1913); in 1948, Sir Russel Brock and Thomas Holmes Sellers in England independently reintroduced the technique. In 1952, Bailey addressed aortic valve stenosis with a transventricular expanding dilator, and in 1953, Forest Dodrill reported 'pulmonary valvuloplasty under direct vision using the mechanical heart for a complete bypass of the right heart in a patient with congenital pulmonary stenosis'.

Valve Management Present

Current management of abnormal cardiac valves includes repair (reconstruction), replacement (prostheses), and interventional catheterization. Digital valvulotomy (commissurotomy) for rheumatic mitral stenosis (see above) improved interleaflet flow by separating the fused commissures, but cardiopulmonary bypass was required to separate fused chordae tendineae and improve interchordal flow. Ruptured chordae tendineae were repaired by Dwight McGoon in 1960, and mitral regurgitation was addressed by Lars Bjork in 1964 using eccentric annuloplasty. The modern era of reconstruction of the mitral apparatus began in 1980 with Alain Carpentier's report of a novel variation of eccentric annuloplasty based on remodeling the mitral annulus by inserting a plastic ring [7].Tricuspid regurgitation of Ebstein's malformation first yielded to reconstruction by C. Walton Lillehei in 1958. Transesophageal echocardiography can now identify the large mobile anterior Ebstein tricuspid leaflet that permits construction of a competent monocuspid right atrioventricular valve mechanism [8].

Abnormal cardiac valves that are not amenable to repair are represented by calcific bicuspid or trileaflet aortic stenosis, incompetent mitral valves with dense annular calcification, parachute mitral valve, and left-sided Ebstein's anomaly of congenitally corrected transposition of the great arteries. Cuspal inequality inherent in a congenitally bicuspid aortic valve (fig. 2d, e) results in unequal distribution of high-pressure diastolic stress onto two unequal leaflets,

prompting fibrocalcific degeneration. Cuspal *equality* in the hydraulically ideal trileaflet aortic valve (fig. 2b) permits equal distribution of diastolic force onto the three leaflets and their sinus attachments. The cuspal *inequality* inherent in many normal trileaflet aortic valves was represented in Leonardo da Vinci's anatomical drawings (fig. 2c), and results in unequal distribution of high pressure diastolic stress among three unequal leaflets and their sinus attachments [9]. Fibrocalcific changes proceed most rapidly in the cusp or cusps that bear the greatest mechanical stress.

Valves that are not amenable to repair can be replaced with exogenous or endogenous bioprosthetic valves or with mechanical valves [10]. Bioprosthetic *homografts* (*allografts*) employ tissue derived from the same species (human cadavers) but of disparate genotype. *Heterografts* (*xenografts*) employ tissue derived from a different species (animal sources). *Autografts* (*autologous grafts*) employ tissue from the individual receiving the autograft as in the Ross procedure (1967) in which a normal endogenous pulmonary valve (*autograft* or *autologous graft*) is used to replace an abnormal aortic valve, and an aortic *homograft* is inserted in the pulmonary position [11].

The caged ball valve originated in a bottle-stopper design (US Patent No. 19323, February 9, 1858) that prefigured Charles Hufnagel's methyl methacrylate (Plexiglas) cage containing a silicone-coated nylon poppet that was inserted into the descending thoracic aorta (September 1952) for the treatment of severe aortic regurgitation [12] (fig. 3a). Inherent limitations of the extracardiac location of the Hufnagel valve were resolved in 1960 by Albert Starr's caged ball prosthesis (fig. 3b) designed for insertion in the mitral position. In 1963, Christian N. Bernard reported 'surgical correction of Ebstein's malformation with a prosthetic tricuspid valve.' The ball-in-cage design, in which flow was necessarily peripheral (around the ball), was superceded by hemodynamically superior and less thrombogenic Pyrolite carbon tilting disc monoleaflet (Bjork/Shiley) or bileaflet (St Jude) central flow valves (fig. 3c), and by the carbomedics ascending aortic prosthesis (fig. 3d) equipped with a bileaflet valve. The one millionth St Jude valve was inserted a few years ago, representing a milestone that surpassed all other prosthetic valves.

Interventional Catheterization for Stenotic Cardiac Valves

Balloon valvuloplasty partially relieves mitral stenosis by separating fused commissures. The results are analogous to the original closed digital mitral commissurotomy (see earlier), but neither digital commissurotomy nor balloon dilatation could address obstruction inherent in fusion of chordae tendineae. Nevertheless, balloon mitral valvuloplasty is safely and usefully employed during pregnancy with dramatic symptomatic results and with a considerable reduction in the gestational risk of pulmonary edema. Balloon dilatation of

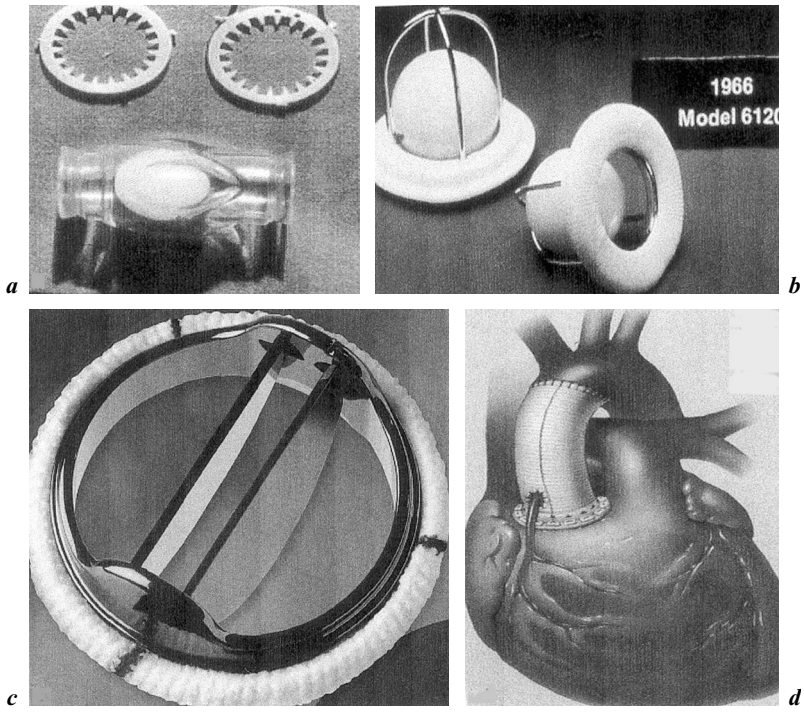

Fig. 3. ***a*** The Hufnagel mechanical valve that was placed in the descending thoracic aorta. ***b*** The Starr caged ball mechanical valve first placed in the mitral position. ***c*** Current model of the St Jude bileaflet mechanical valve. ***d*** Carbomedics ascending aortic prosthesis equipped with St Jude valve (with permission of Gryphon Editions LLC, publishers of The Classics of Medicine Library).

a mobile stenotic bicuspid aortic valve ideally abolishes the gradient and creates a functionally normal mechanism, but necessarily leaves behind a morphologically bicuspid valve and the histologically abnormal media of the ascending aorta [13]. Despite these limitations, a practical application is in the neonate with pinpoint bicuspid aortic stenosis that can be balloon dilated with considerable finesse and without inducing significant regurgitation. The precarious newborn then survives to benefit from a subsequent Ross procedure (see earlier). In the gravida with severe symptomatic bicuspid aortic stenosis, balloon dilatation materially reduces maternal risk without incurring the fetal risk of open heart surgery.

Balloon dilatation is the treatment of choice for mobile dome congenital pulmonary valve stenosis. Separation of the commissures ideally achieves a virtual cure, and secondary hypertrophic subpulmonary stenosis usually regresses.

The procedure can be employed during pregnancy with greater safety and effectiveness than balloon dilatation of either rheumatic mitral stenosis or congenital bicuspid aortic stenosis. A congenitally stenotic dysplastic pulmonary valve is not amenable to dilatation because obstruction is caused by thickened cusps, not by commissural fusion.

Valve Management Future

Improved methods of preparing exogenous bioprosthetic valves continue to evolve. In vitro endothelialization, pre-coating of tissue valves, and novel methods designed to inhibit calcification are in the offing. More refined techniques of repair of incompetent mitral and tricuspid valves are in current use, and at the UCLA Hospital, incompetent bicuspid aortic valves are surgically converted into competent trileaflet valves using a technique of pericardial extension.

It seems intuitive that replacement of abnormal cardiac valves requires surgery. However, replacement of a diseased pulmonary valve by transcatheter placement of a pulmonary valve prosthesis is now a reality [14].

Summary

Where Have We Come From and Where Are We Going?
Valve Management Past, Present and Future

Leonardo da Vinci's anatomical drawings of quadricuspid, tricuspid, and bicuspid aortic valves underscored the hydraulic superiority of a three leaflet valve with cuspal equality. William Harvey demonstrated that venous valves were designed for unidirectional flow and to prevent reflux from the heart, observations that served as the basis of his immortal *de Mortu Cordis*. Joseph Rouanet of Paris proposed that heart sounds originated from the closing movements of cardiac valves. *The Cardiodynamics of Mitral Insufficiency* by Wiggers and Feil was followed three decades later by Paul Wood's *An Appreciation of Mitral Stenosis*. The Bland/Sweet operation indirectly addressed mitral stenosis by means of a venous shunt. Sir Henry Souttar's early digital repair of mitral stenosis was later reintroduced independently by Harken and Bailey; Doyen, Sellers, and Brock employed surgical valvotomy for pulmonary stenosis, and Bailey employed surgical valvotomy for aortic stenosis.

Management of abnormal cardiac valves includes repair (reconstruction), replacement with mechanical or biologic prostheses, and interventional catheterization. The first mechanical valve was inserted extracardiac by Hufnagel into the descending thoracic aorta of patients with severe aortic regurgitation. The Starr caged ball mechanical prosthesis was designed for intracardiac replacement of an

abnormal cardiac valve. The peripheral flow ball valve was followed by hydraulically superior and less thrombogenic central flow monoleaflet or bileaflet mechanical valves, and by homograft and heterograft bioprosthetic valves. Improved methods of preparing exogenous bioprostheses and innovative techniques of aortic valve reconstruction are evolving. Cardiac catheterization as a therapeutic intervention is routinely applied to stenotic mitral, aortic and pulmonary valves, and transcatheter replacement of an abnormal pulmonary valve is now a reality.

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The Epidemiology of Valvular Heart Diseases: The Problem Is Growing

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Valvular heart diseases (VHD) are the most predictable causes of heart failure and sudden death [1–3]. For many years, the prevalence of VHD in our society was believed to be relatively low. However, introduction of the echocardiogram and results from its increasingly widespread use has begun to dispel this belief [4–6]. Recent studies, conducted among widely varying populations, have indicated a remarkably high proportion of patients with hemodynamically mild to severe VHD who remain asymptomatic. This is important because epidemiological studies, using non-invasive imaging as well as clinical evaluation, now reveal that VHD generally follow a prolonged course from hemodynamically mild inception to a state of relative hemodynamic severity and then another relatively long interval to clinical debility or death [7].

Moreover, the population at risk can be expected to increase over time in direct proportion to the increase in global population and life expectancy. As therapeutic options are progressively developed and perfected, this population becomes a potential target for life-enhancing and life-prolonging intervention. The apparent magnitude of VHD prevalence, its projected increase and its potential sequelae would seem to justify the claim that valvular diseases represent a growing public health problem. Nonetheless, there are very few rigorous population-based studies that can help to elucidate the extent of VHD in this country. Indeed, with the exception of a preliminary longitudinal investigation recently published by our group, most published studies in this area are relatively narrow in focus and cross-sectional in design, and have produced widely varying estimates from which extrapolation may be inaccurate [4–6, 8–15].

Therefore, to obtain a larger sampling frame for estimating the prevalence of various forms of VHD, to provide a basis for estimating its incidence, and to add to our existing knowledge about the impact of VHD on the utilization of healthcare resources and outcomes, we expanded our initial research to examine the incidence and associated mortality outcomes of VHD hospitalizations over an 18-year interval in New York State. The primary objectives of our broadened study were: (1) to examine temporal trends in hospitalization and surgery rates among inpatients with VHD, (2) to assess the impact of the affected valve and demographic variables on incidence of VHD-associated hospitalizations and operations, and (3) to quantify in-hospital death rates in this patient population.

Methods

Data for this study were derived from New York's 'State-wide Planning and Research Cooperative System' inpatient database (SPARCS) [16]. The New York State Department of Health developed SPARCS as a comprehensive, integrated computer-based information system to assist hospitals, agencies and other healthcare organizations with decision-making. For each discharge from more than 250 non-federal acute care facilities throughout the state, SPARCS comprises information that has been abstracted from medical records by trained hospital-based personnel. Patient age, gender, race, year and month of discharge, principal and secondary diagnoses, and principal and secondary procedures are included, the latter coded according to the ICD-9 classification system. The objective of SPARCS is to define the incidence of hospitalizations and procedures; therefore, the unit of observation is the case rather than the individual patient. For the current study, data analysis spanned the years 1983 (the first year in which reliable data were available) through 2000 (the last year for which complete records were obtainable). All records with principal or secondary ICD-9 codes for mitral valvular (MV), aortic valvular (AV), tricuspid valvular (TV), and/or pulmonic valvular (PV) heart disease (HD) were analyzed without distinguishing between principal and secondary diagnoses, since these distinctions are highly dependent on the individual coder and hospital. Subject identifiers were not employed for this analysis. For comparison, we also examined trends in the total number of hospitalizations in New York State during this period.

Linear regression analysis was employed to model temporal trends in patient demographics and in other variables of interest including number of hospitalizations, number of invasive therapeutic valve procedures (i.e., open chest valvotomy or other valve repair, valve replacement or percutaneous balloon valvuloplasty), and in-hospital deaths from all causes.

Results

Characteristics of the Patient Population

In total, over 1 million cases met our inclusion criteria. Of these, more than a third were hospitalized during the last 5 years. Most patients were admitted for evaluation and/or medical treatment; a third were noted to have co-existing

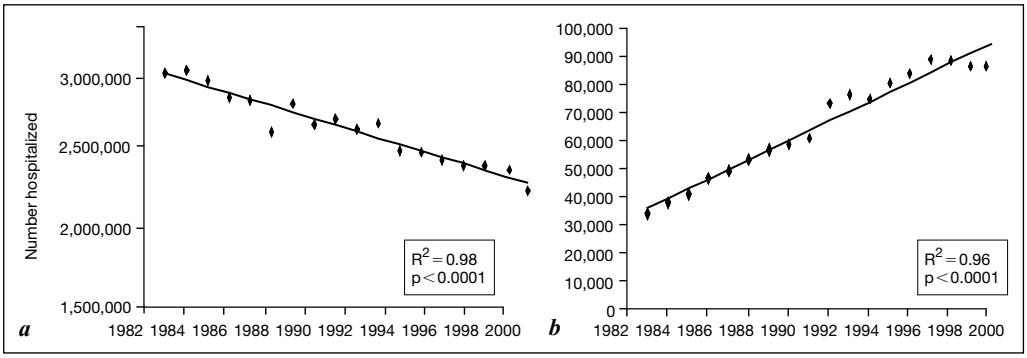

Fig. 1. Temporal changes in number of hospitalizations in New York State between 1983 and 2000: Total number of hospitalizations (all causes) (***a***) versus hospitalizations including a valvular heart disease (VHD) diagnosis (mitral, aortic, tricuspid and/or pulmonic valve diseases) (***b***). p = Probability; R = coefficient of correlation.

coronary artery disease. On average, the patients were 65 years old at hospital discharge or death. Most were white and female; gender and racial composition of the study group remained fairly constant over time. In contrast, the average age of hospitalized patients with VHD increased sharply over the 18-year study interval. Most patients had MV or AV HD, with MV HD predominating. MV HD was most prevalent among younger, white females and AV HD disease was most common among white males. The diagnosis of TV HD, found predominantly among older, non-white males, was relatively rare.

Temporal Changes in Hospitalizations

Hospitalizations for all causes in New York State decreased approximately 20% from 1983 to 2000 ($p < 0.001$, fig. 1a). In sharp contrast, the incidence of hospitalizations including a diagnosis of VHD increased almost 3-fold during this period ($p < 0.001$, fig. 1b). Hospitalization rates increased significantly for all forms of VHD in an approximately linear fashion ($p < 0.001$). However, the rate of increase among patients with mitral stenosis or insufficiency was almost 1.5-fold greater than the rate of increase among patients with aortic stenosis or insufficiency ($p < 0.001$). Though far fewer in number, directionally similar changes were seen for combined MV and AV HD and for TV or PV HD. These trends were found among men and women, younger and older patients, and those of white and non-white race.

Performance of Valve Surgery and Valvuloplasty

More than 80,000 valve-related surgical procedures (predominantly valve replacements) were performed in New York State between 1983 and the year

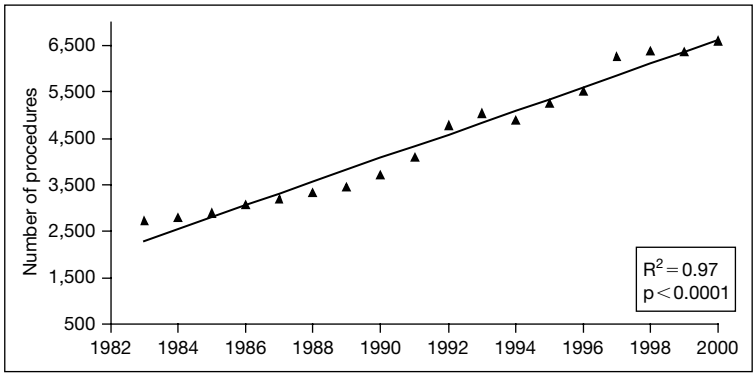

Fig. 2. Temporal change in number of therapeutic valve procedures performed between 1983 and 2002 in New York State. Procedures include open chest valvotomy or other valve repair, valve replacement and percutaneous balloon valvuloplasty. p = Probability; R = coefficient of correlation.

2000. The rate of increase in performance of these procedures was approximately linear and statistically significant ($p < 0.001$, fig. 2). Valve surgery and valvuloplasty increased far more markedly over time among patients ≥65 years of age versus younger patients. Moreover, though women predominated in the cohort, they underwent these procedures less often than men, a pattern that intensified modestly over time. Unfortunately, SPARCS data do not provide information about disease severity or reasons for management decisions; thus, it could not be determined whether this pattern reflects gender bias or more serious illness among men. When white patients were compared with non-white patients, no racial disparities were found. Undoubtedly, these robust increases reflect improvements in surgical techniques during the study interval, allowing application of these treatments to a wider population and, to a lesser extent, from more accurate clinical identification of patients at risk. Nonetheless, at least in part, the numbers also reflect the increase in patients at risk.

Temporal Changes in In-Hospital Deaths

Over 63,000 patients with VHD died in the hospital during the study period. Surprisingly, despite tremendous improvements in medical technology and healthcare delivery, the total number of deaths more than doubled over the entire 18-year study period (fig. 3a, $p < 0.001$). This almost linear increase was consistent with the increase in VHD hospitalizations; thus, death rates (deaths/number of VHD hospitalizations, fig. 3b) remained constant at approximately 5.4%/year. It is reasonable to hypothesize that these findings may be due to increased numbers of older patients with presumably more advanced and

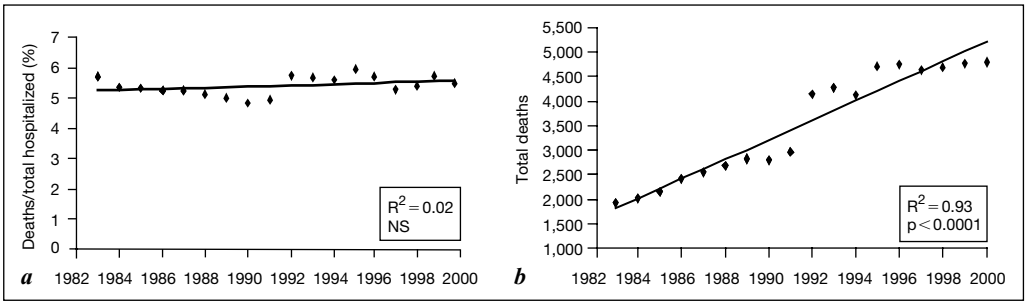

Fig. 3. Temporal change in case fatality rate (5.4%/year) (***a***) and total number (***b***) of in-hospital deaths (n = 63,250, 18 years) among patients hospitalized with valve disease in New York State between 1983 and 2000. n = Number of patients; NS = not significant; p = probability; R = coefficient of correlation.

severe VHD; a second untested hypothesis is that they may relate to reductions in allowable hospital lengths of stay.

Conclusions

A number of factors inherent in SPARCS data limit inferences about VHD prevalence rates. As previously noted, SPARCS data are case- or incidence-based, rather than patient-based. Without subject identifiers, multiple hospitalizations in the same patient cannot be excluded. Nevertheless, Medicare reimbursement rules would tend to limit multiple hospitalizations for the same problem in the same year, particularly in recent years when most VHD hospitalizations were seen. Second, the current data do not include outpatient visits for VHD, which may reflect the largest component of medical visits and undoubtedly involve many patients who have not been hospitalized. This might cause substantial underestimation of the true prevalence of VHD in the population. Third, because cases were selected on the basis of diagnoses of hospitalized patients rather than by population screening, it is not possible to determine whether the observed temporal patterns are due to improved recognition or to increased incidence of illness. Finally, estimates of the clinical risk factors evaluated in this study were dependent on the precision and completeness of the ICD-9 coding system, which, unfortunately, does not permit quantification of disease severity or ready identification of all disease subtypes (e.g., differentiation between aortic stenosis and aortic regurgitation or between ischemic and non-ischemic VHD).

Nonetheless, the data clearly indicate that the incidence of hospitalization and surgical or other invasive therapy for VHD is rising. The trends we observed

are so strong and so sustained that it is also reasonable to conclude that the increase in VHD-related hospitalizations, aggressive interventions and in-hospital deaths that we have noted will continue to escalate as the population ages and expands. Increasingly, health care resources must be targeted to dealing with this growing public health problem.

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Heart Failure in Aortic Regurgitation: The Role of Primary Fibrosis and Its Cellular and Molecular Pathophysiology

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In patients with valvular heart diseases, heart failure and death do not result from the deformed valve, per se, but rather from abnormal myocardial loads (stresses and strains) caused by the hemodynamic effects of the deformed valves. In acute mitral or aortic valvular regurgitation (MR, AR), the sudden increase in left ventricular (LV) volume can overwhelm the capacity of the normal contractile apparatus, leading rapidly to cardiac decompensation with pulmonary vascular congestion, subnormal cardiac output and associated systemic effects. However, in the far more common setting of chronic valvular disease, the contractile machinery gradually adapts to the abnormal loads, ultimately losing capacity to generate normal force after a relatively prolonged compensated phase.

With current technology, it is possible to explore the fundamental cellular and molecular pathophysiology underlying failure of the contractile apparatus. Such investigations already indicate differences in fundamental myocardial responses to mitral and aortic valve diseases and to stenotic versus regurgitant lesions.

In fact, mechanical analysis suggests that AR, but not the other common valvular lesions, causes myocardial loading abnormalities similar to those in the non-infarcted myocardium of patients who have suffered a large myocardial infarction and subsequently develop heart failure [1]. Therefore, clarifying the fundamental basis of heart failure in AR may benefit patients with the more common post-infarction heart failure, as well.

In patients with AR, the ultimate cause of heart failure is loss of contractile function. Indeed, loss of contractility is the best single predictor of outcome in unoperated patients [2] as well as in those who undergo aortic valve replacement [3], as detailed elsewhere in this volume. During the past decade, the concept of the 'contractile element', responsible for generating contractile force, has undergone gradual evolution. For many decades, the contractile element has been understood as the sarcomere, comprising overlapping actin and myosin filaments forming a unit from Z-band to Z-band within the cardiomyocyte, that interact chemically and physically to generate force in response to electrophysiological stimulation. More recently, it has become apparent that, irrespective of the contractile status of the sarcomere and its components, contractility will be normal only if the sarcomere relates appropriately to its physical surroundings. This is necessary to enable normal transmission of generated force. Specifically, the sarcomere is circumscribed by and physically interacts with the actin cytoskeleton of the cardiomyocyte which, in turn is physically bound to a series of proteins, the dystrophins, that reach the sarcolemma and bind to elements of the extracellular matrix (ECM) via mediation of a glycoprotein complex containing, among other components, the ubiquitous non-collagen protein, fibronectin [4, 5]. This concept of the contractile element suggests that the ECM is more than merely the scaffold that organizes the cardiomyocytes; rather, it is an integral part of the functioning unit through which contractile force is transmitted. Alteration of the ECM, then, deranges the myocyte-matrix interaction and can be expected to alter force transmission and, consequently, contractility. Much of the work supporting this new understanding of the contractile element is based on observations in patients with muscular dystrophy and associated cardiomyopathy; in some forms of muscular dystrophy, point mutations result in absence of the dystrophins, accounting for skeletal muscle weakness but also resulting in dilated, hypocontractile cardiomyopathy [5, 6].

The new understanding of the contractile element expands the potential loci of intervention to remedy loss of contractility. Thus, interventions focused on the dystrophins or the ECM may be important in maintaining contractility or in reversing its loss in specific situations. These concepts may be particularly relevant to the pathophysiology of AR. Observational data have clearly demonstrated the development of abnormal quantities of ECM, as myocardial fibrosis, in patients with chronic AR who develop clinical debility and come to surgery [7, 8]. Parallel observations have been made in experimental AR [9]. More recent data indicate that, in experimental AR, abnormal ECM production is a primary response to the mechanical strains of AR, rather than a secondary response to myocyte injury or any other exogenous influence [10]. These same studies indicate that the quantitatively abnormal ECM also is qualitatively abnormal, being particularly rich in non-collagen matrix elements among which

fibronectin is most prominent [10, 11]. Preliminary data suggest that similarly abnormal ECM is produced by human cardiac fibroblasts when they are subjected to the strains of AR in cell culture [12].

Effects of AR and Exogenous Strain on Cardiac Fibroblasts

The ECM is synthesized primarily by cardiac fibroblasts. The potential importance of ECM changes in compromising contractility is suggested by the temporal variation in LV performance after valve replacement for AR. Among patients benefiting from current myocardial protection methods, the Cornell group found that, as compared with pre-operative mildly subnormal LV ejection fraction (EF) at rest that fell with exercise (group averages), within 1 year after operation improvement in both rest and exercise values was seen; however, LVEF continued to increase at rest and during exercise until 3 years after operation, by which time the normal relation (exercise greater than rest) had been re-established [13]. The cellular basis of this finding is unclear: the half-lives of contractile proteins are measured in days; therefore, complete restitution of a new and normal contractile protein system would be expected to have occurred manyfold over the course of 3 years. The time course of recovery is unlikely to have been attributable to remodeling of contractile proteins, alone. Some other processes needed to be invoked to explain the recovery and, probably, also loss of function before operation. These might include peripheral vascular adaptations, known to follow a relatively prolonged course; alternately, remodeling of myocardial elements other than contractile proteins, elements with longer half-lives, might have been responsible for the observed phenomenon.

Histological assessment of microscopic sections from rabbits with experimental AR suggested the likelihood of the latter process [9]. Among animals with AR who developed heart failure, and among some of those that did not, exuberant fibrosis was observed, often enmeshing hypertrophied myocytes, some involved in myocytolysis/necrosis. Normal control animals failed to evidence such findings. Several ECM proteins have relatively long half-lives, potentially explaining the temporal phenomenon observed clinically.

Importantly, the fibrotic changes were seen without evidence of an inflammatory cellular response, suggesting that the fibrotic process might have been a primary response to the volume overload of AR. Additional analysis of the histologic sections indicated that, despite exuberant fibrosis, myocardial collagen content was normal per gram of tissue, suggesting abnormal production of some non-collagen ECM element(s) [11].

To evaluate this observation further [10], cardiac fibroblasts were isolated from rabbits with chronic experimental AR and from rabbits with normal hearts.

The isolates were cultured and then subjected to suppression subtractive hybridization that revealed hyperexpression by AR fibroblasts of several genes coding for non-collagen matrix proteins, but not for collagen isoforms. The most prominent among the abnormally expressed genes was fibronectin. Additionally, cultured AR fibroblasts utilized significantly more tritiated glucosamine than normal fibroblasts, but equal amounts of tritiated proline [10]. This finding, consistent with abnormal synthesis of glycoproteins like fibronectin but not of collagen, also is consistent with abnormal production of proteoglycans normally found in the ECM. Finally, Western blot analysis and gelatin Sepharose affinity chromatography confirmed that fibronectin protein was being abnormally synthesized by AR fibroblasts (but did not exclude the additional hyperproduction of other non-collagen matrix elements), while demonstrating the absence of upregulation of collagen types I and III [10].

To test the hypothesis that the AR-associated variations in gene and protein expression are primary responses to the mechanical effects of AR, normal cardiac fibroblasts were exposed during growth in culture to mechanical strain modeling that caused at the LV midwall by severe AR [10]. Effects of this intervention were compared with effects of no intervention and of mechanical strain of lesser magnitude, modeling that seen at LV midwall in normal hearts [14]. Little difference in gene and protein expression and substrate utilization were seen when comparing no intervention with strain modeling the normal LV [14]. However, results in both these settings were significantly different from the effects of strain mimicking that of AR [10, 14] (e.g., table 1, indicating result of AR strain versus no strain). Though some quantitative differences were apparent, the contrast between unstrained and AR-strained cardiac fibroblasts paralleled those found in comparing cardiac fibroblasts from normal hearts to cardiac fibroblasts from hearts with AR. These findings strongly suggest that ECM remodeling in AR is a primary response to the mechanical stresses of volume loading.

Preliminarily, these results have been reproduced in a single human. Cardiac fibroblasts were isolated from a surgical biopsy obtained from a patient undergoing coronary artery bypass grafting. The patient had not suffered myocardial infarction, was clinically stable at the time of surgery and underwent epicardial biopsy from a region not served by any of the obstructed arteries. When the fibroblasts were isolated and cultured with and without interposition of the strain of AR, production of fibronectin increased by approximately 50% compared with that seen in non-strained cells [12]; analyses were replicated several times, sufficient to establish the significant consistency of the finding by formal statistical testing. In contrast, collagen expression was similar in strained and unstrained cells. Though the magnitude of protein production induced by strain differed between rabbit and human, qualitatively, the

Table 1. Substrate incorporation and protein synthesis in ECM and gene expression in normal cardiac fibroblasts cultured with vs. without exogenous mechanical strain

Cell line	With (+) or without (−) mechanical strain	[^{3}H]glucosamine incorporation (average cpm/mg total protein)	[^{3}H]proline incorporation (average cpm/mg total protein)	Fibronectin gene expression by Northern analysis (average FN:GAPDH)	Fibronectin by Western analysis (average densitometry units[a])	Fibronectin by GSAC (cpm/mg total protein)
Nl 1	+	38,668	248,978	1.6	10,132	5,334
Nl 1	−	17,212	262,363	1.3	6,141	2,065
	+:− ratio	2.2:1	0.9:1	1.2:1	1.7:1	2.6:1
Nl 2	+	33,726	248,780	2.0	30,304	4,836
Nl 2	−	15,912	182,722	1.6	25,369	2,776
	+:− ratio	2.1:1	1.4:1	1.3:1	1.2:1	1.7:1
Nl 3	+	18,694	312,023	1.7	24,505	1,898
Nl 3	−	9,820	350,924	0.9	22,546	1,368
	+:− ratio	1.9:1	0.9:1	1.8:1	1.1:1	1.4:1

FN = Fibronectin, GAPDH = glyceraldehyde 3-P-dehydrogenase, GSAC = gelatin Sepharose affinity chromatography, Nl = normal.

[a]Equal amounts of total cell protein were loaded in all AR and Nl lanes of any single gel; therefore, densitometry units for any +:− ratio are normalized to identical total cell protein values [reprinted from 10, with permission from the American Heart Association].

resemblance was sufficient to suggest similarity between the response of the experimental model and the human subject.

Transduction of Mechanical Perturbations of AR to Gene and Protein Expression

Modulation of the fibrotic process in AR may be therapeutic: normalization of the myocyte-matrix interaction may help to prevent systolic dysfunction and heart failure or may improve the rate of recovery after valve replacement. Non-invasive identification of the characteristics of the process, as with metabolic imaging, may be useful in timing operation (or any novel therapy that becomes available in the future). However, the fibronectin gene is active in many parts of the body. Therefore, generalized suppression of this gene's expression may be deleterious to the patient. For a more focused intervention, it is necessary to understand the pathway by which the mechanical perturbations

of AR are transduced to abnormal gene expression; within this pathway, processes may be selectively overactive in the myocardium that could be partially suppressed with a standard pharmacological approach without causing pathological suppression in other tissues. Thus, it may be useful to elucidate the transduction pathway. However, while fibronectin upregulation is likely to play an important role in the pathogenesis of systolic dysfunction associated with fibrosis, fibronectin is only one of the abnormally expressed ECM genes already identified in AR; comprehensive elucidation of the pathobiology of AR will require more than study of the prototype fibronectin gene, alone, but must account for the complex interaction of many genes activated or suppressed by mechanical stress. Preliminary studies employing computerized 'gene chips' are now ongoing in AR within the authors' program and should provide additional critical information.

Transduction of mechanical perturbations to molecular variations must involve several steps. The initial mechanically-induced alteration may take any one of several forms, but an attractive hypothesis is that mechanical initiation involves interaction of a fibroblast integrin with extracellular fibronectin [15]. The initiating event stimulates a cascade of intracellular reactions that culminate in activation of multiple genes. In the authors' studies, activation of the fibronectin gene has been employed as a prototype for elucidation of relevant transduction pathways. Based on findings in other cell systems, it has been hyopothesized that the mitogen activated kinase (MAPK) pathway is centrally involved in fibronectin gene upregulation in response to the mechanical strain of AR. Preliminary data have supported this hypothesis, indicating the c-jun-N-terminal-kinase (JNK) module and the p38-MAPK module of the MAPK pathway indeed are upregulated by AR, though the extracellular response kinase (ERK) module, activated by various stressors in other systems, is not [16–19]. Preliminary assessment with known selective inhibitors of these modules has confirmed these inferences [19] and indicate the possibility of selective suppression of specific reactions within the modules. This leads to downward modulation of formation of the c-jun/activating transcription factor (ATF)-2 complex formation with the cyclic adenosine monophosphate (c-AMP) response element of the fibronectin promoter which, in other systems, causes activation of the fibronectin gene [18]. Of course, additional work will be needed to demonstrate the safety of module suppression within the intact organism, and the benefit of this approach.

A serendipitous finding during earlier studies led to another potentially useful observation that may enable beneficial modulation of gene expression in AR. To assure the purity of the fibroblast cell cultures, gene expression was evaluated in fibroblasts isolated from animals with AR and from normal animals only after cells had passed through 6 generations in culture. Similarly, normal cardiac

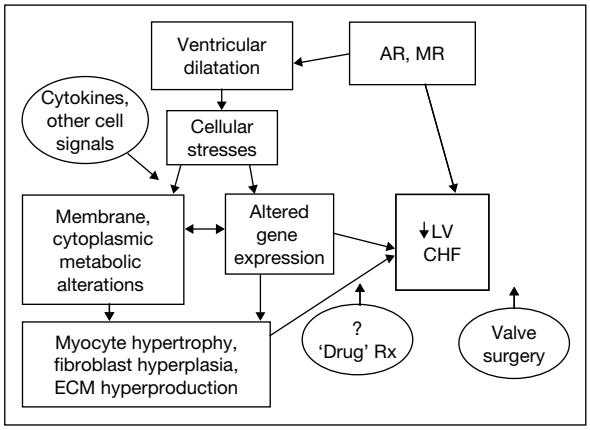

Fig. 1. Schematic of the pathophysiology of heart failure in regurgitant valvular diseases, accounting for some of the molecular and cellular derangements underlying ventricular dysfunction [reprinted from 22, with permission].

fibroblasts subjected to exogenous strain in culture were studied only after they had been maintained for 6 passages after application of strain. Thus, multiple generations had developed in the absence of the mechanical perturbations of AR or of strain modeling AR. Nonetheless, profound differences were consistently identified in gene expression and protein synthesis between AR and normal and between strained versus unstrained fibroblasts. Retention of the gene expression could have resulted from mutation, unlikely to have been consistently directed by a mechanical event, or by the synthesis of an epigenetic factor that affects expression. To seek this autocrine or paracrine factor, culture medium conditioned by growth of AR fibroblasts was applied to normal cardiac fibroblasts. The result was enhancement of fibronectin gene expression in the previously normal fibroblasts [20]. Identification of the inciting factor now is underway; its discovery may enable development of a therapeutic 'antidote'.

Feasibility of Modulating Fibrosis in AR

Considerable additional information must be developed to enable beneficial non-surgical intervention for fibrosis in AR. However, conventional drugs can affect the process. When the quinolone derivative, vesnarinone, is applied to cardiac fibroblasts in culture, survival both of normal fibroblasts and of fibroblasts from hearts with chronic AR is markedly suppressed [21]. The most effective suppressing dose in normal cells is an order of magnitude lower than

doses that were tested clinically for patients with heart failure (and were found to be potentially arrhythmogenic). Cells from AR hearts were affected to a greater extent and at a lower dose, indicating a potentially useful therapeutic advantage.

In summary, heart failure and death in AR are the end result of the effects of abnormal mechanical perturbations on the myocardium, leading to alterations in cell and molecular biology among myocytes, fibroblasts and, probably, the other, less common myocardial cellular elements (fig. 1). Deranged function of the contractile unit, comprising the sarcomere in series with the actin cytoskeleton, dystrophins and ECM, ultimately leads to organ dysfunction and clinical events.

Currently, we detect ventricular dysfunction and apply valve surgery. However, if the disordered cellular and molecular processes can be elucidated, pharmacological or even molecular interventions may be possible to the slow the rate at which myocardial dysfunction develops, reducing the rate of clinical events and, perhaps, the dependence on surgery, and enhancing myocardial recovery once surgery is performed.

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Is Prophylactic β-Adrenergic Blockade Appropriate in Mitral Regurgitation: Impact of Cellular Pathophysiology

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The development of left ventricular (LV) dilatation and systolic dysfunction due to the LV volume overload of mitral regurgitation (MR) carries a high risk of mortality and morbidity. At this time, surgical intervention provides better long-term outlook than does medical therapy. However, a relatively high risk of post-operative morbidity and mortality is associated *chronic* MR and pre-operative LV dysfunction in comparison to those who do not develop systolic dysfunction prior to mitral valve surgery [1, 2]. It is, therefore, important to understand how this disease process progresses to address the issue of whether or not β-adrenergic receptor blockade is a reasonable therapeutic strategy in patients with *chronic* MR. This chapter will clarify the hemodynamic problem, elucidate neurohormonal responses to LV volume overload with a particular focus on the sympathetic nervous system, determine the importance of β-adrenergic receptor responsivity and its linkage to contractile state, address the issue of β-adrenergic blockade and its impact on LV contractility, and define the importance of sympathetic activation, and specifically of norepinephrine, for myocyte viability. The objective is to elucidate the cellular pathophysiology particular to the LV volume overload of MR and, thereby, to provide a rationale to support the hypothesis that β-adrenergic blockade is a reasonable and appropriate therapeutic strategy in patients with *chronic* MR to prevent LV remodeling and systolic dysfunction.

The Hemodynamic Problem

LV volume overload with *chronic* MR leads to adaptation through the utilization of preload reserve. Eccentric LV hypertrophy occurs because of an

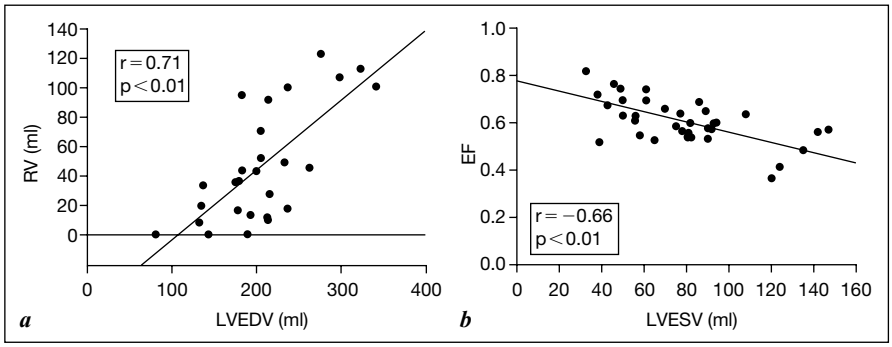

Fig. 1. The relationships between regurgitant volume and LV end-diastolic volume (***a***) and LV ejection fraction and end-systolic volume (***b***) are illustrated for patients with *chronic* MR.

increase in end-diastolic stress as an accommodation for this LV volume overload [3]. Consequently, regurgitant volume has a direct relationship to LV end-diastolic volume, as shown in figure 1a. LV end-diastolic volume of 125–150 ml is not exceeded when little or no regurgitation occurs. As regurgitant volume increases, adaptation with eccentric LV hypertrophy occurs; LV end-diastolic volume increases linearly as a function of the extent of regurgitation. Therefore, in the absence of LV dilatation, regurgitant volume in patients with *chronic* MR must be modest. Also, note that a large range of regurgitant volumes is associated with LV end-diastolic volume of 200 ml; when this volume is reached, extent of regurgitation is, in part, a function of LV systolic performance. In contrast, LV ejection fraction as a measure of systolic performance is unrelated to LV end-diastolic volume or regurgitant volume, but it is inversely related to LV end-systolic volume (fig. 1b). Thus, as LV end-systolic volume increases, LV ejection fraction declines. Ultimately, this reflects the development of myocardial dysfunction.

The development of myocardial dysfunction may occur early in patients with *chronic* MR but may be reversible. Irreversible myocardial dysfunction is associated with more prominent increases in LV end-systolic volume systolic dysfunction [4, 5]. It has been demonstrated in patients with *chronic* MR that LV end-systolic stress is no different than that in control subjects, although LV end-diastolic stress, the stimulus for eccentric hypertrophy and LV remodeling in MR, is greater than in control subject. LV ejection fraction on average is less than that in normal subjects for the same end-systolic stress, suggesting that myocardial performance is impaired even at ejection fractions nominally within normal range [3].

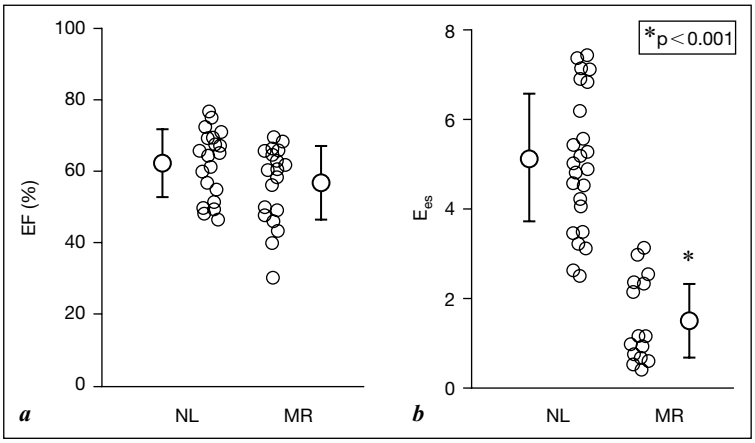

Fig. 2. The comparisons of LV ejection fraction (***a***) and LV chamber elastance (***b***) between control subjects and patients with *chronic* MR are illustrated. The average LV ejection fractions were similar, while the LV contractile index (E_{es}) is significantly diminished in the *chronic* MR patients compared to the control subjects.

Early myocardial dysfunction can be identified more definitively using sophisticated indices of LV contractility, which are independent of loading conditions, than from measures of LV end-systolic volume or ejection fraction [4–6]. In a model of MR produced in animals, Nikano et al. [6] studied LV ejection performance and myocardial contractility prior to the surgical creation of MR, 3 months after the surgical creation of MR, and 1 and 3 months after mitral valve surgery to eliminate MR. They observed that in comparison to the pre-surgical assessment, LV ejection fraction was unchanged with creation of MR and diminished slightly after mitral valve surgery. This was not true for myocardial contractility. In comparison to the pre-operative LV elastance and stiffness calculations, 3 months after surgical creation of MR, LV contractility was significantly impaired. Interestingly, following mitral valve surgery, LV contractility was restored towards normal. Thus, despite nominally normal LV ejection performance after creation of MR, impaired LV contractility had already developed, although it was reversible at this early juncture.

To explore this issue in humans, we have studied control subjects and patients with *chronic* MR in the cardiac catheterization laboratory to precisely evaluate their LV ejection performance and contractility [4, 5]. As illustrated in figure 2, LV ejection fraction, on average, was similar in the control subjects and MR patients, while LV contractility in the majority of patients with *chronic* MR was significantly impaired compared to that in the control subjects. When patients with a normal LV ejection fraction, but impaired LV contractility, were

surgically repaired, there was a short-term decline in LV ejection fraction, as measured 3 months post-surgery, but there was a long-term recovery of LV ejection performance, into the normal range, at 1 year. Although some of this recovery was due to LV remodeling with a mild increase in LV end-diastolic volume at 1 year, this alone was not adequate to explain the extent of post-operative recovery of LV ejection performance. Consequently, we studied patients with an investigative cardiac catheterization both prior to and 1 year following surgical correction of their *chronic* MR [5]. Although myocardial contractility improved in these MR patients, it was clear that two subpopulations existed. One group had a significant improved in LV chamber elastance, while the second group did not. Further examination revealed that the group with normal post-operative LV contractile index, had relatively less pre-operative LV remodeling, manifest by smaller LV end-systolic volume index (averaging $44 \pm 12\,ml/m^2$) and preserved LV ejection fraction (averaging 0.63 ± 0.09), than those who had persistent LV contractile dysfunction, who had a larger LV end-systolic volume index ($89 \pm 28\,ml/m^2$ ($p < 0.001$)) and lower LV ejection fraction (0.49 ± 0.12 ($p < 0.05$)). These data confirm the concept in figure 1: as LV end-systolic volume increases, LV ejection fraction declines; more modest degrees of LV systolic dilatation reflect reversible LV contractile dysfunction, while larger degrees of LV systolic dilatation indicate the evolution to irreversible LV contractile dysfunction. Thus, we sought a pathophysiologic mechanism affecting myocyte performance to explain both progressive LV remodeling and the observed initially reversible and subsequently irreversible LV contractile dysfunction.

Neurohumoral Activation

Some years ago, we developed a simple unifying hypothesis to provide such an explanation, focusing on the sympathetic nervous system and flowing from the old observation that 'MR begets more MR.' In other words, as LV regurgitant volume increases, forward stroke volume declines, and compensatory mechanisms are activated. These compensatory mechanisms include LV dilatation and remodeling with eccentric hypertrophy and activation of neurohumoral systems. We hypothesized that the systemic sympathetic nervous system would be activated early in this disease process as a compensatory mechanism and, that, after long-term activation of this system, β-adrenergic receptor responsivity would decline, leading to impaired LV contractility. To address this hypothesis, we used a sophisticated modeling approach to assess systemic sympathetic nervous system activity, which focused on the complex physiology of the sympathetic nerve system and utilizing a [^{3}H]-norepinephrine (NE)

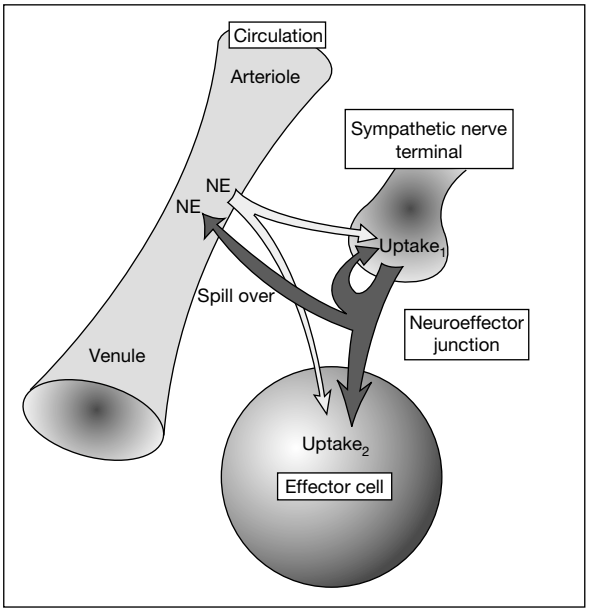

Fig. 3. A characterization of the complexities of the systemic or organ-specific sympathetic nervous systems is illustrated. The sympathetic nerve terminal resides in the interstitial space and releases NE into the neuroeffector junction. NE can then be taken up by the effector cell, retaken up into the nerve terminal, metabolized, or spill over into the circulation. Similarly, NE entering an organ from the arterial system may spill over into the interstitial space and be processed. Thus, the physiology of the sympathetic nervous system is complex and requires a similarly complex but physiologically sound approach to it characterization, if insightful data are to be obtained regarding systemic or *cardiac-specific* sympathetic activities [reprinted from 8, with permission].

infusion to characterize the individual components of this complex system (fig. 3). As can be seen in figure 3, the sympathetic nervous system resides in the interstitial space and secretes NE into that space, which can either be taken up by an effector cell, can be metabolized, can be taken back up by the sympathetic nerve terminal for processing, or can spill over into the circulation. Similarly, NE in the arterial system can move out of the arterial system into the interstitial space and can be taken up by the effector cell or by the sympathetic nerve terminal to be subsequently processed.

There are several approaches to characterizing the sympathetic nervous system. Our approach takes advantage of the [^{3}H]-NE infusion and decay for both the systemic and *cardiac-specific* sympathetic nervous systems. As can be seen at the termination of the 60-min infusion, there is a non-linear decay in

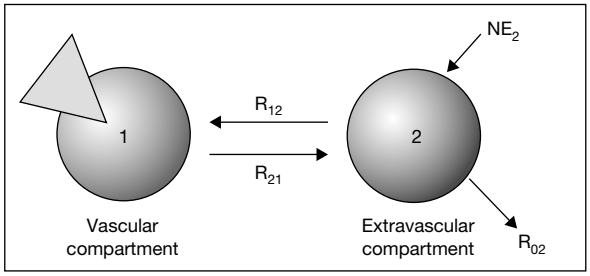

Fig. 4. The components of the two-compartment model are schematically represented to illustrate the relationship between the modeling parameters and the physiologic principles of the systemic sympathetic nervous system. Compartment 1 represents the vascular space, which is accessible for sampling. Compartment 2 represents the interstitial space into which NE is secreted from the nerve terminal. Additional constants relating transfer of NE from compartment 2 to 1, from compartment 1 to 2, and metabolism are considered. The extravascular NE release rate, NE_2, represents, therefore, a proximate index of systemic sympathetic nervous system tone. The approach to modeling *cardiac-specific* sympathetic tone is more complex and is not shown here, but it adheres to these principles [reprinted from 8, with permission].

[^{3}H]-NE from both systems. These findings indicate that, in the systemic circulation or in the heart, NE kinetics are best fit by a minimal two-compartment model, rather than a single-compartment model [7]. By using this model, we are able to develop a reliable index of activity of the systemic (fig. 4), and *cardiac-specific* sympathetic nervous systems. Thus, NE_2 represents the NE secretion rate into the extravascular compartment and represents a physiologically relevant index of sympathetic tone. Although the characterization of the *cardiac-specific* sympathetic nervous system is far more complex than for the systemic system, these principles pertain to both systems.

To determine whether systemic sympathetic nervous system activity is heightened in patients with *chronic* MR, we compared 37 patients with 23 age-matched control subjects [8]. There was no significant difference between the control subjects and patients with MR in arterial NE, despite the fact that NE_2 was increased in the patient *chronic* with MR ($p = 0.007$). The reason the average arterial NE was not different was that the NE spillover fraction in the *chronic* MR patients was less than that in the control subjects ($p = 0.0001$). The higher systemic NE release rate into the interstitial space (NE_2) and reduced spillover from the interstitial space into the vascular space implied that reuptake into the nerve terminal was enhanced. The combination of abnormal release rate and abnormal reuptake suggest heightened activity of the systemic sympathetic nervous system in *chronic* MR patients. NE appearance and clearance rates did differ in MR versus control, but these represent a steady-state analysis that is not

optimally undertaken with our data. Thus, it can be concluded that neither arterial NE concentrations nor steady-state data are linked to characterize systemic sympathetic nervous system activity in *chronic* MR patients sufficiently to clarify pathophysiology, a conclusion that is consistent with other findings [9].

Subsequently, to determine whether the systemic sympathetic nervous system was activated early in the disease process, we decided to evaluate three subpopulations with *chronic* MR, which were not mutually independent. The first population consisted of those MR patients who were asymptomatic. Interestingly, all *chronic* MR patients, irrespective of whether they were in clinical class I, II, or III/IV, had higher average NE_2 values in comparison to the control subjects ($p = 0.05$ for all comparisons). When we evaluated MR patients who had a pulmonary capillary wedge pressure of 12 mm Hg or less, a similar relationship was evident. Thus, both *chronic* MR patients with a pulmonary capillary wedge pressure of <12 mm Hg and those with wedge pressures ≥ 12 mm Hg had higher NE_2 values than control subjects ($p = 0.05$ for both comparisons). Finally, when MR patients with LV ejection fraction $\geq 60\%$ were compared to control subjects, average NE_2 level was marginally higher in the patients; this value was even more abnormal in those *chronic* MR patients with LV ejection fraction of $<60\%$ ($p = 0.06$ and 0.02, respectively). Thus, it can be concluded that patients with *chronic* MR, who are early in their disease process, have an activated systemic sympathetic nervous system to compensate for LV volume overload.

In addition, consistent with the relationship shown in figure 1b, both systemic and *cardiac-specific* sympathetic nervous system activities are directly related to an increase in LV end-systolic volume and inversely related to a decline in LV ejection performance. These observations both imply that as LV end-systolic volume increases and LV ejection performance declines as a result of worsening LV contractility, that both systemic and *cardiac-specific* sympathetic tone increases. Whether systemic and/or *cardiac-specific* sympathetic tone contributes directly to impaired LV contractility and to irreversibility of myocardial damage remains at issue. Two potential ways to infer a cause-and-effect relation between heightened systemic and *cardiac-specific* sympathetic tones and LV remodeling and systolic dysfunction would be, first, through linking changes in these parameters following an intervention, and, second, by linking heightened sympathetic tones to LV systolic dysfunction through changes in β-adrenergic receptor number or responsivity and, ultimately, LV contractility.

To support the inference of a cause-and-effect relationship between activation of the systemic sympathetic nervous system and LV remodeling and systolic dysfunction, changes in LV size and systolic performance should be related to changes in systemic sympathetic nervous system NE release rates following an intervention. To assess this possibility, we used echocardiography

and [^{3}H]-NE infusions to study 14 patients with *chronic* MR prior to and 1 year following mitral valve repair. Although there was no relation between changes in regurgitant volume, which was completely eliminated by mitral valve repair, or LV end-diastolic dimension, there was a strong positive relation between the changes in LV end-systolic dimension and the changes in NE_2. There was also a strong inverse relationship between the changes in LV fractional shortening and ejection fraction and the changes in NE_2. Thus, systemic sympathetic nervous system activity is not diminished following successful mitral valve repair and removal of the LV volume overload and, in addition, the changes in systemic sympathetic nervous system activity are linked to LV remodeling and systolic performance. This suggests that the systemic sympathetic nervous system may play a causal role in LV remodeling and systolic dysfunction in chronic MR. Whether a similar relationship also exists between changes in *cardiac-specific* sympathetic nervous system activity and changes in LV remodeling and systolic performance prior to and following mitral valve repair remains to be elucidated.

β-Adrenergic Receptor Responsivity and Contractility

The physiologic regulation of contractility is complex [10]. There are at least three modulators of myocardial contractility that include β-adrenergic receptor responsivity, the force-frequency relationship, and length dependence of activation. In addition, the force-frequency relationship may be modulated by the β-adrenergic receptor system. Using epicardial muscle strips from patients with *chronic* MR, Mulieri et al. [11] demonstrated that the force-frequency relationship was substantially diminished in the myocardium of the *chronic* MR patients compared to the myocardium of normal donor hearts. They also demonstrated that the administration of forskolin, an agent that directly stimulates the β-adrenergic receptor system, restored the force-frequency relationship towards normal suggesting that the β-adrenergic receptor system may have a substantial modulating role on the force-frequency relationship.

The data previously presented imply that the systemic sympathetic nervous system is activated early in the disease process, probably as a compensatory mechanism. If activation of this neurohormonal system continues, over a protracted period of time, a decrease in the number of β-adrenergic receptors and/or their responsivity to stimulation would be expected. If heightened systemic and/or *cardiac-specific* systemic nervous system activity can be related to the development of altered β-adrenergic receptor number and/or responsivity and, ultimately, impaired to LV contractility, it would be reasonable to suggest a cause-and-effect relationship.

To test whether impaired cyclic AMP production by the β-adrenergic receptor system is related to LV contractility in patients with *chronic* MR, we studied patients in the cardiac catheterization laboratory prior to mitral valve surgery and, at the time of mitral valve surgery, we obtained endomyocardial biopsies for β-adrenergic receptor number and responsivity. When we compared the percent increase in cyclic AMP from the basal level in response to isoproterenol doses of 10^{-8}, 10^{-6} and 10^{-4} *M*, we observed strong correlations between the individual percentage increase and LV chamber elastance values ($r = 0.73$, 0.62 and 0.69, respectively). When we developed the slope of the dose-response relation to isoproterenol stimulation of the β-adrenergic receptor system and related it to LV chamber elastance, a similar correlation was observed ($r = 0.60$). A correlation was also established when sodium fluoride was given to stimulate the G-transduction protein ($r = 0.67$), but there was no correlation when forskolin was given to stimulate adenylyl cyclase. It can be concluded from these data that β-adrenergic receptor responsivity is directly related to LV chamber elastance in patients with *chronic* MR. This may explain the early LV contractile dysfunction observed in some *chronic* MR patients. Can β-adrenergic receptor blockade effect an improvement in the LV contractile dysfunction observed in this disease process? If this were the case, β-adrenergic receptor blockade might be a useful strategy to delay the progression and development of myocardial dysfunction and/or the need for mitral valve surgery.

β-Adrenergic Receptor Blockade in MR

The first evidence that β-adrenergic receptor blockade might be valuable in MR was provided in an animal model of surgically created MR by Tsutsui et al. [12]. The surgery led to a regurgitant fraction that averaged approximately 60%. With the surgical creation of MR, there was an increase in plasma NE that was progressive over 3 months to nearly double the pre-surgical level. At 3 months, animals were either treated with a β-adrenergic receptor blocker or remained untreated. In the β-adrenergic receptor blocker-treated animals, plasma NE further increased, average heart rate declined ($p < 0.04$), pulmonary capillary wedge pressure declined ($p < 0.05$), and indices of myocardial contractility improved ($p < 0.05$ for all comparisons to the control MR animals). This suggested for the first time that β-adrenergic receptor blockade in MR has a favorable effect on myocardial performance, as well as on hemodynamic parameters. These data do not indicate whether the β-blocker effect resulted directly from whether alteration in β-adrenergic receptor responsivity or indirectly, because of the altered heart rate. Nevertheless, benefit has indeed been demonstrated. More recent data [13] suggest that this effect is not seen with an angiotensin-converting

enzyme inhibitor, providing further substantive data to support the use of β-adrenergic receptor blockade in this disease process.

Norepinephrine Myocyte Toxicity

It is also known that NE may be toxic to myocytes. This may, in part, explain the progression to irreversible myocardial dysfunction if mitral valve surgery is substantially delayed. Mann et al. [14] demonstrated that when isolated myocytes in culture were exposed to increasing physiologic concentrations of NE, viability was reduced. However, if increasing concentrations of propranalol were placed in the solution, viability of myocytes was preserved. This benefit was not seen with an α-blocking agent. At the cellular level, exposing myocytes to NE caused a rapid increase in cyclic AMP followed by a progressive increase in cytosolic calcium. Both of these effects were attenuated with the pre-administration of propranalol, suggesting that calcium toxicity to myocytes can be prevented with β-adrenergic blockade.

Clinical Implications

The data suggest that, in patients with *chronic* MR, both systemic and *cardiac-specific* sympathetic nervous system activities increase as LV remodeling progresses and systolic dysfunction supervenes. In addition, the data support the concept of cause and effect, in that changes in systemic sympathetic tone are strongly related to changes in LV end-systolic dimension and ejection performance, while β-adrenergic receptor responsivity is related to LV contractility. Also, large LV end-systolic dimensions and subnormal ejection fractions are consistent with irreversible myocardial dysfunction and each of these is associated with heightened systemic and *cardiac-specific* sympathetic tone. These data and those of Mann et al. [14] suggest the potential for NE toxicity as a cause for irreversible myocardial dysfunction in patients with *chronic* MR.

Presently, only animal and cell culture data are available to support the concept that β-adrenergic receptor blockade may improve contractile dysfunction and protect myocytes from direct NE myocyte toxicity. With these data, however, it is reasonable to hypothesize that early, prophylactic β-adrenergic receptor blockade in patients with *chronic* MR may beneficially modulate the negative effects of heightened systemic and *cardiac-specific* sympathetic tones on myocardial contractility, myocyte viability and disease progression. This could delay the development of LV dilatation and systolic dysfunction and delay the need for mitral valve surgery. This hypothesis must be tested in patients with *chronic* MR.

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Valve Surgery in the Asymptomatic Patient with Aortic Regurgitation: Current Indications and the Effect of Change Rates in Objective Measures

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Among patients with isolated, pure aortic regurgitation (AR), the emergence of congestive symptoms and, perhaps, but less clearly, of the relatively uncommon symptoms of angina or presyncope/syncope ('pseudo-Nothnagel episodes') generally is accepted as an indication for aortic valve replacement (AVR). The primary justification for this strategy is that operation minimizes or relieves symptoms with an acceptable risk (perioperative mortality for isolated AVR now is approximately 2% at high volume centers [1], stroke risk 2%, etc.) and may improve survival in symptomatic patients. The latter benefit is inferred but not well demonstrated: early experience generated important questions as to survival improvement [2], though operated patients often were severely symptomatic (equal to or more than New York Heart Association Functional Class (NYHAFC) III for heart failure (CHF)) with markedly subnormal left ventricular (LV) function, now known to seriously mitigate post-operative outcome [3], and surgical techniques and prostheses that were substantially less effective than those now employed. However, recent retrospective data suggest that, even in these severely ill symptomatic patients, survival may be improved by AVR [3].

Among asymptomatic patients, the situation has been less clear: the only unequivocal benefit for such patients can be prolongation of life. The requisite clinical trials to support this benefit from AVR never have been performed

Table 1. Natural history studies of the 678 well-characterized asymptomatic patients with AR whose data are the basis of current recommendations

Study (first author)	Ref.	Population size, n	Follow-up years
Scognamiglio	19	30	4.7
Siemienczuk	10	50	3.7
Tornos	14	101	4.6
Ishii	15	27	14.2
Scognamiglio	16	74	6.0
Bonow	13	104	8.0
Borer	12	104	7.3
Dujardin	17	113	7.0
Tarasoutchi	18	75	10.0

and are unlikely to emerge in the future. Instead, inferences are based on epidemiological and pathophysiological data, and comparisons with US Census data for age- and sex-matched comparators. However, in contradistinction to the relatively large populations usually invoked to support claims about natural history and its predictors for coronary artery disease, only 678 well-characterized patients provide the world's knowledge about the natural history of asymptomatic AR; data from these patients are the basis for currently employed prognostic indices. The relative dearth of natural history data relate in large part to the very gradual natural course of AR, requiring many years of observation to support firm conclusions. The relevant studies (table 1) vary widely in size, duration of follow-up and design (retrospective vs. prospective, choice of objective testing modalities, normal vs. subnormal LV ejection fraction (LVEF) at rest, extent of 'prophylactic' drug use, etc.). Therefore, it is not surprising that no algorithm for selecting asymptomatic patients for AVR has been accepted universally. Nonetheless, despite some variation in the predictive value of specific descriptors measured in different studies, a relatively consistent overarching picture emerges from the published data: (a) systolic phase descriptors are reasonably efficient prognosticators in patients with AR and (b) several algorithms can be defended as plausible bases for AVR in asymptomatic patients. In addition, recent preliminary data have re-focused attention on the prognostic utility of change rates of specific descriptors from year to year. This chapter will review evidence supporting the application of specific predictors, including descriptors measured at a single time point ('single-point' prognostic indices) and change rates in these descriptors, the confidence with which management decisions can be based on them.

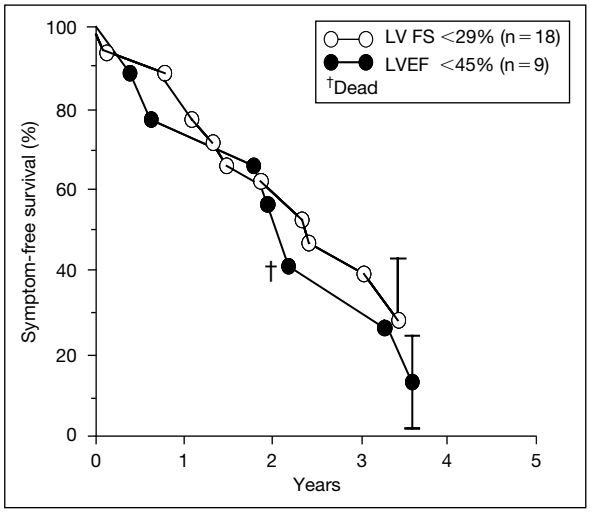

Fig. 1. Progression to congestive heart failure or death among asymptomatic patients with severe AR and subnormal LV performance at rest [from 6, with permission].

Subnormal LVEF at Rest

If LVEF at rest is subnormal at the initial evaluation of an asymptomatic patient, progression to symptoms or death occurs at a rate of 25%/year [4–6] (fig. 1). Echocardiographic fractional shortening (FS) is analogous to ejection fraction (EF); subnormality of this variable supports inferences similar to those associated with LVEF. However, the accuracy of FS as an index of global systolic function depends on assumptions about the uniformity of regional LV function that often are not met in patients with AR. Therefore, while subnormal FS has well-demonstrated prognostic importance in population studies [4, 7], LVEF itself is the preferable prognostic index, particularly if available with a technique that has minimal dependence on geometric formulations (e.g., radionuclide cineangiography, magnetic resonance imaging).

The data supporting the rapid rate of clinical progression among asymptomatic patients with subnormal $LVEF_{rest}$ are derived from two studies involving a total of 27 patients evaluated before 1980 [4, 5], all of whom had subnormal LV performance at index evaluation. In a later combination and re-analysis of these studies, inter-study consistency was quite high, supporting the validity of the data [6]. However, the duration of subnormal LVEF/FS was not known. A more recent retrospective study suggests that progression to CHF may be slower than 25%/year if assessed from the time LV performance falls below

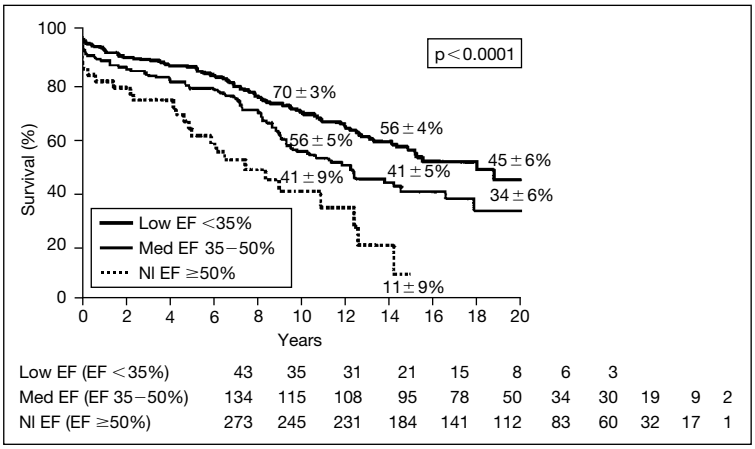

Fig. 2. Relation of preoperative LVEF to post-operative survival in patients with AR [from 3, with permission].

normal [3, 8]. Nonetheless, the seminal studies are unlikely to be repeated and the inferences they support will continue to be accepted because (a) it is well demonstrated that, once a patient with subnormal LVEF *and symptoms* undergoes valve replacement, long-term survival is considerably less good than when LVEF is normal [3, 6, 9], (b) among patients with subnormal LVEF who undergo AVR, post-operative survival is inversely related to preoperative LVEF irrespective of symptoms [3] (fig. 2) and (c) among asymptomatic patients whose contractility already is markedly compromised, LVEF at rest falls at an average rate of approximately 1%/year [10]. Therefore, in view of the relatively low perioperative risk of AVR, previously noted, it is unacceptably imprudent to withhold AVR from an asymptomatic patient with subnormal $LVEF_{rest}$.

Normal $LVEF_{rest}$

Systolic Phase Descriptors at Rest and Exercise

The appropriate basis for AVR is less clear in an asymptomatic patient with normal $LVEF_{rest}$. Among such patients, progression to heart failure, subnormal $LVEF_{rest}$ or, far less frequently, sudden death, occurs at a rate of 2–6%/year [9, 11, 12–20]. However, reasonable strategies for selection of patients relatively imminently at risk, for whom the hazards of early operation probably are less than those of continued observation, are inferable from the results of epidemiological studies. Table 2 presents a comparison of results from the two

Table 2. Relative prognostic strength of descriptors of LV size and function measured at index study in asymptomatic patients with severe AR and initially normal LV fraction at rest [from 25, with permission]

Predictor	Univariate		Multivariate	
	Bonow et al. [13]	Borer et al. [12]	Bonow et al. [13]	Borer et al. [12]
ΔLVEF-ΔESS	Not tested	++++	Not tested	+++
ΔLVEF	+	+++	−	−
LVEFex	+	++	−	−
LVIDS	++	+	++	−
LVIDD	++	−	−	−
FS	+	+	−	−

prospectively designed studies that provided the longest follow-up (average 7–8 years in event-free survivors, maximum 15 years) [12, 13]; coincidentally, each included 104 patients, among the largest published series. These studies were separated in their time of initiation by 9 years and, therefore, spanned eras involving some technological differences in accuracy of evaluation methodology; nonetheless, overall, the results were strikingly similar: (1) although the strength of the specific predictors on univariate analysis varied between the studies, both showed that the 'composite end-point' of heart failure, subnormal LVEF or sudden death was predicted by several systolic phase descriptors measured at rest and/or during exercise (echocardiographic LV systolic dimension (IDs), LVEF change (Δ) from rest to exercise, LVEF at peak exercise). The predictive value of the echocardiographic LV diastolic dimension (IDd), a contributor to afterload as the point from which active contraction begins, differed more markedly between the two studies, but even here, some similarity is apparent: LVIDd was predictive for the composite end-point in one study and for development of subnormal $LVEF_{rest}$, alone, in the other. The latter finding suggests that LVIDd may be less predictive than primary systolic phase descriptors. This conclusion is supported by independent data indicating that preoperative LVIDd predicts post-operative survival, though not as well as $LVEF_{rest}$ [20]. In the latter study (which included both symptomatic and asymptomatic patients with normal or subnormal $LVEF_{rest}$), age- and sex-matched mortality data from the US census were used as a reference point; survival was slightly but significantly less good than the census comparator among those whose LVIDd was ≥80 mm, while those with smaller ventricles survived as well as the matched census population. Anecdotal data have suggested that LVIDd >75 or 80 mm may predict sudden death risk in unoperated asymptomatic patients

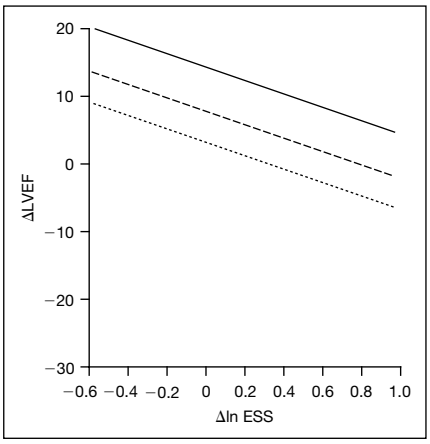

Fig. 3. Relation of change in LVEF from rest to exercise (ΔLVEF) to change in LV wall stress from rest to exercise (ΔLVESS) in normal subjects. Solid line is mean relation; dashed lines represent 1 and 2 standard deviations lower than the mean relation [adapted from 12, with permission].

[9, 13]; this conclusion specifically was not supported by post-hoc analysis of the later of the two large prospective studies [21].

While the two highlighted studies are predominantly similar in findings and outcome, they differ in the results of multivariate assessment to define independent strength of individual predictors. In the earlier study, LV performance surrogates for LV contractility, alone, were measured; among these, only LVIDs was independently predictive. The later study prospectively measured intrinsic LV contractility directly and found that this measure carried all independent prognostic information, i.e., it was superior to all surrogate (performance) measures [12].

The method employed for measuring contractility is simple to apply in practice [12]. It involves adjustment of the performance descriptor, ΔLVEF, for the simultaneous change in end-systolic wall stress (ΔLVESS) from rest to exercise. These values are defined by combination of echocardiographic and radionuclide cineangiographic data. The relation of these descriptors in normal subjects has been published [12] and, thus, is available for application by clinicians (fig. 3). After the ΔLVESS is measured in an individual patient, the examiner uses the normative data to determine the ΔLVEF that would correspond to that ΔLVESS in a normal subject; the LVEF actually measured then is subtracted from the expected value. The difference between measured and expected values is an index of contractility, either depressed (if lower than the expected value), normal or supernormal. In other words, contractility is measured as the decrement in LV systolic performance for an increment in afterload. Use of the values for the change from rest to exercise in LVEF and LVESS minimizes ambiguities in interpreting contractility based on rest or exercise values, alone; such ambiguities might result from the wide range of normal EF/ESS values;

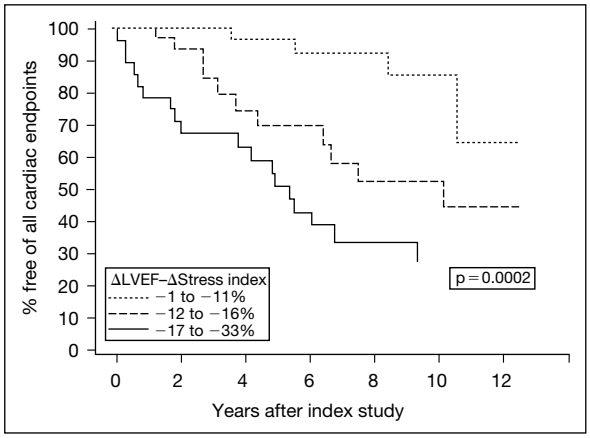

Fig. 4. Relation of LV contractility and freedom from congestive symptoms, subnormal LVEF at rest or sudden death among initially asymptomatic patients with AR and normal LV fraction at rest [from 12, with permission].

this approach also minimizes potential problems in applying the normative data because of variations in measurement techniques among laboratories (e.g., single end-diastolic region of interest for radionuclide cineangiographic LVEF calculation might result in different absolute LVEF values compared with using separate systolic and diastolic regions, but the change from rest to exercise should not be affected importantly).

When contractility was measured, the study population (all with normal $LVEF_{rest}$) was divided arbitrarily into contractility terciles (to avoid biased selection of segregation points) (fig. 4). The tercile with best preserved contractility at study entry developed heart failure or subnormal LVEF at rest at a rate of approximately 11/2% per year. The tercile with the lowest contractility values at study entry, despite normal $LVEF_{rest}$, developed end-points almost 10 times more rapidly (approximately 40% event likelihood over 3 years); the middle tercile developed end-points at a rate midway between the two extremes. Importantly, contractility significantly predicted sudden death: all sudden deaths occurred in patients with markedly compromised contractility, despite normal LVEF and absence of symptoms.

More recently, the predictive value of the contractility measure has been validated in a separate population comprising patients studied shortly prior to AVR [22]. In the later study, mortality was employed as the outcome variable. Among the 71 consecutive study participants (including patients who were symptomatic or asymptomatic, with normal or subnormal $LVEF_{rest}$), subgroup boundaries, or segregation points, were defined exactly as they had been in the

earlier study of unoperated patients, that is, the tercile boundaries from the earlier study were applied. In addition, survival in contractility-based subgroups was compared with that reported in age- and sex-matched individuals from an otherwise unselected US census cohort. In the tercile with the best preserved contractility (that is, the group defined identically as that with the best outcome in the non-operated group in the earlier study), survival after operation was indistinguishable from that in the census-based comparator. Survival in the lowest tercile was markedly and significantly worse than both the highest tercile and the census comparator; in this group, survival likelihood at 5 years was about half that found in the highest tercile. Survival in the middle tercile also was modestly but significantly worse than in the upper tercile or the comparator group. Importantly, when separated into subgroups based on $LVEF_{rest}$, those with normal pre-operative $LVEF_{rest}$ manifested contractility-based survival patterns similar to those with subnormal $LVEF_{rest}$.

Taken together, data from the non-operated cohort and the pre-operative cohort do not prove that operation improves survival in asymptomatic patients with normal $LVEF_{rest}$ and markedly depressed intrinsic contractility. However, it indicates that outcome, including survival if operation ultimately is performed, deteriorates as contractility falls and suggests that, if operation is not performed by the time the 'high-risk' contractility descriptor is reached, long-term survival will be further compromised.

While contractility measurement, per se, was the most powerful predictor of pre-operative events and of post-operative mortality on multivariate analyses in the studies in which contractility was prospectively assessed, marked fall in LVEF from rest to exercise ($-\Delta$LVEF), without adjustment for load, also is a significant predictor of events [9, 11, 12, 13]. Measurement of ΔLVEF is less cumbersome than contractility assessment and, together with LVIDs, represents a powerful additional prognosticator that can be usefully applied in patients with normal $LVEF_{rest}$.

Change Rates of Risk Descriptors

Intuitively, prognosis also should be inferable from the deterioration rate of systolic phase descriptors even if, nominally, these descriptors remain within normal range. Data support this inference. Several parameters have demonstrated predictive value when used to segregate populations for risk assessment [10, 13, 23]. For example, in one study [13], patients with normal $LVEF_{rest}$ whose period of observation began when LVIDs was >40 mm and whose LVIDs increased by ≥ 1 mm/year developed symptoms at a rate approximately 5-fold greater than that of patients who were similar except that LVIDs increased <1 mm/year. In the same study, change rate of $LVEF_{rest}$ also was a significant predictor of symptom development, though optimal segregation

points were not defined [13]; change rates of other parameters were not predictive. Preliminary data from the Cornell database [23] confirm the utility of change rates of $LVEF_{rest}$ and LVIDs, and also indicate significant predictive value of ΔLVEF and $LVEF_{exercise}$; with the latter parameter, the best segregation point on preliminary post-hoc analysis was −0.32%/year, which identifies two groups that differ by approximately 5-fold in risk; however, the high-risk group manifests absolute risk <10%, substantially lower than high-risk groups identified by single-point systolic phase prognosticators [23]. These data also indicate that $LVEF_{rest}$ can be expected to deteriorate at a rate of approximately 1%/year among patients with clearly subnormal contractility at index study [10]. Despite their promise, at present, the utility of change rates is limited for selecting surgical candidates. First, all functional parameters have intrinsic variability, attributable both to technical and biological factors. While this variability affects confidence in single-point determinants like absolute $LVEF_{rest}$, are passed, at least three such points must be collected before a line defining change rate can be calculated with any reasonable confidence. (Preliminary data suggest that systolic phase indices change in approximately linear fashion for many years [24].) Thus, the intrinsic variability must be considered for each of multiple points in determining confidence for a calculated change rate. Moreover, both published and preliminary data indicate that systolic phase descriptors change relatively slowly. Therefore, at the very least, 2 years of data collection are required to define the three points minimally needed to establish a statistically stable change rate; indeed, a substantially longer collection interval, in which many more single points are measured, is desirable to assure resolution sufficient to identify a change if, indeed, it exists. Consequently, change rates may not provide prognostically important information at a time substantially earlier than such information would be obtained from single-point descriptors, and any benefit from potentially earlier detection may be offset by the greater variability and wider confidence bounds of the change rate than of the single-point descriptor. Finally and most importantly, relatively few data exist to define prognostically useful change rate segregation values; none of the current candidates has been evaluated prospectively in studies designed to test its validity. In summary, at present, change rates have potential for prognostic utility, but should be considered only supportive or adjunctive to better established single-point functional/geometric descriptors.

Conclusion

In summary, in asymptomatic patients with AR, natural history is predicted best by $LVEF_{rest}$, using the lower limit of normal to segregate high- and low-risk

subgroups. If this parameter is subnormal, progression to symptoms or death occurs at a rate that may approach 25%/year. These asymptomatic patients should all undergo operation.

Among patients with normal $LVEF_{rest}$, the best predictors are systolic phase descriptors including intrinsic myocardial contractility (which may be the most efficient), and contractility surrogates, LVIDs and ΔLVEF. When established segregation points are applied, these parameters can identify a subgroup that will progress to symptoms, subnormal LVEF at rest or sudden death at a rate of 10–20% per year. Asymptomatic patients who are found to be at relatively high risk based on these measures should undergo operation, though prudence requires replication of the predictive test result before proceeding to surgery.

In asymptomatic patients with normal $LVEF_{rest}$, outcome also is predicted by LVIDd and by change rates of systolic phase descriptors over several years, even if the absolute value of the descriptor remains within the nominally normal range. For LVIDd, a segregation point of 75–80 mm can be defended, though supporting data are modest. For change rates, segregation points are less well defined. For this entire group of predictors, end-points occur at a rate of 7–10% per year when published segregation points are applied. Operation may be appropriate in some patients when thresholds are passed, though this strategy requires additional supporting evidence before it can be accepted generally. As a practical matter, if surgery in asymptomatic patients is to be based on findings in the latter group of parameters, alone, the procedure should be considered only if multiple predictors consistently indicate relatively high-risk status.

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Valve Repair versus Replacement When Aortic Regurgitation Is Caused by Aortic Root Aneurysms: Relative Advantages and Disadvantages and the Impact of Decision on Surgical Indications

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Significant aortic valve regurgitation (AR) secondary to aortic root dilatation requires treatment of both disease processes in order to achieve successful short- and long-term results. A thorough understanding of normal aortic root and valve anatomy and function allows the surgeon to implement sound operative strategies. Comprehensive review of an individual's aortic root pathophysiology permits a variety of surgical options to be considered. As always, the goals of the operation should be to: (1) eliminate the risk of aortic wall rupture or dissection when root dilatation is present; (2) eliminate aortic valve insufficiency; (3) perform the procedure with a reproducibly low operative mortality and morbidity, and (4) assure the patient of excellent long-term performance of the procedure. This article will summarize our current interpretation of the literature regarding the two most common methods of aortic root reconstruction, aortic valve-sparing root replacement and composite valve graft replacement. Patients with ascending aortic aneurysms, AR and non-dilated sinuses of Valsalva may not require total root reconstruction and will not be considered further in this review. Additionally, patients with destruction of the aortic root secondary to endocarditis may require homograft or autograft root reconstruction. These procedures will also be left for discussion in another setting. Our experience with aortic root reconstruction will be summarized and guidelines for the appropriate application of the various surgical techniques will be proposed.

Table 1. Aortic regurgitation and aortic root disease: When to intervene?

- Ascending aorta diameter >5.5 cm
- Documented growth >1 cm/year
- Ascending aortic diameter >5.0 cm in patients with *connective tissue disorder* and family history of early dissection or rupture
- Ascending aortic diameter >5.0 cm in patients requiring *open heart surgery* for valvular disease or coronary artery disease
- Aortic or type A aortic dissection

Pathologic Considerations in Surgical Decisions

Aortic root pathology is multifactorial. Excluding destructive processes of the aortic root such as aggressive aortic valve endocarditis, a majority of the surgical indications for aortic root reconstruction occur in the setting of connective tissue disorders (CTD). Patients with named CTD such as Marfan's syndrome have a well-defined genetic deficiency in the expression of the fibrillin gene [1]. This leads to a deficiency of elastin in the aortic root and the aortic valve that may ultimately lead to aneurysmal degeneration, aortic dissection and AR. Patients with familial aneurysm and dissection syndromes have similar protein deficiencies, although the genetic locus responsible for this entity is separate from that of patients with Marfan's syndrome [2]. Finally, patients with bicuspid aortic valve disease have also been found to have a genetic component to their aortic dilatation. In the past, ascending aneurysms in patients with bicuspid aortic valves were thought to be secondary to a combination of abnormal systolic flow patterns and post-stenotic dilatation. However, a number of centers report consistent elastin fragmentation and smooth muscle apoptosis in the aortic wall of patients requiring surgery for insufficient or stenotic bicuspid valves [3, 4]. As this relationship becomes better understood, and with an approximately 1–2% incidence of bicuspid valves in the entire population, it is quite likely that this group of patients will far exceed those with CTD for consideration of aortic root repair.

Regardless of the etiology, the indications for operative intervention remain the same (table 1). Patients with aortic diameters of ≥5.5 cm should have aortic replacement. If growth of the aorta has been documented at approximately 1 cm/year, surgery should be strongly considered. In patients with strong family histories of early dissection or aneurysm rupture, prophylactic surgery is appropriate with an aortic root diameter of 5.0 cm. Similar recommendations should be made for patients with a 5.0 cm ascending aorta who are having open heart surgery for another indication, especially those having aortic valve replacement for degenerative bicuspid aortic valves [5].

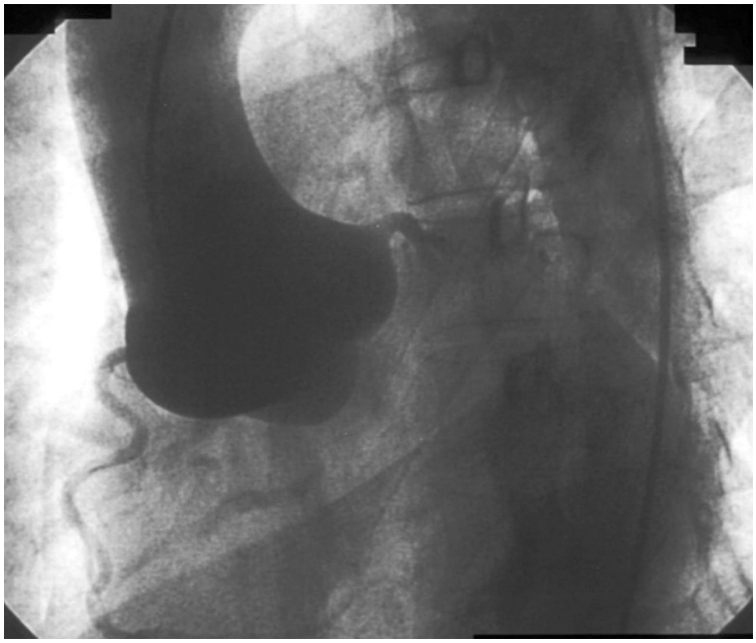

Fig. 1. Aortogram of an ascending aortic aneurysm in a patient with a CTD. The sinuses of Valsalva are markedly dilated and the coronary arteries are effaced high into their respective sinuses. The remainder of the ascending aorta is of relatively normal diameter.

Finally, all patients with acute or chronic type A dissections should have aortic reconstruction.

An aortogram taken during cardiac catheterization of a typical patient with a CTD is shown in figure 1. The sinuses of Valsalva are markedly dilated, the aortic annulus is enlarged and the coronary arteries are effaced and sit high in their respective sinuses. Central AR is usually present. The remainder of the ascending aorta is normal in diameter. For patients without specific connective disorders, as in the setting of a bicuspid aortic valve, the ascending aorta may not taper at the sinotubular junction. Rather, the aneurysm extends throughout the entirety of the ascending aorta and usually into the aortic arch. In either of these settings, the two most commonly performed procedures for root reconstruction are valve-sparing aortic root replacement and composite valve graft replacement.

Yacoub et al. [6] were the first to report a series of patients having valve-sparing ascending aortic repair. With his remodeling technique, the patient is placed on cardiopulmonary bypass, the heart is arrested and the ascending aorta is resected in its entirety to within 2 or 3 mm of the aortic annulus. Coronary

artery buttons are created from the sinuses of Valsalva and the aortic valve is left intact. A Dacron tube graft of the appropriate size is then sculpted to re-create the sinuses of Valsalva. The tongues of graft that arise from the caudal portion of the graft are then sewn to the aortic annulus. The coronary arteries are reattached and the distal end of the graft is handled in whatever manner necessary depending on the size of the aortic arch. David et al. [7] have also championed aortic valve-sparing root replacement. Their technique, reimplantation, may offer the benefit of annular reduction and stabilization, especially in patients with CTDs. The disassembly of the aortic root is identical in the two procedures. However, in a reimplantation the aortic graft is not tailored to recreate the sinuses of Valsalva. Rather, the graft is anastomosed to the aortic root outside and below the aortic annulus. In the region of the fibrous trigone, annular reduction can be performed if needed. The aortic valve inside the graft and is then reimplanted by sewing the aortic valve commissures and annulus to the aortic graft, similar to the technique of stentless porcine valve implantation.

The most recent data on the Yacoub remodeling valve-sparing procedure was reported in 1998, and the operative mortality was 4.6% [8]. The next most important outcome, the need for reoperation for significant AR, occurred in 11% of the patients during their first 5 post-operative years. An additional 30% of patients had developed moderate to severe AR that had not yet required reoperation. The actuarial survival at 15 years was 58%.

Looking specifically at patients with CTDs, this same group summarized their experience with aortic root remodeling in 82 patients with Marfan's syndrome [9]. The range in age of the patients in this series was quite wide with children as young as 2 years of age being included in the analysis. Of this cohort, 21% were less than 18 years old. The operative mortality was 4.9%, and the incidence of moderate to severe AR was 22% at a median 3 years after surgery. An additional 45% of patients developed mild AR during this same period of follow-up. The need for reoperation in the first 5 years was 17.3% and the 5-year actuarial survival of these rather young patients was 87%.

David et al.'s [10] most comprehensive report appeared in the literature in 2001, and outlined results for the last 120 patients undergoing aortic valve-sparing surgery with both the reimplantation and remodeling techniques. The mean age of these patients was approximately 45 years and they had a mean aortic diameter of 53 mm. Nearly 50% of patients had mild or no AR and only 11% had severe AR. The operative mortality was a very respectable 2.5%. Approximately 12% of patients had severe AR within the first 5 years after reconstruction. Interestingly, many of those presenting with severe preoperative AR were operated on in the setting of an acute type A dissection where standard valve resuspension techniques yield excellent short- and long-term outcomes. Surprisingly, the 5-year actuarial survival was only 88% despite a very young patient population.

Suggested Surgical Therapeutic Approaches

Based on the available data, the following can be recommended in patients being considered for valve-sparing aortic root replacement. Aortic leaflet integrity is the most important determinant of the appropriateness of this procedure. Patients with 3+ or 4+ AR or multileaflet prolapse are poor candidates for aortic valve preservation. Similarly, the preservation of leaflets with multiple fenestrations portends a poor long-term outcome and usually results in the need for reoperation in a disappointingly short period of time. Patients with annular diameters over 55 mm, especially in the setting of a CTD, should also be cautioned about the higher incidence of late AR and reoperation. Whether one is able to prevent late dilatation of the fibrous trigone of the heart with a reimplantation technique over a remodeling technique is debatable. The ideal patient has an aortic diameter closer to 5 cm with mild to moderate AR. Patients with family histories of early aortic dissection or aneurysm rupture are ideal candidates for valve-sparing approaches as prophylaxis. In addition, those with absolute contraindications to anticoagulation should be considered for this procedure provided they meet the appropriate anatomic criteria outlined above. Whether or not patients with non-stenotic bicuspid valves should be considered for valve preservation remains to be determined.

Composite valve graft replacement of the ascending aorta and aortic valve remains the gold standard operation against which all root replacement or remodeling procedures must be compared (fig. 2). Developed in 1968 by Bentall and DeBono [11], this procedure consists of total aortic root replacement with a single unit consisting of a Dacron tube graft and a prosthetic aortic valve. At the time this procedure was developed, premanufactured composites were not yet commercially available. Instead, the graft was hand sewn to the sewing ring of the valve and implanted into the aortic root via the graft inclusion technique. With this method the aortic root was not dissected or modified. Rather, the composite was placed inside the dilated aortic root and the aorta wrapped around the prosthetic after attaching the valve to the aortic annulus and reimplanting the coronary arteries. Because the Dacron grafts of this era were quite porous, the inclusion wrap dramatically reduced the incidence of serious postoperative hemorrhage, the most common cause of postoperative mortality. The surgical results improved immediately with the operative mortality for ascending aneurysm repair decreasing from nearly 20% to less than 10%. Commercially available composite valve grafts are now constructed of collagen impregnated, near zero porosity Dacron that has essentially eliminated transgraft bleeding [12]. In addition, modern bileaflet, central flow, pyrolite carbon valves have reduced the need for high levels of anticoagulation. With these technical advances, the inclusion technique is no longer necessary. Instead, the

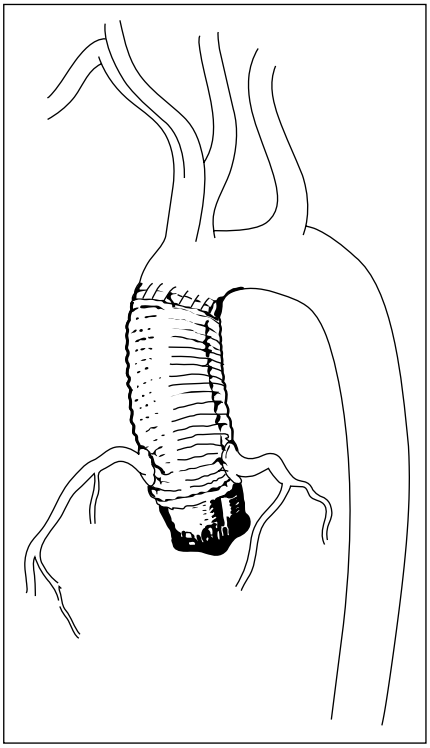

Fig. 2. Composite valve graft reconstruction of the aortic root. The entire ascending aorta and aortic valve have been excised. The coronary arteries are reimplanted into their anatomic locations [from 12, with permission].

exclusion method allows for complete excision of all aortic tissue and the aortic valve [13]. The coronary buttons are reimplanted and all suture lines can be inspected for hemorrhage. This has reduced the operative mortality even further such that low single digit mortality is expected in the hands of experienced surgeons. The technique and results for implantation of a tissue valve-based composite differs only in that the two components must be sewn together by the surgeon at the time of implantation [14]. The short- and long-term success of composite root replacement with stentless, porcine valved conduits remains in question and cannot be recommended by this author at the present time [15].

Over the last 56 months, we have operated on 338 patients who have required replacement of their ascending aorta, with or without the need for aortic arch replacement (table 2). Approximately 20% of patients have had aortic valve-sparing root reconstruction while an additional 20% have required separate valve replacement and aortic replacement, and 87 patients have not required any valve related procedure during ascending aneurysm repair. A total of 113 patients have met the criteria for total root replacement with a composite valve

Table 2. Ascending aortic aneurysm repair (n = 338) – the New York experience

Ascending tube graft	214
With aortic valve replacement	66
With aortic valve-sparing	65
Without aortic valve replacement	87
Homograft root replacement	7
Composite valve graft	113

Table 3. Demographics of patients (n = 113) having composite valve graft aortic root replacement

Mean age, years	52
Male:female	2:1
Mean ejection fraction, %	43
Mean aortic diameter, mm	65
Amount aortic regurgitation	
1+	11
2+	11
3+	17
4+	74

graft. Their mean age was 52 years, with a range of 16–78 years, and the majority were males. The mean diameter of the aneurysms was 65 mm and approximately 80% had moderate to severe AR (table 3).

There were no intraoperative deaths, and our in-hospital and 30-day mortality was 0.9%. Approximately 7% of the patients required re-exploration for bleeding in the immediate postoperative period, and this includes patients having prolonged periods of cardiopulmonary bypass for arch reconstructions requiring profound hypothermic circulatory arrest. However, 65% of all patients having composite valve graft replacement did not require any blood transfusion. There have not been any reoperations for valve or graft failure and no patient has developed significant prosthetic valve insufficiency.

While our experience has been too recent to generate long-term survival data, we can extrapolate from a recent large multicenter collection of nearly 675 composite valve graft procedures performed specifically on patients with Marfan's syndrome [16]. The mortality for an elective procedure in this series was only 1.5% and the 10-year actuarial survival was greater than 90%. Freedom from thromboembolic complications exceeded 90% at 20 years. Nearly all of the patients experiencing coumadin-related complications had complete neurologic recovery. Long-term durability was evident with only 3.4% of patients requiring reoperation on any part of their aorta for the remainder of their lifetime.

Conclusion

In conclusion, patients with CTDs still comprise the greatest proportion of patients requiring aortic root reconstruction. This may change as we gain a greater understanding of the relationship between the ascending aorta and bicuspid aortic valves. The gold standard of operative root replacement remains the exclusion composite valve graft replacement. The operative mortality is nearly zero and the long-term results are excellent. The risks of lifelong anticoagulation appear to be quite small given the current advances in mechanical valve technology. The freedom from a high-risk reoperation on the aortic root should not be understated [17]. Frank discussion about the risk of a second operation should be standard protocol when considering the option of valve-sparing root reconstruction. For patients with smaller aortic diameters, lesser degrees of AR or absolute contraindications to anticoagulation, aortic valve-sparing procedures may be appropriate. However, there is a steep learning curve to the procedure and the intermediate term results are less than ideal, especially in patients with CTDs. The application of these surgical techniques for patients with ascending aneurysms and bicuspid aortic valves is likely to increase as our understanding of this entity increases.

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Assessment of Myocardial Damage in Regurgitant Valvular Disease

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Outcome trials have dictated that valve replacement or repair in aortic regurgitation (AR) should be performed before the development of irreversible left ventricular (LV) dysfunction but not so early that the patient is unnecessarily exposed to infective endocarditis, embolic stroke, bleeding from anticoagulation or valvular degeneration. Accordingly, surgical intervention is performed before the patient becomes significantly symptomatic, demonstrates subnormal LV function or increased LV dimensions. However, despite interventions based on proposed estimates of LV ejection phase indices or chamber size, some patients do demonstrate poor postoperative results. On the other hand, many patients with impaired LV function do well postoperatively. It is reasonable to assume that in the pathophysiologic cascade of chronic valvular regurgitation, LV dysfunction should be preceded by progressive myocardial and subendocardial damage. With this premise, Borer et al. [1] evaluated the extent of myocardial damage using antimyosin antibodies in an experimental model of chronic AR. Intravenously administered radiolabeled antimyosin antibody allows evaluation of myocardial necrosis. Localization of antimyosin was not observed in control rabbits, consistent with the macroautoradiographic findings. In comparison, the animals with chronic AR present for 1 year demonstrated significant antimyosin uptake in scintigraphic and autoradiographic images, suggesting occurrence of myocyte damage. The investigators proposed that antimyosin uptake in AR could predict myocardial damage before the decline in LV systolic function. In an accompanying editorial to this study, we recognized a need for a non-invasive and repeatable investigative modality that is capable of accurately identifying the extent of myocardial damage [2]. The antimyosin scans evaluated myocardial dynamics, unlike conventional modalities that

address chamber dynamics. It seems logical that the integrity of the ventricular wall should be preserved to maintain its structure.

Necrosis and Myocardial Damage

Traditionally the myocyte death in heart has been equated to necrosis. Cell death by the necrotic process can be considered a 'passive' phenomenon, wherein the cell dies acutely as a result of exogenous noxious stimuli without an active response. In necrosis the cells swell and rupture, inducing an inflammatory process that is frequently followed by fibrosis. The hallmark of myocyte death by necrosis is the loss of cell membrane integrity, which has been exploited for noninvasive assessment of myocyte necrosis [3]. The intact cell membrane does not allow traffic of intracellular macromolecules from within intracellular compartment to the outside, nor does not it allow entry of any macromolecules into the cell. During necrosis, this cell membrane barrier function is lost. Various intracellular macromolecules, which are soluble in physiologic solutions, such as blood, are washed out of the dying cell and can be measured in the peripheral circulation as an indicator of the severity of necrosis. Such molecules include myoglobins, troponins, and myosin light chains. On the other hand, those intracellular macromolecules which are not soluble in physiologic solutions, such as myosin heavy chain, remain inside the necrotic myocyte carcass until removed by scavenging macrophages. Therefore, an antibody specifically directed against the myosin heavy chain should be able to distinguish between a necrotic cell, which has lost its sarcolemmal integrity, and a normal cell with an intact cellular membrane. Further, an appropriately radiolabeled antimyosin antibody may allow noninvasive assessment of necrotic myocytes by radionuclide imaging methods. The proof of principle was provided in an in vitro experiment, wherein neonatal murine myocytes were incubated with antimyosin-coated polystyrene beads. Scanning electron micrographic study revealed extrusion through cell membranes of myosin filaments which entangled the antimyosin beads. The indium-111-labeled antimyosin antibody has been used with a very high diagnostic accuracy to identify myocardial necrosis associated with acute myocardial infarction. In patients with acute coronary syndromes, the uptake is confined to a coronary arterial territorial distribution [4]. On the other hand, diffuse LV uptake is observed in cardiovascular diseases which are associated with multifocal myocardial necrosis such as myocarditis and cardiac transplant rejection [4, 5]. In patients presenting with recent worsening of heart failure, antimyosin antibody imaging has demonstrated near perfect sensitivity for the diagnosis of biopsy-verified myocarditis [6]. Similarly, patients with a negative scan have a negligible likelihood of histologically verified myocarditis.

However, in a large proportion of patients with a positive scan, myocarditis was not confirmed by endomyocardial biopsy. Such discordance has been attributed to sampling error of biopsy techniques and has been substantiated by a greater likelihood of functional improvement patients with a positive scan. On the other hand, in transplant recipients serial antimyosin scans performed in the first 3 months after transplantation provide useful prognostic information. Resolution of antimyosin uptake is usually associated with favorable outcomes and immunosuppressive treatments in such patients can be reduced to baseline levels and it is easier to wean from corticosteroids. Conversely, the patients with a persistent or increasing uptake suffer rejection-related complications such as accelerated vasculopathy, myocardial infarction, heart failure or require retransplantation. In these patients, closer surveillance and more aggressive immunosuppression have been proposed. It has been further suggested that antimyosin imaging can replace endomyocardial biopsy after the first year of transplantation in a large number of allograft recipients.

Apoptosis and Myocardial Damage

It is now increasingly realized that apoptosis, in addition to necrosis, is a distinct form of cell death that plays significant role in various cardiovascular diseases [7, 8]. Apoptosis is an active process of gene-directed cell suicide program. Whereas cells swell and explode in necrosis, they implode in the process of apoptosis with condensation of cytoplasm and fragmentation of nucleus as they are removed by neighboring cells or phagocytes almost without a trace. Apoptosis is almost never associated with an inflammatory response. In contrast, rupture of cells and extrusion of intracellular contents leads to an inflammatory reaction in necrotic death, which, in addition to loss of large number of cells, leads to healing by fibrosis with disruption of tissue architecture. During the upstream cascade of events in apoptosis, the damage to the cytoplasmic proteins and the nucleus is induced by the activation of very specific proteolytic enzymes such as caspase-3. Activation of caspase-3 also leads to significant changes in the cell membrane including random distribution of phospholipids with in the cell membrane. These phospholipid alterations can be exploited for the non-invasive identification of apoptosis.

The principle of noninvasive imaging of apoptosis can be conceptualized in as follows [9]. The sarcolemma is a lipid bilayer and distribution of phospholipids in these two layers is asymmetrical but specific, which is accomplished by two energy-requiring enzymes, *translocase* and *floppase*. These two enzymes are inactivated during apoptosis and activity of another enzyme, scrambalase, is initiated. Loss of orderly activity with institution of disorderly enzyme activation

leads to significant expression of phosphatidylserine on outer cell membrane, which is normally confined to the inner leaflet. A naturally occurring protein, annexin-A5, possesses a very high affinity for binding to phosphatidylserine and has been radiolabeled for noninvasive identification of apoptotic cells. Annexin-A5 imaging has been used successfully for the noninvasive localization of apoptosis associated with acute myocardial infarction, myocarditis, malignant intracardiac tumors, and cardiac allograft rejection [10–12].

Unlike necrosis, the genetically programmed process of apoptosis can be modified by use of various caspase inhibitors. A marked reduction to abrogation of apoptosis has been demonstrated in experimentally induced severe myocardial ischemia and early myocardial infarction. Similarly a protective effect of enipiride has also been shown. Enipiride is Na/H exchange inhibitor that restricts completion of apoptosis. On the other hand, long-term administration of caspase inhibitors has been associated with retardation of development of cardiomyopathy and heart failure along with preserved ventricular contractile indices in genetically-altered mice susceptible to development of peripartum heart failure. Recognition of apoptosis, because it can be regulated, appears to be a more useful clinical strategy. Annexin imaging has not been studied in regurgitant valvular diseases. Until investigated, it can only be presumed that myocardial damage manifested by apoptosis should precede occurrence of irreversible damage, and that its incidence can be regulated. Both presumptions should contribute to better management of valvular dysfunction.

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Cholesterol-Lowering Studies for Aortic Stenosis

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Valvular heart disease is emerging as one of the leading problems in clinical cardiology today, and despite the excellent ability to diagnose the problem early in its course, often prior to the onset of symptoms or clinical manifestations, to date the therapeutic options are limited to the timing of surgery or balloon valvuloplasty. Emerging notions of an association between valvular heart disease and atherosclerosis invite the possibility of intervening earlier in the course of the disease and limiting its progression. Understanding how the pathophysiology of the disease is changing as mankind evolves is critical to both diagnosis and management.

Valvular Heart Disease: Changes in Etiology

In the past the majority of valvular heart disease cases was limited to patients with a history of rheumatic fever, whereas today an aging population is presenting with degenerative valve disease as the leading etiology [1]. Prior to age 70, the etiologies of aortic valve stenosis include a bicuspid aortic valve (50%), post-inflammatory (25%) and degenerative (18%). After age 70, degenerative valve disease accounts for 48% and bicuspid aortic valve decreases to 23%, with post-inflammatory comprising the remainder [2]. In particular the aortic valve is affected, and, data from the Mayo Clinic shows that after age 70, degenerative aortic valvular stenosis (DAVS) is the leading cause of aortic stenosis (AS) [3]. In patients under age 70, a bicuspid aortic valve is the leading cause of AS; however, DAVS represents a significant proportion of the valvular heart disease in this population as well (fig. 1) [3].

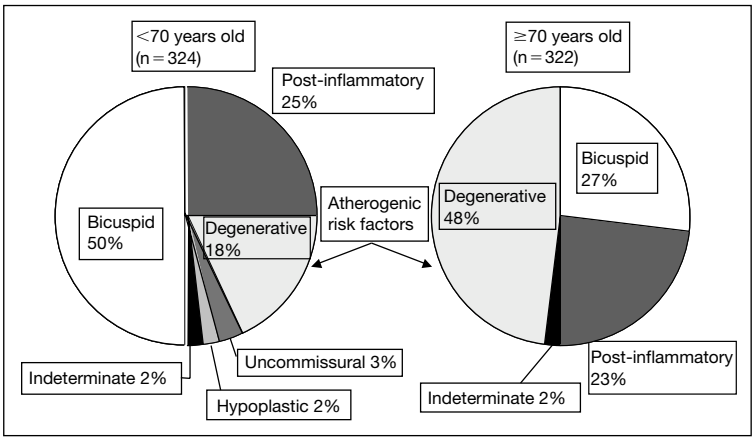


Fig. 1. Changing etiology of valvular AS [adapted from 2, with permission].

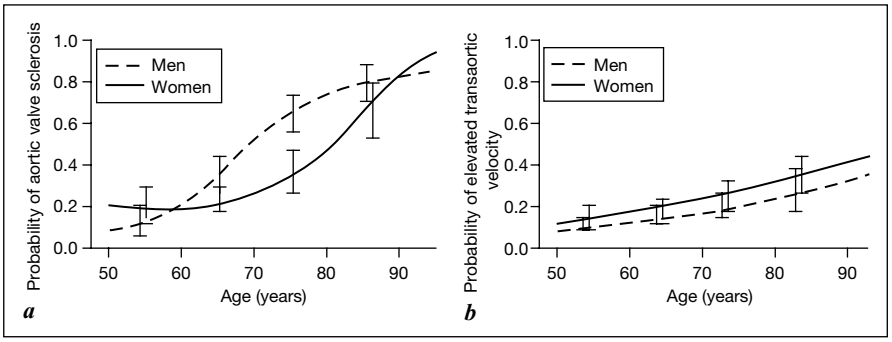


Fig. 2. Relation of age to AS (***a***) and transthoracic velocity (***b***) [reprinted from 5, with permission].

The Elderly: Aortic Valvular Sclerosis/Stenosis

Studies from the International Longevity Center in different countries demonstrate an aging worldwide population, and understanding that DAVS is a disease of the elderly, the implication is that more men and women are living to age 80 and will develop AS [4]. With age there is an increasing incidence of aortic valve calcification leading to aortic sclerosis and eventually AS (fig. 2) [5]. Data from the Mayo Clinic show that approximately 75% of patients have a sclerotic aortic valve by age 80, and that 30–40% of these patients have

Table 1. Aortic valve sclerosis and stenosis: association with cardiovascular mortality/morbidity in the elderly ≥65 years old [from 6, with permission]

Event	Normal valves, % (n = 3,919)	Aortic sclerosis, % (n = 1,610)	Aortic stenosis, % (n = 92)	p value
Death/any cause	14.9	21.9	41.3	<0.001
Death/cardio-vascular causes	6.1	10.1	19.6	<0.001
Myocardial infarction	6.0	8.6	11.3	<0.001
Angina	11.0	13.0	24.3	<0.001
Congestive heart failure	8.9	12.6	24.7	<0.001
Stroke	6.3	8.0	11.6	0.003

Table 2. Relation of aortic valve area to mean pressure gradient [from 7, with permission]

Aortic valve area cm^2	Mean gradient mm Hg
4	1
3	3
2	7
1	26
0.9	32
0.8	41
0.7	53
0.6	73
0.5	105

developed AS. In addition, the diagnosis of AS worsens the prognosis of the most commonly associated cardiovascular conditions (table 1) [6]. Aortic sclerosis is distinguished from stenosis by the degree of valvular impairment. Initially the valve leaflets become thickened, but outflow is not obstructed. Not all aortic valvular sclerosis progresses to stenosis, but if the process continues, the functional valve area decreases, the obstruction to outflow increases, and a gradient is generated (table 2) [7]. While little hemodynamic effect is seen initially, as the valve area decreases to half its normal size, e.g., as it progressively decreases from 2 to 1 cm^2, there is a dramatic increase in the gradient leading to pressure overload of the left ventricle.

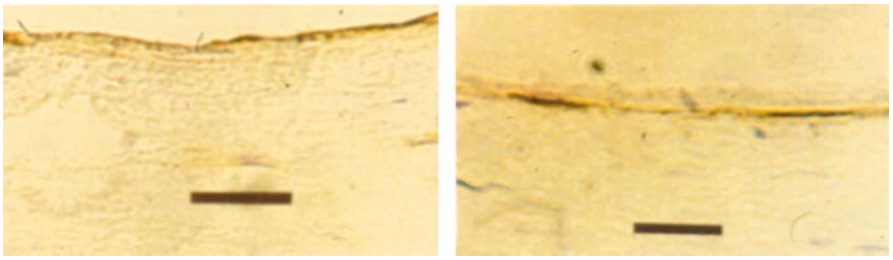
Table 3. Reports of risk factors associated with AS [from 7, with permission]

Study	Patients, n	Age, years	Positive risk factors
Deutscher (1983) Case control	54 cases, 359 controls	NA	Cholesterol, diabetes
Hoagland (1985) Case control	105 cases (41 BAV), 439 controls	66	None
Aronow (1987) Hospital survey	571	82	Hypertension, cholesterol, diabetes, low HDL
Mohler (1991) Retrospective	39 BAV, 30 degenerative	62	Low triglycerides
Lindroos (1994) Prospective	501	>75	Smoking, hypertension
Boon (1997) Retrospective database	515 cases, 562 controls	67	Hypertension, cholesterol
Stewart (1997) Prospective	5,201	73	Hypertension, cholesterol
Wilmhurst (1999) Prospective case control	20 cases (6 BAV), 20 controls (no BAV)	66	Cholesterol
Palta (2000) Retrospective	170 cases	71	Smoking
Chan (2001) Prospective	48 cases (BAV), 52 controls	56	Hypertension, cholesterol
Pohle (2001) Prospective	104 cases	65	Cholesterol, progression
Aronow (2001) Retrospective	205 cases, 505 controls	⩾60	Smoking, hypertension, diabetes, statins

BAV = Bicuspid aortic valve; HDL = high-density lipoproteins.

Atherogenic Risk Factors and Aortic Valvular Stenosis

The potential now exists for an epidemic of significant aortic valvular stenosis as aortic sclerosis progresses in people over the age of 70–80 years. The broad scope of the problem has focused attention on etiological considerations that in turn may lead to improved prevention, diagnosis, and management. The increase in DAVS in the elderly has raised interest in atherogenic risk factors known to predominate in this age group. A positive relationship has been demonstrated between age, male gender, smoking, hypertension, diabetes, low-density lipoprotein (LDL), and high-density lipoproteins and the progression of AS (table 3) [7, 8]. Furthermore, not receiving a statin has been positively



a ***b***

Fig. 3. Similarity of pathologic processes in atherosclerosis (***a***) and DAVS (***b***) (see text for description).

associated with an increase in the progression of valvular disease [9]. The similarities that have emerged between DAVS and atherosclerosis focus on exposure of the endothelium to macrophages, as some of the same adhesion molecules are present on both the valves and vascular endothelium (fig. 3) [10]. As such the mechanism of aortic valve degeneration and subsequent sclerosis may be similar to the atherosclerotic process occurring in the coronary vasculature.

Atherogenesis of the Aortic Valve: Aortic Stenosis and the Potential Role of Statins

New biologic insight into development of AS suggests that infiltration and oxidation of lipoproteins are important in initiation of the early valvular lesion [11]. Apolipoproteins accumulate in the valve and are associated with the majority of extracellular valvular lipid. These findings are consistent with the hypothesis that lipoprotein accumulation in the aortic valve contributes to pathogenesis of degenerative AS [12].

In the normal coronary artery, a complex set of events combine to maintain homeostasis in the integrity of the vessel wall. Importantly, laminar flow is unimpeded and the cascade of events, including macrophage adhesion and migration with smooth muscle cell proliferation, does not occur (fig. 4). However, with the development of atherosclerotic disease in the coronary arteries, there is disruption of laminar flow, and resulting turbulent blood flow causes damage to the endothelium (fig. 5). Endothelial injury allows deposition of circulating lipoproteins into the subendothelial space. Sequestered in a microenvironment in which actively metabolizing cells (i.e., resident fibroblasts and endothelial cells) consume antioxidants, these lipoproteins become minimally oxidized and potentially stimulate leukocyte adhesion. Circulating monocytes now react with the damaged endothelium, entering the vessel wall. After more

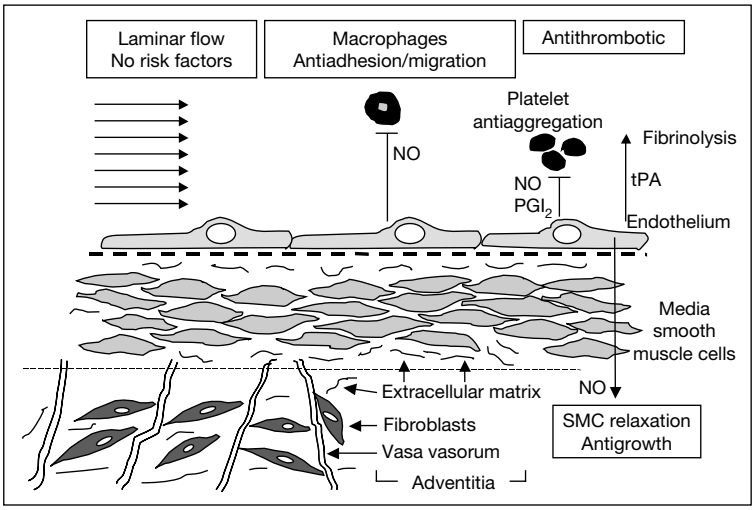


Fig. 4. Homeostasis of normal coronary arterial vessel wall. NO = Nitric oxide; PGI_2 = prostacyclin; SMC = smooth muscle cell; tPA = tissue plasminogen activator (see text for description).

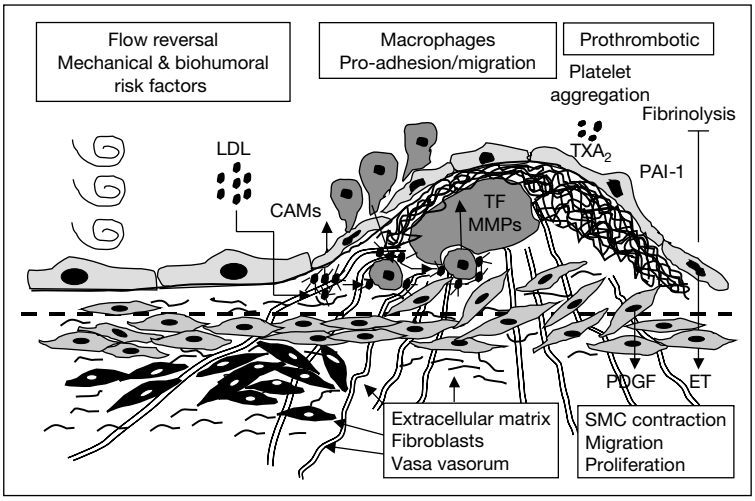


Fig. 5. Alterations of coronary arterial vessel wall in atherosclerosis. CAMs = Cell adhesion molecules; ET = endothelin; LDL = low-density lipoprotein; MMPs = matrix metalloproteases; PAI-1 = plasminogen activation inhibitor-1; PDGF = platelet-derived growth factor; SMC = smooth muscle cell; TF = tissue factor; tPA = tissue plasminogen activator; TXA_2 = thromboxane A_2 (see text for description).

extensive oxidative modification, lipoproteins taken up by macrophage scavenger receptors, result in foam cell formation [12]. At the same time LDL is actively deposited, and in turn there is disruption of both the smooth muscle cell layer and the extracellular matrix leading to proliferation, macrophage migration, and vasoconstriction. Understanding that statins can reverse this process coupled with the finding that there is an increased incidence of AS in patients not on statins has generated interest in treatment strategies such as statins for valvular stenosis.

While the similarities between coronary atherosclerotic plaque and valvular AS are intriguing, there are important differences as well. A critical difference between the aortic valve and the coronary arteries lies in the role of the endothelium. DAVS involves calcification of the leaflets, which over time become stiff and limit the flow of blood. The initial event leading to valve sclerosis, as explained earlier, is one of injury associated with the deposition of lipid that is oxidized in the same way as in the atherosclerotic process in the arteries [11]. The loss of endothelium on the aortic valve, as described earlier, occurs much more rapidly, and the subsequent fibrotic process takes place even before there is significant fat deposition into the vessel wall, as a reaction to injury. Calcification occurs where fibrotic tissue is developing, which is why degenerative aortic valve stenosis can worsen rapidly under high flow conditions, as compared with coronary artery disease that may take decades to develop. As such, the role of statins is not likely to be the same on the aortic valve leaflets as it is in the coronary arteries. Rather, the process likely involves improving endothelial cell function, such that the process of calcification and fibrosis are avoided in the first place. Recently published data supports the concept that in patients on statins, as compared with controls having the same baseline aortic valve area, there was less progression of disease as indicated by a smaller increase in mean pressure gradient and a smaller decrease in aortic valve area [11].

Summarizing these important processes, flow in both the coronary arteries and across the aortic valve may be the inciting event that leads to endothelial cell injury prompting monocyte and macrophage migration and lipid deposition with subsequent oxidization. As such, flow itself would be inducing the inflammation that propagates the cascade. In the coronary arteries, lipid-lowering agents work by removing fat, which in turn initiates fibrosis and calcification that increases plaque stability. At the level of the aortic valve, statins may be acting to limit the initial inflammatory injury to the endothelium covering the valve leaflets. In the coronary arteries, under the influence of statin therapy, a fibrotic process replaces the lipid deposition, and calcification takes place in that artery to convert a dangerously friable, weak, and rupture prone plaque into a more stable one. On the aortic valve, the effect of statins may be to lessen

Table 4. Prevalence of coronary artery disease in older men and women with and without aortic valve cuspal calcium [from 13, with permission]

	Coronary artery disease, %	
	aortic cuspal calcium	no aortic cuspal calcium
Men (n = 752)	57	38*
Women (n = 1,663)	54	37*
Men and women	54	37*

*$p < 0.0001$.

endothelial inflammation, resulting in less damage to the endothelial layer, less fibrosis and less calcification, and subsequently less stenosis.

Relation and Prevalence of Calcification of the Aortic Valve and of the Coronary Arteries

Electron beam computed tomography (EBCT) has also contributed to the association between aortic valve calcification and coronary calcification. Among patients who have calcium in the aortic valve by EBCT, 54–57% have coronary artery disease (table 4) [9, 13]. If there is no aortic valve calcification, the incidence of coronary artery disease is much less. Similarly, among patients with aortic atherosclerotic disease, for example, those with plaque in the thoracic aorta, 86% have significant aortic valvular stenosis (table 5) [5]. In terms of aortic valve calcification lesions, if one observes an aortic plaque of >4 mm diameter in a patient, 43% of these patients already have significant valvular AS. This finding suggests a relationship between both coronary and aortic plaque burden, and the aortic valve atherosclerotic process.

Progression of Aortic Valvular Stenosis and Its Modification with Statins

With regard to risk factors, hypertension and hyperlipidemia are the most highly associated risk factors for aortic valvular sclerosis and stenosis. Cigarette smoking has also been linked with DAVS (table 3) [14]. Once the

Table 5. Aortic atherosclerosis in subjects with aortic valve sclerosis and different transaortic velocities [from 5, with permission]

	Aortic valve sclerosis, %		Transaortic velocities, %	
	present	absent	upper quintile	lower quintile
Any aortic plaque	86$^{\times}$	60	75	68
Plaque-ascending aorta	12$^{\times}$	2	15^{+}	4
Aortic plaque ≥4 mm	54$^{\times}$	16	43*	27
Aortic plaque ≥6 mm	20$^{\times}$	5	16	9

*$p \leq 0.05$; $^{+}p < 0.01$; $^{\times}p < 0.001$.

Table 6. Rate of progression of AS in patients at least 60 years old (n = 236) [from 15, with permission]

	Mean reduction in aortic valve area, cm^2/year	Mean increase in systolic gradient across aortic valve, mm Hg/year
Mild AS	0.12 ± 0.10	4.31 ± 4.17
Moderate AS	0.11 ± 0.11	7.12 ± 7.46
Severe AS	0.11 ± 0.11	15.78 ± 17.82
Men aged 60–74 years	0.12 ± 0.12	6.97 ± 5.93
Men aged ≥75 years	0.11 ± 0.10	9.26 ± 5.85
Women aged 60–74 years	0.08 ± 0.06	3.04 ± 2.66
Women aged ≥75 years	0.12 ± 0.13	10.30 ± 12.88
MAC	0.12 ± 0.12	5.39 ± 4.32
No MAC	0.10 ± 0.08	2.60 ± 3.09

AS = Aortic stenosis; MAC = mitral annular calcium.

process of DAVS is detected, it progresses at a fairly predictable rate. In a study based at Mount Sinai Hospital, New York, the rate of progression of AS in 236 patients over the age of 60 years was followed with at least two echocardiographic evaluations over a 1-year period (table 6) [15]. On a yearly basis, regardless of underlying conditions, the systolic pressure gradient across the aortic valve increased by about 4–10 mm Hg while the aortic valve area decreased by approximately 0.1 cm^2 over the same time period.

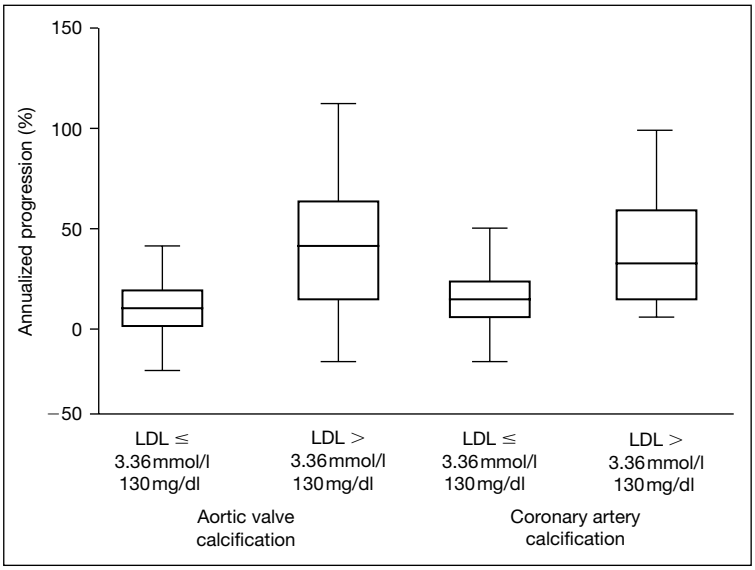


Fig. 6. Relationship between low-density lipoproteins (LDL) and aortic valve and coronary arterial calcification [from 16, with permission].

Whereas the risk factors appear to correlate, the next step is to establish benefit from treatment with the use of cholesterol-lowering medications. Data from Pohle et al. [16] in Germany points out the relationship between LDL and aortic valve calcification and coronary calcification. They studied the risk factor profile, disease of the aortic valve, and disease of the coronary arteries, and found that progression of the aortic valve disease as well as disease in the coronary arteries is related to the level of cholesterol at baseline (fig. 6). Notably, the higher the level of LDL, the more rapid is the progression of both the coronary calcification and the aortic valve calcification, as the two appear to be closely linked. Furthermore, when the use of statins is incorporated into the progression of AS, regardless of the initial level of LDL, the use of statins is associated with a smaller increase in peak systolic pressure gradient across the aortic valve (table 7) [9]. When the initial LDL cholesterol level was ≥125 mg/dl and patients were not treated with statins, the progression of the peak systolic pressure gradient was 6.3 mm Hg per year. When the initial LDL cholesterol was ≥125 mg/dl and statins were administered, gradient progression was 3.4 mm Hg per year. Similar findings have been observed by others (fig. 7) [17].

The weight of the evidence at this time supports a role of similar risk factors in both coronary atherosclerosis and DAVS, along with a role of statins in slowing the progression of AS. The concept now being developed begins

Table 7. Association of serum lipids and use of statins with progression (≥2 years) of mild valvular AS [from 9, with permission]

	Increase in peak systolic gradient across aortic valve/year, mm Hg	p value
1 Initial serum LDL cholesterol ≥125 mg/dl no statins (n = 69)	6.3 ± 1.4	<0.0001*
2 Initial serum LDL cholesterol ≥125 mg/dl statins (n = 62)	3.4 ± 1.0	
3 Initial serum LDL cholesterol <125 mg/dl no statins (n = 49)	3.1 ± 1.1	
Follow-up		
LDL cholesterol ≥125 mg/dl (n = 79)	6.1 ± 1.5	<0.0001
LDL cholesterol <125 mg/dl (n = 101)	3.2 ± 0.9	
HDL cholesterol ≤35 mg/dl (n = 41)	5.5 ± 2.3	0.006
HDL cholesterol >35 mg/dl (n = 139)	4.1 ± 1.7	
Triglycerides ≥190 mg/dl (15)	4.8 ± 1.9	0.534
Triglycerides <190 mg/dl (n = 165)	4.4 ± 1.9	

HDL = High-density lipoprotein; LDL = low-density lipoprotein; *p < 0.0001 comparing 1 with 2, and 1 with 3.

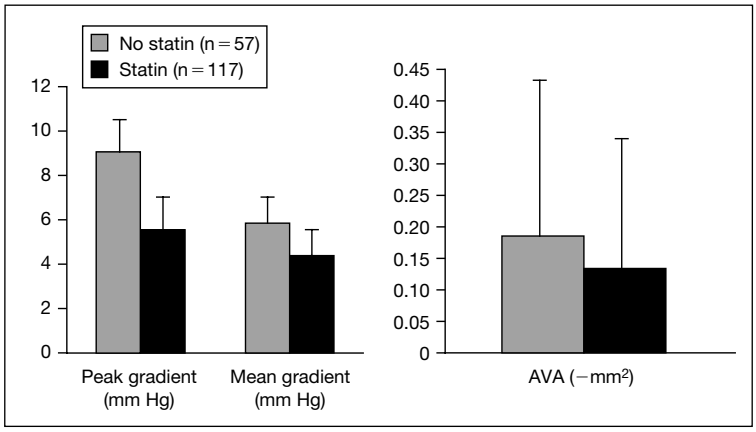


Fig. 7. Effect of statins on progression of AS. AVA = Aortic valve area [from 8, with permission].

Table 8. Proposed research protocol for assessment of AS progression and statins [from Fuster et al., unpubl. results]

Echocardiographic screening of patients ≥65 years old	
↓	
Aortic stenosis (valve area <2.0 cm^2, peak gradient >10 mm Hg)	
↓	
Statins (n = 147) vs. control (n = 147)	
↓	
6 weeks and 6 months: lipid profile, LFTs, CK	
1 year and 2 years	1. Echo-Doppler study 2. UFCT 3. MRI 4. Mini-Mental Examination 5. Blood tests

CK = Creatine kinase; LFTs = liver function tests; MRI = magnetic resonance imaging; UFCT = ultrafast computed tomography.

with vascular biology and the idea that hypertension and high flow velocities are critical in damaging the endothelium of the aortic valve whereas hypercholesterolemia accelerates the process. If one treats the hyperlipidemia or the hypertension, progression of the disease can be slowed, probably because there is less inflammation and subsequent damage to the endothelium with the less fibrosis. Therefore, when we treat risk factors for coronary artery disease, while the mechanisms are different, the progression of AS may also be slowed. These findings have led to a prospective randomized study involving collaboration of the Mayo Clinic and our group at Mt. Sinai Medical Center in patients over the age of 65 years that have AS with a valve area <2 cm^2 and a peak pressure gradient of >10 mm Hg (table 8). The primary endpoint is to determine if in patients on statin therapy compared with placebo there is less progression of the disease as measured by changes in the aortic valve area. A secondary endpoint is total aortic valvular calcification and changes in the tissue of the aortic valve as determined by standardized ultrasonography and by magnetic resonance imaging. Ultimately the goal is to better understand the relationship between risk factors for atherosclerotic disease, aortic valve stenosis, and progression of both.

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Perspectives on Diseases of the Thoracic Aorta

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The natural history of aneurysms of the thoracic aorta has never been completely known. As a corollary, rigorous scientific information on appropriate criteria for elective aneurysm resection of thoracic aneurysms has been lacking. As late as 1995, our literature review disclosed over 294 papers on *how* to do thoracic aortic operations, but only 7 papers on the natural history of aortic aneurysm or *when* to operate on the thoracic aorta. Our team at Yale University took on the challenge to define the behavior of these aneurysms. These investigations were done in conjunction with Dr. John Rizzo of the School of Epidemiology and Public Health, who developed specific statistical methodologies for this purpose. Our computerized database now includes information on over 1,400 patients with thoracic aortic aneurysm, including over 4,000 tabulated serial imaging studies and over 4,000 patient-years of follow-up. This database and these methods of analysis have permitted the assessment of multiple fundamental topics and questions regarding the natural behavior of the thoracic aorta and the development of appropriate criteria for surgical intervention. In the following paragraphs, we will address the rate at which the aneurysmal aorta grows, the size at which complications in the natural history of the aorta occur, the yearly risk of rupture or dissection in aortas of different sizes, the appropriate criteria for elective surgical resection of the thoracic aorta, and insights into the etiology of aneurysm and dissection of the thoracic aorta.

Growth Rate of the Thoracic Aorta

Calculation of growth rate of the aorta is more complicated than simply subtracting the original size of the aorta from the current size and dividing by

the length of follow-up. Different modalities (echocardiographic, computerized tomography scan, and magnetic resonance imaging) may give different values. There may be inter-observer variability in size assessment, and, most importantly, some scans may show *smaller* size than original measurements. (This does not imply that the aorta gets smaller, but rather that there is variability in size measurement, especially in huge samples of data.) If these negative changes are truncated, then falsely high growth rates will result. Via specifically developed statistical methods designed to account for these potential sources of error, our team has found that the aneurysmal thoracic aorta grows, on average, at 0.10 cm/year. The descending aorta grows faster than the ascending aorta, at 0.19 vs. 0.07 cm/year. Also, the larger the aorta, at initial evaluation, the faster it grows.

Size at Time of Rupture or Dissection

Critical to decision-making in aortic surgery is an understanding of when complications occur in the natural history of unoperated thoracic aortic aneurysms. In the case of the thoracic aorta, the two most important complications are rupture and dissection. To know when these complications occur would permit rational decision-making regarding elective, preemptive surgical intervention to prevent rupture and dissection.

It should be emphasized that these criteria apply to asymptomatic aneurysms and that *symptomatic aneurysms should be resected regardless of size*. Caregivers have misinterpreted size criteria to the point of not resecting symptomatic aortic aneurysms that have not achieved the criterion levels. The usual symptom produced by an aortic aneurysm is pain. For ascending aneurysms, this pain is usually felt anteriorly under the sternum. For descending thoracic aneurysms, the pain is usually felt in the interscapular region of the upper back. For thoracoabdominal aneurysms, the pain is usually felt lower in the back and in the left flank. Other symptoms may occasionally be produced by thoracic aortic aneurysms, including bronchial obstruction, esophageal obstruction, and phrenic nerve dysfunction, which also constitute indications for surgical intervention.

It is not necessarily easy to distinguish aneurysm-related pain from pain of other sources. The patient usually has a good sense as to whether his pain is originating from muscles and joints. The clinician usually gets an additional sense on questioning. If the pain is influenced by motion or position it is more likely musculoskeletal in origin. If there is a history of lumbosacral spine disease or chronic low back pain the symptoms may not be aortic in origin. Pain felt in the interscapular region of the back is almost certainly related to an extant thoracic

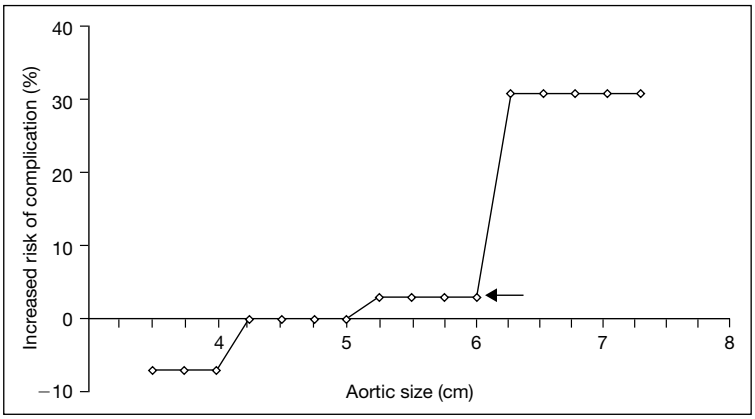

Fig. 1. Thoracic aortic size and risk of rupture or dissection of aortic aneurysms. Arrow indicates 'hinge' point [from 1, with permission].

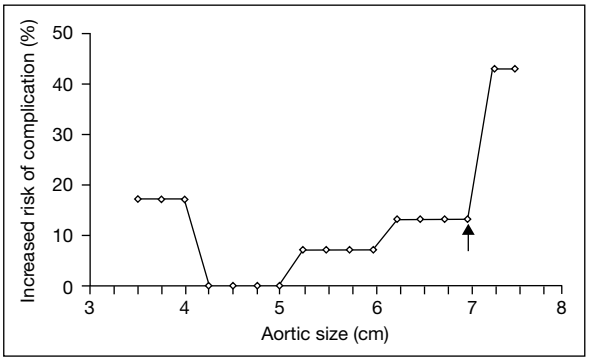

Fig. 2. Descending aortic size and risk of rupture or dissection of aortic aneurysms. Arrow indicates 'hinge' point [from 1, with permission].

aortic aneurysm. Perhaps the most important point to make is the following: one must presume that the pain is aortic in origin if no other cause can be conclusively established. This is the only posture that can prevent rupture.

Our initial statistical analysis revealed sharp 'hinge points' in aortic size at which rupture or dissection occurred as shown in figure 1 [1]. For the thoracic aorta, the hinge point is seen at 6.0 cm. By the time patients' aortas reach this size, 31% have suffered rupture or dissection of the thoracic aorta. For the descending aorta, the hinge point is found at 7.0 cm (fig. 2 [1]). By the time patients reach this size, 43% have suffered rupture or dissection [2].

Table 1. Size criteria (in cm) for surgical intervention for symptomatic thoracic aortic aneurysm [from 1, with permission]

Area of thoracic aorta	Non-Marfan's	Marfan's (or familial)
Ascending	5.5	5.0
Descending	6.5	6.0

Table 2. Aortic manifestations of connective tissue disease (in %)

Aortic tissue disease	Incidence	Incidence of aortic dissection
Marfan's syndrome	0.01	40
Bicuspid aortic valve	1–2	5

It is important to realize that if a surgeon were to wait for the aorta to achieve the median size observed at the time of complications in order to intervene, rupture or dissection would occur in half of the patients. Accordingly, it is important to intervene before the median value is attained. Our recommendations take this factor into account, permitting preemptive surgical extirpation before rupture or dissection should be expected in the majority of patients.

Our current recommendations are as indicated below in table 1. These criteria are based on the 'hinge points' noted above. It is well known that patients with Marfan's disease are prone to unpredictable dissection at an early size. For this reason, we intervene earlier in Marfan's patients.

We have also observed familial patterns of aortic diseases. For patients with a positive family history, we apply the same criteria as we do for Marfan's disease, as our data indicate malignant behavior for these patients as well. It is also recognized more and more that patients with a bicuspid aortic valve commonly also have variant connective tissue in the aortic wall that predisposes to aneurysm formation. We use the lower intervention dimensions for patients with bicuspid aortic valves as well. As table 2 indicates, bicuspid aortic valve is actually a more common cause of aortic dissection than Marfan's disease. While 40% of patients with Marfan's disease can expect dissection, Marfan's disease occurs only in 1 of 10,000 individuals. In bicuspid aortic valve, while chance of dissection is only 1 in 20, the underlying condition is much more common. In fact, bicuspid aortic valve is the most common congenital disorder affecting the human heart affecting one or two of each 100 live births. The mathematics of these ratios indicate that bicuspid aortic valve is associated with many more

Table 3. Yearly complication rates (in %) of aortic aneurysms as a function of aortic size [from 1, with permission]

Complication	Aortic size, cm			
	≥3.5 to <4	≥4 to <5	≥5 to <6	≥6
Rupture	0.0	0.3	1.7	3.6
Dissection	2.2	1.5	2.5	3.7
Death	5.9	4.6	4.8	10.8
Any of above	7.2	5.3	6.5	14.1

aortic dissections than Marfan's disease. It is important to recognize that dissection usually occurs before the onset of symptoms of aortic stenosis or insufficiency related to the valve disease itself. All the evidence points toward a primary structural deficiency in the aortas of patients with bicuspid aortic valves. As is well known, aortic coarctation is closely interrelated with bicuspid aortic valve and is another condition that predisposes to aortic dissection.

Yearly Rates of Rupture or Dissection for Thoracic Aortic Aneurysms

The discussion above addresses the cumulative *lifetime* rates of dissection or rupture relative to the time required for the aorta to reach a certain size. To determine the *yearly* risk of complications from the natural history of thoracic aortic aneurysm has been more or less a 'holy grail' because such a determination requires extremely robust data. Enough firm end-points must be reached within a year's time to permit analysis for different size strata. Dr. Randall Griepp and his group at Mount Sinai [3] were able to accomplish this goal, elegantly producing an equation which permits calculation of the yearly rate of rupture, λ, of a thoracic aneurysm: $\mathrm{Ln}\,\lambda = -21.055 + 0.0093$ (age) $+ 0.842$ (pain) $+ 1.282$ (COPD) $+ 0.643$ (desc dia) $+ 0.405$ (abd dia), where desc dia = maximal diameter of descending aorta (in cm), abd dia = maximal diameter of abdominal aorta (in cm), pain and COPD are scored 0 if absent and 1 if present. Probability of rupture within 1 year $= 1 - e^{-1(365)}$.

Recently we also have been able to produce calculations of yearly rates of rupture or other complications based on size of the aorta from the Yale database [4]. We have chosen to express these as yearly rates based simply on the size of the aorta as shown in table 3.

These data all point to a diameter of 6 cm as representing a very dangerous threshold. As a mnemonic point of reference, we often indicate that a 6-cm

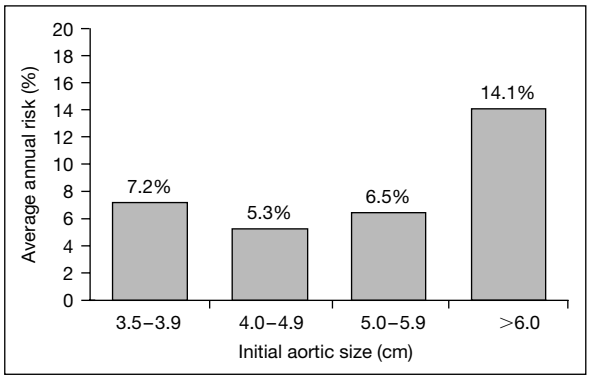

Fig. 3. Yearly risk of rupture, dissection, or death complicating aortic aneurysms [from 1, with permission].

aneurysm is about the diameter of a soft-drink can. When a thoracic aortic aneurysm achieves the diameter of a soda can, it has certainly reached the point where it poses a major risk to the patient.

The intent of these analyses is to permit accurate decision-making for patients being considered for preemptive surgical extirpation of thoracic aneurysms. These data allow the physician to form a reasonable estimate of the patient's risk of dissection, rupture, or death from his/her diseased aorta for each future year of his life if the aorta is not resected. The risk of rupture, dissection, or death based on aortic size is presented graphically in figure 3.

Risks of Aortic Surgery

It is certainly helpful to know numerically and statistically the cumulative and yearly rates of rupture, dissection and death associated with an aortic aneurysm of a specific size. On the other hand, the equation is incomplete without consideration of the risks inherent in elective, prophylactic surgical extirpation of the thoracic aorta. We have recently published reports on both mortality rates and rates of other complications after aortic surgery [5]. For the most experienced operators at our institution in the most recent 3-year period, these rates are as indicated in table 4, which includes data for all comers. Rates for elective patients presumably would be lower. The rates shown are typical of those at other centers with a focused interest and specific programs in thoracic aortic diseases.

By considering the rates of natural rupture, dissection and death from the thoracic aneurysm itself versus the risks of operation, the physician can make

Table 4. Current risks of thoracic aortic surgery (in %) [adapted from 6, with permission]

Aortic aneurysm location	Mortality	Stroke	Paraplegia
Ascending/arch	2.5	8.3	0
Descending/thoracoabdominal	8.2	4.1	2.0

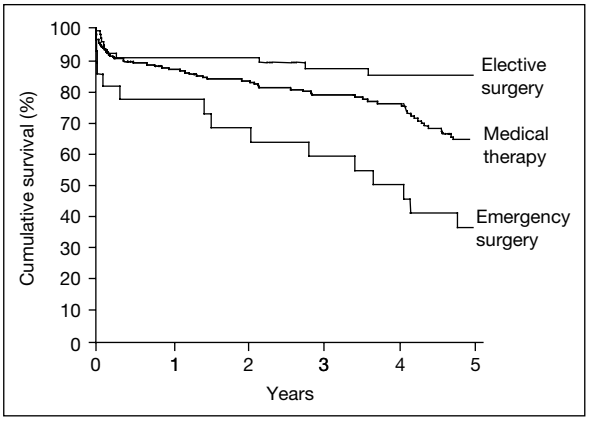

Fig. 4. Long-term survival according to treatment status for surgery for aortic aneurysms [from 4, with permission].

an informed recommendation to the patient about elective, preemptive surgical extirpation of an aortic aneurysm. We also find that the patients and their families, once provided natural history and surgical risk data, often have strong opinions of their own. Some families are reluctant to undergo major surgery, with significant attendant risks, for an asymptomatic problem. However, most families seem not to be comfortable until elective, preemptive surgical extirpation of the aneurysm has been performed.

One more very important general point needs to be considered. Once the aorta has suffered the complication of dissection, the prognosis will henceforth be adversely affected. This is illustrated in figure 4. The patients who had undergone urgent operations not only had a higher early mortality rate, but their long-term survival curve was dramatically poorer, whereas the electively operated patients approached a survival rate very similar to that of the normal population (fig. 4) [6].

Etiology of Aortic Aneurysm

The genetics of Marfan's disease have been well delineated, with over 85 mutations identified at one locus on the fibrillin gene. It is being increasingly appreciated that non-Marfan's patients also manifest familial clustering of thoracic aortic aneurysms and dissections. It is truly impressive how often one obtains an affirmative answer in asking the patient with an aneurysm the questions: 'Do you have any family members with aneurysms anywhere in their bodies? Did any of your relatives die suddenly or unexpectedly, of apparent cardiac causes?' In our database, we have done detailed family trees on 300 of our 1,400 patients, and have observed that 21% of our probands with an aneurysm have a first-order relative with a known or likely aortic aneurysm. The true number is certainly much higher, as these estimates are based only on family interviews and not on head-to-toe imaging of relatives. Figure 5 shows the family trees for the first genealogical group we analyzed. The most likely pattern of inheritance appears to be autosomal dominant with incomplete penetrance [7]. Autosomal recessive and sex-linked genes, as well as more complex pedigrees, have been demonstrated as well. We have found that the aorta of a patient with a positive family history grows faster than that of patients without a family history and faster even than that of patients with Marfan's syndrome. This rapid growth rate in the familial patients strongly suggests an inherent genetic defect in the structural integrity of the aortic wall in these patients.

Having embarked on a concerted effort to identify the errant genes responsible for thoracic aortic aneurysm and dissection, we are performing both linkage analysis in families as well as single nucleotide polymorphism analysis in large groups of patients with aneurysm as well as controls. We are hopeful that we will soon achieve identification of at least some of the mutations responsible for these aortic disorders.

What About Aortic Ulcer and Intramural Hematoma of the Aorta?

Aortic ulcer looks just like a duodenal ulcer on radiographic examination, but affects the thoracic aorta with an outpouching of dye extending beyond the aortic lumen. Intramural hematoma presents as a crescentic collection of blood in the wall of the aorta. Both conditions are distinguished by their lack of a flap traversing the aortic lumen. In this respect they differ from typical dissection, which does have a flap [8]. We say, 'No flap, no dissection'.

As these variant pathologic conditions are largely diseases of the recent era of three-dimensional aortic imaging by computerized tomography, magnetic

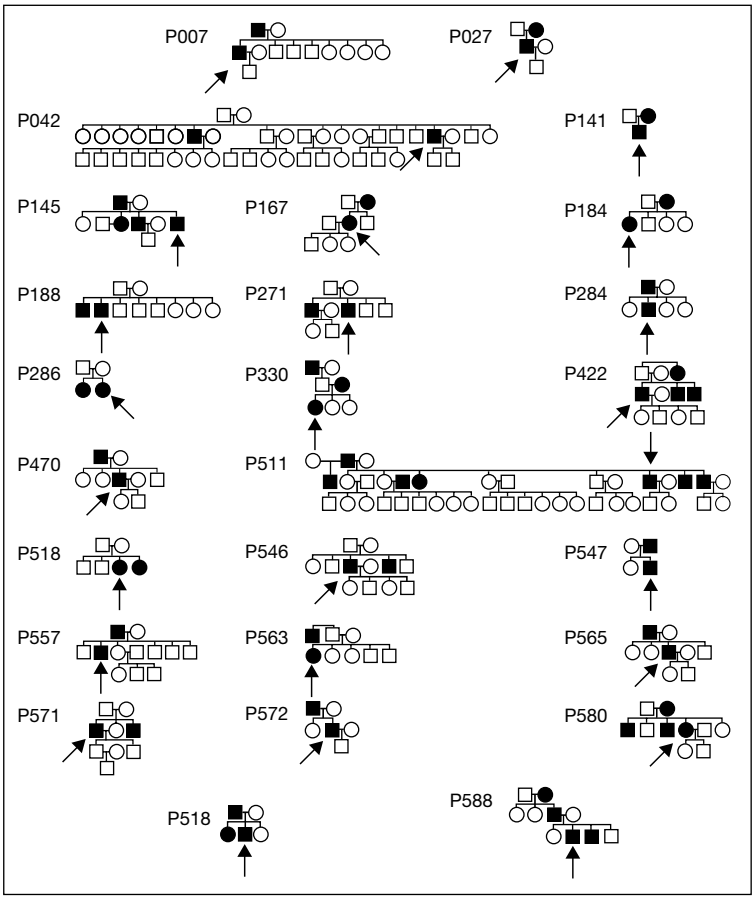

Fig. 5. Genealogy of patients with thoracic aortic aneurysms and dissections. Solid circles and bars = affected individuals. More than one specific complication was present in same patients. Arrows = proband [from 7, with permission].

resonance imaging and echocardiography, their behavior over time is just now being clarified [9]. Our follow-up has recently been extended to the medium term (mean 47 months). We have noted three characteristics that render these lesions even more serious than typical dissection: (1) the rate of rupture on initial presentation is high (45%); (2) the rate of radiographic progression is high (>50%), and (3) late rupture does occur frequently and is lethal. Accordingly, for these variant lesions we are now recommending routine surgical correction during the initial hospital admission, providing that age, debility, or co-morbidity do not render the patient an inappropriate surgical candidate.

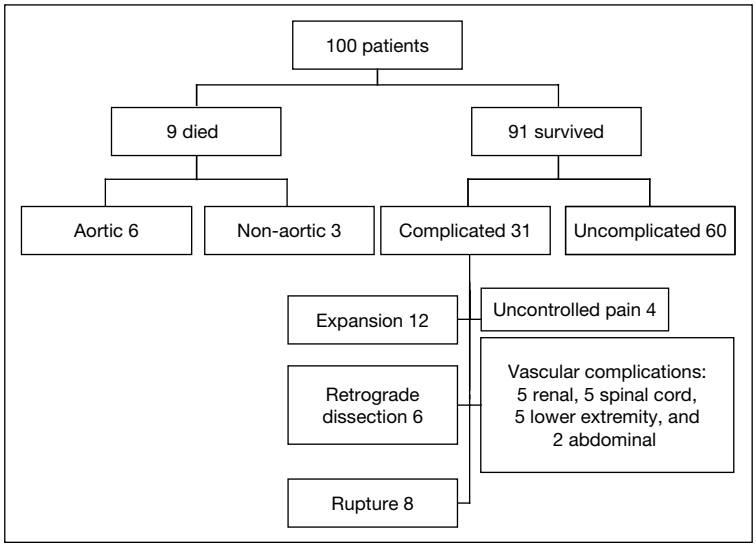

Fig. 6. Early outcomes of 100 consecutive cases of acute descending aortic dissection.

Surgery for Realized Dissection

Preemptive intervention criteria are aimed at preventing dissection before it occurs. What if dissection is the presenting symptom? What are the indications for intervention?

Type A (ascending) dissection requires urgent intervention to prevent mortality. We know historically that, if not promptly operated, most patients die, from intrapericardial rupture and tamponade, from cardiogenic shock, from acute aortic insufficiency, from free rupture into the pleural space, or from coronary dissection and cardiac ischemia. Surgery is uniformly indicated.

For type B (descending) dissection, surgery is not indicated. Medical treatment with 'anti-impulse' therapy suffices. We recently reviewed 100 consecutive patients presenting with acute type B aortic dissection. As seen in figure 6, nearly two-thirds had a good outcome with medical management alone. The remainder died or required surgery. A 'complication-specific' approach is warranted for acute type B dissection, with surgery only for specific complications.

For patients with chronic type A dissection who have miraculously 'cheated' death during their original presentation, we usually recommend elective surgical correction. For patients with chronic type B dissection, we monitor the aortic size and intervene when it reaches the standard aneurysm size criteria enumerated above.

Conclusion

An analogy suggests itself between elective, preemptive resection of an asymptomatic thoracic aortic aneurysm and refinancing a mortgage. Each has up-front costs. For the mortgage, there are up-front closing costs. For the aneurysm, there is the risk of operation. Both refinancing and aneurysm resection have major, long-term subsequent benefits. For the mortgage, there will be a lower long-term interest rate. For the aneurysm, there will be virtual elimination of risk of rupture from the resected aortic segment.

The data presented above permit the conclusion that preemptive aortic surgery for large aneurysms can be carried out with a mortality 'closing cost' less than (or for ascending and arch, *much* less than) 1 year's natural history of rupture, dissection, or aneurysm-related death.

Almost a century ago, Sir William Osler said, 'There is no condition more conducive to clinical humility than aneurysm of the thoracic aorta.' This is just as true today as it was at that time. However, we are beginning to tame the fierce enemy of thoracic aortic aneurysm and dissection. By clarifying size at time of rupture, we are able to strike preemptively. Surgical techniques are ever improving, rendering risk of surgical intervention lower and lower. Above all, we are on the trail of the underlying genetic mutations that underlie aneurysms and dissections. When we identify the genetic abnormalities, we will be able to recognize and neutralize the virulent foe of thoracic aortic aneurysm and dissection before the foe has a chance to strike.

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Natural History of Mitral Stenosis and Echocardiographic Criteria and Pitfalls in Selecting Patients for Balloon Valvuloplasty

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Mitral stenosis (MS) is a chronic progressive disorder characterized by a long latent period between the initial episode of acute rheumatic fever and the development of cardiac symptoms [1]. Progression is generally slow in asymptomatic patients, but becomes more rapid after the onset of symptoms. In the United States, the incidence of acute rheumatic fever has fallen dramatically over the past several decades resulting in a corresponding decrease in the number of cases of MS. More recently however, this trend appears to have changed due to an influx of young immigrants from underdeveloped countries where the prevalence of acute rheumatic fever remains high [2].

The Natural History of Mitral Stenosis

Cardiac surgery has had a major impact on the clinical course of MS. Therefore, to better understand the natural history of MS, it is necessary to review data obtained before surgery became widely available. Oleson [3], in a study of 271 patients with MS in Denmark, reported a survival rate of 34% after 10 years and 14% after 20 years. In the classic study by Rowe et al. [4], the 10-year mortality in 250 patients with MS was 40%. Horstkotte et al. [5] found a survival rate of 8% at 15 years in patients with symptomatic MS who refused surgery. Carabello [6] combined data from several sources to obtain a composite of the natural history of MS without surgical intervention and found that the

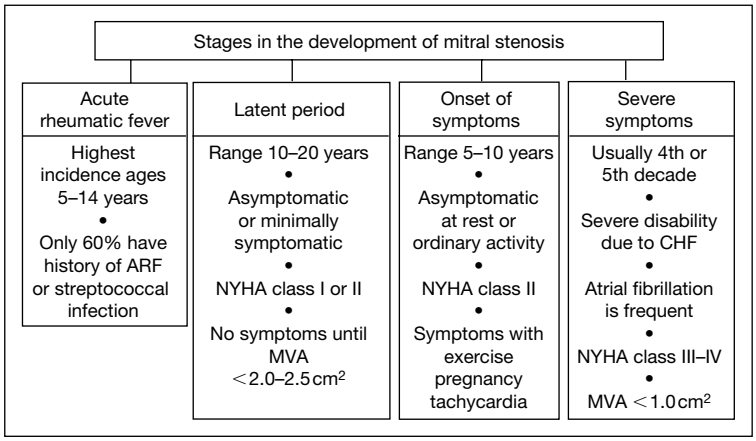


Fig. 1. Stages in the development of mitral stenosis. ARF = Acute rheumatic fever; CHF = congestive heart failure; MVA = mitral valve area; NYHA = New York Heart Association.

degree of clinical impairment was the best predictor of outcome. Patients presenting in New York Heart Association (NYHA) functional class I had an expected 10-year survival rate of 85%. For those in NYHA class II, the expected 10-year survival rate was about 50% and for those in NYHA class III, it was only 20%. Of patients presenting in NYHA functional class IV, none were expected to be alive at the end of 5 years.

Characteristically, MS evolves through several fairly well-defined stages (fig. 1). Acute rheumatic fever is the initial manifestation and occurs most commonly between the ages of 5 and 14 years. Interestingly, as many as 40% of patients with MS do not give a history of acute rheumatic fever or of an antecedent streptococcal infection. In temperate zones such as the United States and Western Europe, there is a latent period of approximately 10–20 years before symptoms appear. In developing countries, especially in tropical and subtropical regions, progression may be more rapid [2]. During the latent period, patients remain in NYHA functional class I or II until the mitral valve area decreases to 2.0–2.5 cm^2. At this point, patients are still symptom-free at rest or with ordinary physical activity. However, conditions that increase cardiac output or shorten diastolic filling time may precipitate symptoms. Pregnancy, atrial tachyarrhythmias, exercise, emotional stress and fever are included in this category. This phase may persist for about 5–10 years with more severe symptoms often developing during the fourth and fifth decade. Progression of anatomic stenosis tends to be variable but is usually slower in asymptomatic patients and more rapid once symptoms appear. When the mitral valve area approaches 1.0 cm^2, there is

a further increase in symptomatology and in its final stages MS produces extreme disability (NYHA functional class III or IV). The clinical picture is dominated by severe congestive heart failure, atrial fibrillation, and thromboembolic complications.

Echocardiography can provide additional information about the natural history of MS. Two recent studies found that the mitral valve area decreased at a mean rate of 0.09 cm^2/year [7, 8]. However, the rate of narrowing varied from patient to patient.

Percutaneous Balloon Mitral Valvuloplasty in Mitral Stenosis: Role of Echocardiography

Percutaneous balloon mitral valvuloplasty (PMV) is now considered the preferred treatment for most patients with MS who require mechanical relief of obstruction and gives results comparable to those achieved with surgical commissurotomy [9]. The technique involves transseptal catheterization of the left heart and dilatation of the mitral valve using a balloon catheter. Numerous studies have shown that PMV usually results in a doubling of the valve area from 1.0 to 2.0 cm^2 [10–14]. Both transthoracic echocardiography (TTE) and transesophageal echocardiography (TEE) play important roles in patients undergoing PMV. There is a critical role for TTE in the selection of patients who are likely to benefit from this procedure, while TEE is useful in screening for intracardiac thrombi, guiding transseptal puncture, detecting complications and assessing results.

Role of Echocardiography in Selection of Patients for Percutaneous Balloon Mitral Valvuloplasty

There is also an important role for TTE to accurately assess the severity of MS and provide important information about valvular and subvalvular morphology. Other important information such as chamber size and function and the presence of associated valvular lesions can also be obtained. Doppler echocardiography provides important hemodynamic measurements including mitral valve area, transmitral gradient and pulmonary artery pressure. In addition, it can detect and assess the degree of mitral regurgitation. If the severity of mitral regurgitation is $>2+$, the PMV procedure should not be performed. Similarly, TEE is useful in the screening of patients for a left atrial or left atrial appendage thrombus. The presence of a thrombus is a contraindication to both transseptal puncture and mitral valve dilatation.

Mitral valve morphology assessed by two-dimensional echocardiography is the most reliable predictor of immediate and long-term outcome after PMV. Structural characteristics that appear to be important include leaflet calcification, leaflet thickness and mobility, commissural fusion and calcification and subvalvular involvement. Although several echocardiographic methods to assess valvular morphology have been proposed, the one most commonly employed is a scoring system originally described by Wilkins et al. [15]. Using this approach, leaflet mobility, leaflet thickness, leaflet calcification and subvalvular involvement are each graded from 1 to 4 giving a maximal total score of 16. The more severe the pathology, the higher the score. A score of <8 is generally considered to be predictive of a good outcome and a low complication rate. Palacios et al. [14] recently reported the immediate and long-term results in 879 consecutive patients who underwent PMV at the Massachusetts General Hospital. Success rates were inversely related to the echocardiographic score. Patients with a baseline score <8 had a significantly greater increase in mitral valve area following PMV ($2.0 \pm 0.6\,cm^2$) than those with a score >8 ($1.6 \pm 0.6\,cm^2$). The actuarial survival rate at 12-year follow-up was 82% for patients with an echocardiographic score <8 and 57% when the score was >8. In another recent study, Wang et al. [16] found that an echocardiographic score <8 was associated with a restenosis rate of 20% at 5 years versus 61% for a score >8 [16]. In general, patients with a valve score <8 are considered good candidates for the procedure, while those with a score >12 should undergo mitral valve replacement. For those with a score between 9 and 11, percutaneous valvuloplasty can be performed although the results will not be as favorable as in those patients with a score of <8 [14]. In general, patients with a valve score <8 are considered good candidates for the procedure, while those with a score >12 should undergo mitral valve replacement. For those with a score between 9 and 11, percutaneous valvuloplasty can be performed although the results will not be as favorable as in those patients with a score of <8 [14].

Although mitral valve morphology as determined by two-dimensional echocardiography is the most useful predictor of outcome in patients undergoing PMV, other factors may also influence the results. Among these are the patient's age and sex, duration of symptoms, functional class, history of prior commissurotomy, as well as the presence of atrial fibrillation, degree of mitral regurgitation, pulmonary artery pressure and fluoroscopically visible calcium. Valve morphology may also be helpful in predicting which patients will develop mitral regurgitation following PMV [17]. Uneven leaflet thickening and calcification, marked leaflet thickening and calcification, and extensive subvalvular disease are findings that have been associated with an increased likelihood of developing mitral regurgitation.

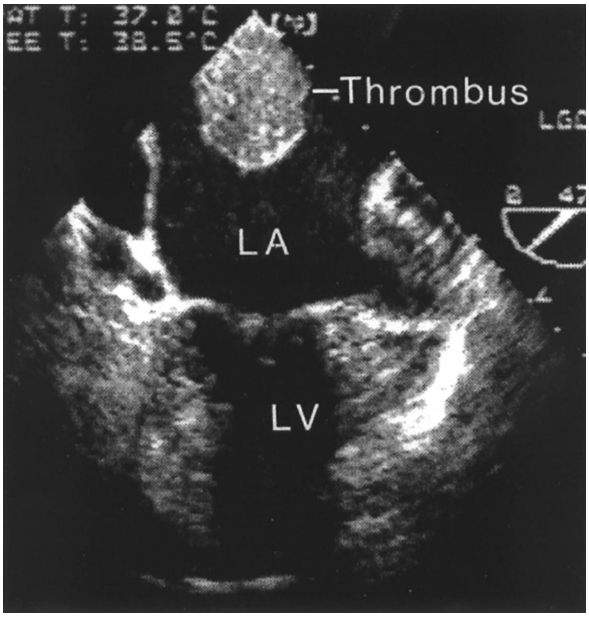
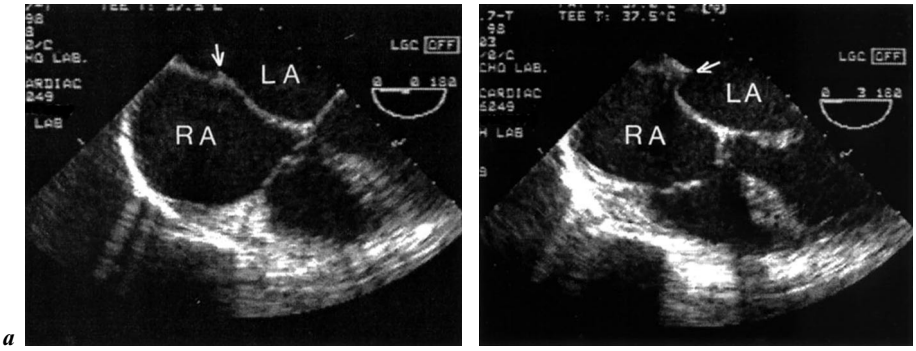


Fig. 2. Transesophageal echocardiogram showing a large left atrial thrombus. LA = Left atrium; LV = left ventricle.

Role of Echocardiography Before and During Percutaneous Balloon Mitral Valvuloplasty

Although TTE is usually adequate for evaluating the mitral valve prior to PMV, there are some patients in whom a technically adequate study cannot be obtained. In these patients, TEE is useful in assessing mitral valve morphology. Another important function of TEE is to exclude the presence of a thrombus in the left atrium or left atrial appendage, as shown in figure 2. As noted earlier, patients in whom a thrombus is detected should not undergo PMV until a later date when there has been resolution of the thrombus. The use of TEE can also help quantify the severity of mitral regurgitation. The presence of mitral regurgitation >2+ constitutes a contraindication to the PMV procedure.

During valvuloplasty, TEE has been found to be useful in guiding the transseptal puncture (fig. 3), positioning the balloon across the mitral valve and obtaining an immediate assessment of mitral valve area and the degree of mitral regurgitation after each dilatation. Other complications such as hemopericardium can also be rapidly detected. After the last dilatation, TEE can provide a final assessment of the adequacy of the procedure by measuring the mitral valve area



a *b*

Fig. 3. Transesophageal echocardiogram during transseptal puncture. ***a*** Tenting of the interatrial septum (arrow) produced by the tip of transseptal wire. ***b*** Tip of the catheter penetrating the interatrial septum (arrow). LA = Left atrium; RA = right atrium.

Table 1. Complications of PMV

Complication	%
Mortality	1–2
Mitral regurgitation (total)	30–50
Mitral regurgitation >2 grades	12–15
Mitral regurgitation requiring surgery	2–0
Emboli	1–3
Tamponade (related to transseptal puncture or ventricular rupture)	1–0
Atrial septal defect (oximetry)	10–30
Atrial septal defect (TEE)	>90

TEE = Transesophageal echocardiography.

and mean mitral gradient and by providing an evaluation of the severity of mitral regurgitation. Furthermore, TEE will also detect the presence and size of an atrial septal defect resulting from the transseptal puncture [18–20].

Complications of Mitral Valvuloplasty

The complication rate of PMV is low, especially in patients with an echocardiographic score <8 (table 1). The overall per procedure mortality averages from 1 to 2% [10–13, 21]. However, in some high volume centers, the

mortality rate has been reported to be considerably less than 1%. Although mitral regurgitation occurs in 30–50% of patients, the degree of mitral regurgitation is usually mild [21–23]. Nevertheless, an increase in mitral regurgitation >2 grades occurs in 12–15% of cases and is severe enough to require surgery in 2%. Other major complications include embolic events, tamponade, and atrial septal defect. The incidence of embolic events has been decreased by the use of TEE screening prior to the procedure. More than 90% of patients will have an atrial septal defect detected by TEE following the PMV [18–20]. By oximetry, the incidence ranges from 10 to 30% with shunt ratios >1.5:1 occurring in <5.0% of patients. A summary of the complication rate based on combined data from multiple studies is shown in table 1.

Summary and Conclusions

In summary, MS is a progressive disease characterized by a long latent period between the initial attack of acute rheumatic fever and the development of symptoms. For patients with MS who require mechanical relief of obstruction PMV is the preferred treatment and gives results comparable to surgical commissurotomy. Two-dimensional echocardiographic assessment of mitral valve morphology is the most important predictor of outcome. An echocardiographic score <8 predicts good immediate and long-term results. In patients undergoing PMV, TEE is useful for detecting left atrial and left atrial appendage thrombi, guiding transseptal puncture, assessing results and detecting complications.

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Surgical Treatment of Degenerative Mitral Regurgitation: Should We Approach Differently Patients with Flail Leaflets of Simple Mitral Valve Prolapse?

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The treatment and management of patients with degenerative mitral regurgitation (MR) has been transformed by mitral valve repair [1, 2]. However, an issue that remains unclear is whether different types of degenerative MR should be approached and managed differently. Indeed, different types of degenerative mitral valve disease have been described as having a benign or severe outcome and as benefiting variably from valve repair [3–5]. Indeed, American College of Cardiology/American Heart Association guidelines suggest that patients with asymptomatic chronic MR due to mitral flail leaflets may be approached more aggressively than other forms of MR [6].

The question of whether different types of degenerative MR deserve different approaches hinges on two issues. First, is the morbidity and mortality of these patients under conservative management different according to the lesions causing degenerative MR? The second aspect is focused on mitral valve repair. Previous studies have suggested that mitral valve repair should be the preferred procedure for patients with MR who require surgery as it provides better outcome than mitral valve replacement [7–9]. However, the preference for repair is simple to apply in patients who require surgery on the basis of severe symptoms, but as the quality of repair depends on the lesions [5], it is unclear whether all patients with MR irrespective of the lesions causing MR should be approached with an equally aggressive stance.

The aim of this article is to reassess the management of severe MR due to degenerative mitral lesions in view of new data on natural history and recent data on the long-term outcome after surgery.

Degenerative Mitral Regurgitation

Degenerative MR is the second most common mitral valvular disease leading to surgical intervention in western countries due to the aging of the population and the regression of rheumatic disease [10]. Degenerative lesions are those due to mitral vale prolapse and flail mitral leaflets with or without mitral annular calcification. The etiology of the valve lesions involve myxomatous infiltration, with or without ruptured chordae, and the mechanism of the regurgitation is excessive valve motion with loss of coaptation.

The prevalence of flail leaflets is not known but that of simple mitral valve prolapse (MVP) has been noted in the Cardia and Framingham studies to vary from 0.6 to 2.4%, and the reasons for this difference are not clear [3, 11]. This implies that between slightly less than 2 million and slightly more than 7 million Americans have lesions susceptible to causing degenerative MR. Of note, the prevalence of significant MR was found to be 4% in men and 2% in women aged 60 years or older [12].

Outcome of Degenerative Mitral Regurgitation with Conservative Management

The general reputation of MR is that it is well tolerated for many years and that its surgical indications are mostly based on the occurrence of symptoms or overt left ventricular dysfunction [6, 13]. However, recent data have been obtained shedding new light on the outcome of degenerative MR. Indeed, patients with flail mitral leaflets have been shown to have a mediocre outcome under conservative management [4]. Patients with this type of degenerative MR experience excess mortality with medical treatment compared to the general population. Although severe symptoms and reduced left ventricular ejection fraction are predictive of higher mortality, there is no subgroup at lower risk. Importantly, sudden death occurs at a rate of 1.8% per year overall. Whereas this rate is highest in patients with severe symptoms or reduced ejection fraction, most events occur in patients with normal ejection fraction and no or minimal symptoms. Moreover, morbidity under conservative management is high with heart failure, occurring in two-thirds of patients within 10 years of diagnosis [4]. Atrial fibrillation is a complication of degenerative MR that occurs in approximately 50% of patients within 10 years of diagnosis and is associated with excess mortality after its occurrence [14]. High rates of atrial fibrillation occur in older patients and in

those with an enlarged left atrium, but notable rates are observed in patients without these risk factors. In view of these frequent complications, surgery is needed in more than 80% of patients within 10 years of diagnosis and 90% of them either die or undergo surgery during that time frame [4]. Hence, these data suggest that surgery in these patients is almost unavoidable and that, when performed early in the course of the disease it may avoid the complications and mortality associated with degenerative MR [15].

Important questions are raised by these data. Is the seriousness of the outcome of MR due to flail leaflets an artifact of referral bias or does it reflect the severity and rate of progression of the MR? [16, 17]. To try to resolve this important question, one should assess the natural history of simple MVP in comparison to flail leaflets. The clinical diagnosis of MVP has been by the typical click and late systolic murmur [18]. Echocardiography allowed noninvasive diagnosis but created ambiguity. Using the initially proposed echocardiographic diagnostic criteria, MVP prevalence was reported as 5% or even 17% [19–21]. Three-dimensional echocardiographic analysis resulted in new diagnostic criteria, and in lower prevalence of MVP [3, 11, 22].

There are wide discrepancies between studies regarding the risk of serious complications, which ranges from 5 to 44% [3, 23–27]. These divergent results reflect, in part, design issues, particularly referral bias. Recently a study from Framingham suggested that patients with MVP have a uniformly excellent prognosis, and, therefore, tended to suggest that MVP may be far more benign than degenerative MR due to flail leaflets [3]. However, this report was based on a small number of subjects and raised concerns. To resolve these uncertainties, we conducted a new study in the community of Olmsted County, Minnesota [28]. This community-based approach provided large population and prospectively noted outcome events after MVP diagnosis. We followed 833 patients with asymptomatic MVP diagnosed using current echocardiographic criteria between 1989 and 1998. Total mortality was 19% at 10 years. The most powerful risk factor for cardiovascular mortality was a degree of MR ≥moderate. A decreased ejection fraction was rare but also affected mortality. Secondary risk factors independently predictive of cardiovascular morbidity were slight MR, left atrium dimension ≥40 mm, flail leaflet, atrial fibrillation, and age ≥50 years (table 1). Half of the patients with no or only 1 secondary risk factor had excellent outcomes, with 10-year mortality of 5 (fig. 1), cardiovascular morbidity of 0.5% per year (fig. 2) and MVP-related events of 0.2% per year. Patients with ≥2 secondary risk factors had mortality similar to that expected but increased cardiovascular morbidity (6.2% per year) and notable MVP-related events (1.7% per year). Approximately 20% of patients had primary risk factors (MR ≥moderate or left ventricular ejection fraction <50%) and experienced excess mortality, and increased morbidity (18.5% per year) and MVP-related events (15% per year) [28].

Table 1. Risk stratification in mitral valve prolapse [from 28, with permission]

Primary risk factors (excess mortality)	Secondary risk factors (cardiovascular morbidity)
Ejection fraction <50%	Slight mitral regurgitation
Mitral regurgitation ≥moderate	Flail leaflet
	Left atrial diameter >40 mm
	Atrial fibrillation
	Age ≥50 years

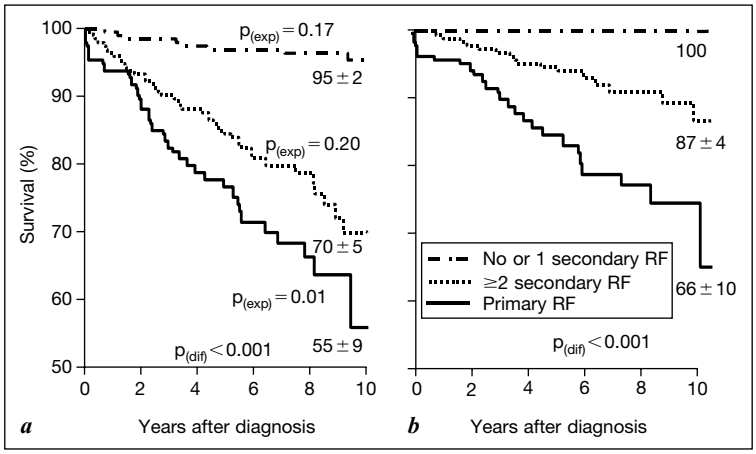

Fig. 1. Overall survival (***a***) and cardiac survival (***b***) (survival free of cardiovascular mortality according to three categories of baseline risk factors (RF)). $p_{(exp)}$ = Probability values for observed and expected mortality within each subgroup; $p_{(dif)}$ = probability values for the difference in total mortality between subgroups [from 28, with permission].

In summary, a unique outcome pattern applied to MVP is a misconception as the natural history of asymptomatic MVP in the community is widely heterogeneous and may be severe. Patients with severe MR experience increased morbidity and mortality during follow-up as a direct consequence of MVP. Remarkably, the rates of atrial fibrillation are identical in patients with flail leaflets or with simple MVP and severe MR [14]. Therefore, it is clear from these data that the major determinant of outcome under conservative management in degenerative mitral valve diseases is not the type of lesions but the degree of MR, and patients with severe MR uniformly exhibit high complication rates.

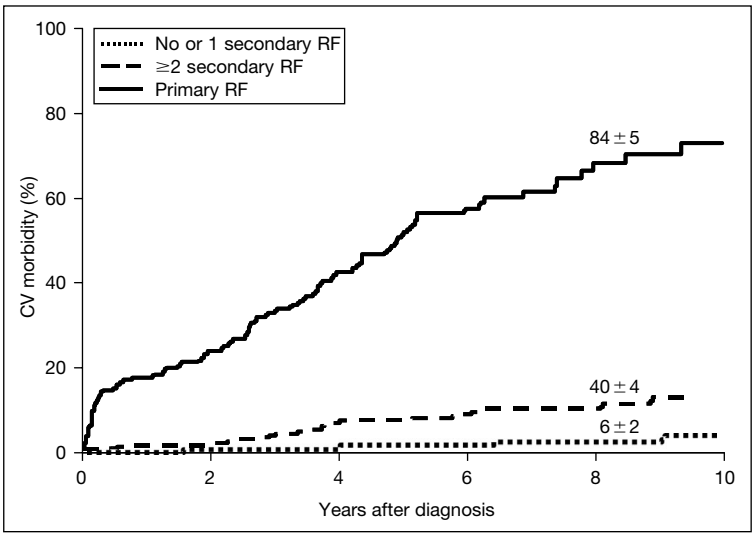

Fig. 2. Cardiovascular (CV) morbidity according to three categories of baseline risk factors (RF) [from 28, with permission].

Postoperative Outcome in Degenerative MR – Is Valve Repair Similarly Feasible and Successful in Different Types of Degenerative MR?

General predictors of outcome are valid whether degenerative MR is considered or not. Preoperative advanced NYHA functional class, and preoperative reduced left ventricular function are independent predictors of poor postoperative long-term outcome [10, 29, 30]. These observations have led to the concept of early surgery in MR, i.e., before the occurrence of severe symptoms or left ventricular dysfunction.

A major determinant of outcome is the type of surgical procedure performed (repair vs. replacement) irrespective of age or associated coronary artery disease [7]. The outstanding results of mitral valve repair have made it an essential incentive for the desired early surgical approach to degenerative MR. Hence, the question to be resolved is whether the patients with MVP, in whom the lesion often involves the anterior or both leaflets, benefit from similarly good results of valve repair as patients with flail leaflets. From a technical standpoint, the issue regards the treatment of anterior leaflet lesions and the quality of the repair of these lesions.

Techniques of Mitral Valve Repair. Mitral valve repair was initiated by McGoon [2] who performed valve plications. Carpentier et al. [1] then codified the repair of redundant mitral valve. The techniques involve annular, valvular

and subvalvular components combined to correct the specific lesions. Prosthetic ring annuloplasty is used almost universally to correct the annular dilatation that accompanies severe chronic MR. Variations exist among surgeons regarding sizing, i.e., regarding annuloplasty ring used, from simple bands to flexible incomplete rings to rigid complete rings. It is uncertain whether these technical variations affect long-term outcomes of valve repair but it is now widely accepted that prosthetic annuloplasty is an essential part of repair of degenerative mitral valve lesions [5].

Repair of posterior leaflet degenerative lesions is generally simple. Beyond the ring annuloplasty, it involves a triangular or quadrangular resection of the prolapsed portion and suture of the free edges of the leaflets. If the posterior leaflet tissue is markedly excessive, a sliding plasty, which removes the basis of the leaflet, can be performed. Removing annular calcifications is possible but rarely indispensable.

Repair of anterior leaflet degenerative lesions may be more challenging than that of the posterior leaflet but new techniques have considerably improved the odds of a successful repair. Resection of anterior leaflet tissue is possible but should be very conservative because this leaflet is narrow and excision of tissue leads to lack of coaptation and residual MR [31]. To provide support to the prolapsed segment, chordal shortening has been initially proposed but recent data shown that it is associated with a high rate of reoperation [5]. Transposition of native chordae uses healthy chordae from the region of the posterior leaflet corresponding to the prolapsed anterior leaflet [32]. The supporting papillary muscle can be mobilized to add mobility to the leaflet. A strip of posterior leaflet attached to the chord is sutured to the free edge of the anterior leaflet. This method provides better support than chordal shortening and better clinical results. Chordal replacement with Teflon artificial chords involves a suture passed through the papillary muscle that anchors the prolapsing area of the anterior (or posterior) leaflet [33]. This technique is superior to chordal shortening with lower failure and reoperation rates [34]. Repair of bileaflet lesions can be simple as a ring annuloplasty sometimes proves sufficient to re-establish coaptation in isolation or with posterior leaflet repair [35]. However, in the setting of excess tissue or extensive lesions, a complex repair often requires procedures correcting both the anterior and posterior lesions. However, as these have become standard process, such corrections are not overwhelming.

Prevention of postoperative systolic anterior motion (SAM) of the mitral valve is subject of controversy. Although SAM has frequently been encountered immediately postoperatively, it is rarely a long-term major problem [36, 37]. Obstruction may result from SAM with poor hemodynamics and residual MR, sometimes severe [38]. A particularly redundant posterior leaflet tissue in a smaller, hypercontractile ventricle has been suggested as causing the SAM.

Therefore, SAM is usually reversed by discontinuation of inotropic drugs, β-blockers and fluid replacement. Rarely is a second pump run and mitral valve replacement necessary because of intractable residual SAM. The use of a sliding plasty in patients with particularly redundant tissue has been advocated, but the necessity of its use remains controversial.

Results of Mitral Valve Repair for Degenerative Lesions. Operative mortality is lower after valve repair (0–3%) than after valve replacement [7]. Advanced age (≥75 years) and associated coronary artery disease are the most important predictors of higher operative mortality [39]. Importantly, class III or IV symptoms are associated with higher operative risk providing another rationale for surgery in patients with no or minimal symptoms, in whom the risk is extremely low [29]. The presence of a flail leaflet with ruptured chord versus a simple prolapse and the valve involved by the prolapse do not affect operative mortality [5, 7, 40, 41]. Hence, the operative risk does not justify a different approach to different types of degenerative MR.

The long-term outcome of mitral valve repair for degenerative MR is important to consider as the concept of early surgery is applicable only in the subsets in which the result of surgery is excellent. From that point of view it is essential to examine the outcome beyond 10 years and two recent studies provide substantive information [40, 42].

First and foremost an important question is whether valve repair as compared to valve replacement improves long-term survival similarly in patients with the most complex repairs (i.e., involving the anterior leaflet) as it does in the simplest form of repair. Indeed, if valve repair tends to deteriorate late after surgery, an early survival advantage may be lost later. The answer to that question is now clear. In a study of 917 patients with degenerative MR who had mitral repair (679) or replacement (238) at our institution between 1980 and 1995, survival rates at 15–20 years after surgery was significantly better after repair than after replacement, even after adjustment for all predictors of outcome [40]. Most remarkably, in both posterior and anterior leaflet prolapse, the benefit of repair was similar in both groups (adjusted risk ratio 0.61 and 0.67 respectively; fig. 3). Therefore, mitral valve repair is the preferred mode of surgery in degenerative MR, not only with posterior leaflet prolapse but also with anterior leaflet prolapse, despite all possible concerns with this type of lesion. Furthermore, comparisons to expected mortality show that the survival with repair is extremely close to that expected in the general population [7, 40, 42]. There is no difference in postoperative survival according to the presence of a flail leaflet with ruptured chordae or of a simple MVP as the cause of MR.

With regard to postoperative left ventricular function and risk of heart failure, patients who undergo mitral valve repair enjoy better postoperative left ventricular function and lower rate of late postoperative congestive heart failure

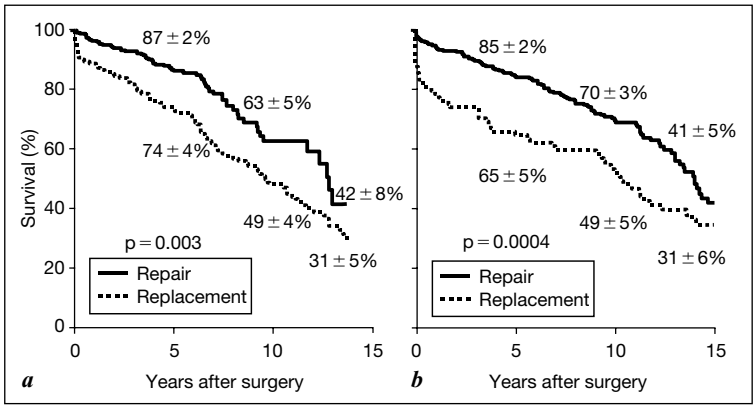

Fig. 3. Long-term survival after surgery for isolated mitral regurgitation due to valve prolapse. Note that survival beyond 10 years after mitral surgery is improved by mitral valve repair whether the mitral valve prolapse involves the anterior leaflet (***a***) or exclusively the posterior leaflet (***b***). Values plotted are percent survival on the vertical axis over time in years on the horizontal axis [from 40, with permission].

as compared to those who receive mitral replacement [7, 43, 44]. This improved result is in part due to better preservation of chordae tendinae attachment to papillary muscles. There is no difference in changes in left ventricular ejection fraction or in risk of heart failure depending on the presence of a simple MVP or flail leaflet as the cause of degenerative MR.

Recurrence of severe MR after repair is a complication that may appear under two circumstances. First is incomplete correction, which should be in part preventable by intraoperative transesophageal echocardiography (TEE). Residual MR left at the end of repair may be missed due to insufficient loading conditions when the TEE was performed. In our analysis of the long-term post-operative results of surgery of degenerative MR, residual MR even mild, at the end of surgery was associated with a high rate of reoperation, higher than in patients without residual MR (14 and 21% at 10 and 15 years vs. 9 and 14% respectively, $p = 0.002$) [40]. These results were similar whether MR was due to posterior or anterior leaflet prolapse or whether the degenerative MR was due to a flail leaflet or not. This result suggests that a 'small amount' of residual MR at the end of surgery is not benign and may lead to delayed reoperation. Hence, intraoperative TEE is an indispensable tool for mitral valve surgery. Pre-bypass, the in-vivo examination of lesions helps determine the approach to mitral valve repair [45, 46]. Post-bypass, TEE is essential in defining the presence and degree of MR and the mechanisms of failure of mitral valve repair while the patient is still in the operating room [47]. Fortunately, most often it verifies the

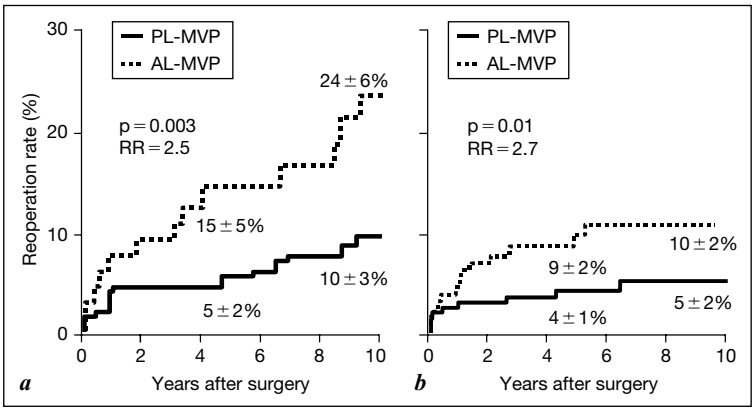

Fig. 4. Temporal change in reoperation rate after mitral valve repair for isolated mitral regurgitation due to valve prolapse. Note that in the 1980s (***a***) and 1990s (***b***) the reoperation rate (all causes) after repair of mitral valve prolapse involving the anterior leaflet (AL-MVP) was higher than after repair of mitral valve prolapse exclusively of the posterior leaflet (PL-MVP). RR = Relative risk [from 40, with permission].

success of the repair and absence of residual MR. In addition to improved surgical techniques, extensive use of intraoperative TEE, by allowing immediate control of the quality of repair before chest closure, has contributed, to improved results of long-term mitral valve repair. Our results suggest that the post-bypass TEE should be extremely careful and that the only really acceptable result of mitral valve repair is a perfect result.

The second cause of recurrent MR is the development of new degenerative lesions, which accounts for the majority of patients requiring reoperation [48]. The need for reoperation after mitral valve repair for degenerative mitral disease is low and repair has excellent durability, at least as good as valve replacement within the first 10 years after surgery [7]. The important new information now available is that durability of repair is sustained up to 20 years, and even beyond [40, 42]. Furthermore, there is no trend for accelerated degeneration of repaired valves over time, which would mimic the course with bioprostheses. Nevertheless, the new very long-term data provides information particularly relevant to the decision for early surgery and is of particular importance for patients with anterior leaflet prolapse. Indeed, the need for reoperation is higher after repair of prolapse involving the anterior leaflet than that involving posterior leaflet [5, 40]. However, there has been a temporal improvement in long-term results. Comparing surgery in the 1980s and 1990s, we found that the 10-year reoperation rate markedly and significantly declined in both posterior and anterior MVP in the 1990s: from 10 to 5% in posterior MVP and from 24 to 10% for anterior MVP (fig. 4) [40].

Hence, the current results of surgery have improved considerably as a result of extensive surgical experience, of new repair techniques and of the use of intraoperative TEE. These results now allow consideration of early surgery in patients with degenerative MR whether anterior and posterior leaflet prolapse is involved and whether the MR is on the basis of simple MVP or on the basis of flail leaflets.

Conclusion

New information regarding patients with degenerative mitral valve lesions has shown that (1) under conservative management the outcome is similarly serious in patients with flail leaflets and MVP, depending on the presence of severe MR; (2) compared to mitral valve replacement, mitral repair provides an improved postoperative survival which is maintained up to 20 years after the operation irrespective of the type of lesions and the location of the prolapse; (3) durability of mitral valve repair is excellent and sustained up to 20 years postoperatively, and (4) reoperation is required more often after repair of a prolapse involving the anterior than the posterior leaflet, but dramatic improvement of surgical long-term results have been observed recently.

The clinical implications of these data are that mitral valve repair is the preferred mode of surgical treatment of all types of severe degenerative MR and that early surgery for degenerative MR is a consideration in patients with all types of severe degenerative MR in centers that offer low operative risk and high repair rates for these lesions.

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Ventricular Arrhythmias in Mitral Regurgitation: Frequency, Clinical and Prognostic Importance, Management Before and After Mitral Valve Surgery

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Sudden death now is recognized as an important problem in patients with chronic, non-ischemic mitral regurgitation (MR). However, the predictors of this catastrophic event are incompletely described, particularly among those who are asymptomatic with well-preserved ventricular function as this term now is understood for MR, that is, patients with left ventricular (LV) ejection fraction (LVEF) more than 10% above the nominal lower normal limit with the patient at rest, and resting right ventricular (RV) ejection fraction (RVEF) within normal limits. This chapter will review current data about the prevalence of ventricular arrhythmias in patients with MR, the apparent prognostic importance of the finding, and preliminary data suggesting management strategies.

Prevalence of Ventricular Arrhythmias in Patients with MR

In an early report from the Cornell group, when patients consecutively admitted to a prospective study of the natural history of regurgitant valvular diseases were evaluated, of 53 patients with pure severe MR who underwent protocol mandated 24-hour ambulatory electrocardiography (A-ECG) at study initiation, 29% manifested non-sustained ventricular tachycardia (VT)

(≥3 sequential VPCs) [1]. Follow-up at the time of the report averaged 2.5 years; during that interval, 5 patients had died among the 35 who were deemed inappropriate for surgery, most because they were asymptomatic. Four of these 5 patients died suddenly, and 4 of 5 had VT on A-ECG.

The deaths during non-surgical follow-up were clustered among those patients with subnormal LVEF and/or RVEF at rest [1]. However, further analysis indicated that the sudden deaths occurred almost invariably in patients who had both ventricular dysfunction and VT on a routine 24-hour A-ECG [2]. Also, though the most common etiology for MR is mitral valve prolapse (MVP), complex ventricular arrhythmias (including VT, R on T PVCs, etc.) were equally common in patients with severe MR with MVP versus those patients with MR due to other etiologies, while complex arrhythmias were significantly less common in patients with MVP without MR [3].

Since these initial observations, the relatively high prevalence of ventricular arrhythmias and of sudden death in MR have been reported by other authors [4–6]. In 1991, Delahaye et al. [4] reported that, among cardiac deaths occurring during non-surgical follow-up in patients with severe MR, 60% were sudden. Five out of 8 sudden deaths occurred in patients with normal LVEF at rest, but neither RV function nor ventricular rhythm characteristics on A-ECG were reported. The rate of sudden death was ~2.5%/year. In 1992, Delahaye et al. [5] reported on a larger group of 75 patients with MR of whom 8 (10.7%) had VT prior to any mitral valve surgery. This study also reported a follow-up after surgery in subsets of the population: VT was present on A-ECG in 11 of 63 (17.5%) patients early after surgery and in 3% (1/33) patients late after operation. Post-surgical clinical events were not reported in detail. However, it was noted that perioperative mortality was 2.7%, that 1 patient died 2.5 months after surgery and that 3 patients with pre-operative VT were alive 6 months after operation.

More recently, Grigioni et al. [6] reported on sudden death in the absence of operation among patients with MR due to flail leaflet. The rate of sudden death was 1.8%/year. The highest incidence of sudden death was found in a subgroup of patients with poorly preserved LVEF, symptoms or atrial fibrillation (8–12%/year incidence of sudden death). Even among patients with none of these risk factors at study entry, mortality rate was 0.8%/year; however, interpretation of this finding is confounded somewhat by the fact that some of these deaths occurred after new symptoms had occurred and were ameliorated by medications [6]. Moreover, no data were presented concerning the incidence of ventricular arrhythmias or RVEF, though the latter usually becomes subnormal during exercise, if not at rest, before symptoms develop [7]. Sudden death was believed to be less likely after surgery than in patients with similar characteristics who had not undergone operation before death; however, 7 sudden deaths were observed during post-operative follow-up [6].

Prediction of Sudden Death after Mitral Valve Surgery

The foregoing review indicates that sudden death is an important risk for patients with MR. Though the data are insufficient for firm conclusions, it seems clear that the combination of ventricular arrhythmias and LV *or RV* dysfunction identifies patients at particular risk for sudden death. Since RV dysfunction, particularly during exercise alone, often is present in patients with well-preserved LVEF and no symptoms [7], it is possible that some or all of the sudden deaths reported among patients with well-preserved LVEF may have been among patients with RV dysfunction and/or with non-sustained VT. More data will be needed to elucidate this issue. However, the data of Grigioni et al. [6] suggested that mitral valve surgery might, at least in part, ameliorate the sudden death risk after operation. Nonetheless, sudden deaths occurred even after surgery, raising the possibility that additional anti-arrhythmic treatment, with drugs and/or devices, might be appropriate for some patients if risk factors could be defined. In this regard, our recent preliminary data may prove useful. In our prospective study [8], because of the predictive value of A-ECG in other settings and before operation, this procedure was performed routinely on an annual basis. Among patients who underwent A-ECG both before and after operation, 17% died during multi-year post-operative follow-up; two-thirds of these deaths were sudden. Most importantly, sudden death occurred only in those patients who had non-sustained VT on multiple post-operative A-ECG studies. Sudden death risk was greatest among those who also had LV and/or RV dysfunction, but even in the absence of mechanical abnormality or symptoms, VT indicated sudden death risk, albeit modest. Further study must determine if additional diagnostic tests can further refine risk, and whether anti-arrhythmia therapies can obviate or minimize this risk. However, these preliminary data suggest that mitral valve surgery, alone, may not be sufficient protection against sudden death risk among patients who survive surgery without symptoms and with normal LVEF; risk may be better assessed by additional evaluation of rhythm status by A-ECG and by attention to RV, as well as LV, function.

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The Case for Bioprosthetic Mitral Valve Replacement in Patients Aged 60–70

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There are approximately 75,000 mitral valve repairs or replacements (MVR), (isolated MVR or MVR plus coronary artery bypass grafting), performed in the United States annually [1]. As patient longevity continues to increase, surgeons are faced with increasingly difficult decisions regarding age-appropriate selection of mechanical versus bioprosthetic valves. In this discussion we trace the developmental innovations of bioprosthetic valves and evaluate the results of MVR in patients aged 60–70 years.

Mechanical versus Bioprosthetic Valves

Since the 1960s, more than 80 different artificial heart valves have been designed [2]. Nevertheless, the ideal prosthetic heart valve still awaits us. In general, the advantages of mechanical valves are their excellent durability while the disadvantages are the risk of thromboembolism and the consequent need for long-term anticoagulation with associated bleeding risks. The high durability of mechanical valves is illustrated in table 1 in a report by Zellner et al. [3] of 292 patients who received the St. Jude's mechanical valve. At 15 years, there was a 100% actuarial freedom from structural valve degeneration (SVD) and a 90% actuarial freedom from reoperation. However, the actuarial freedoms from thromboembolic events (TE) and bleeding were only 59 and 79% respectively.

In contrast, bioprosthetic valves do not require anticoagulation but have historically had limited durability, potentially subjecting a patient to a higher risk reoperation. In practice, bioprosthetic MVR has largely been reserved for

Table 1. Comparative performance of prosthetic mitral valve replacements

	Valve	Patients n	Mean age	Early mortality %	Survival		SVD freedom		TE freedom		Bleeding freedom		Reop. freedom	
					%	years	%	years	%	years	%	years	%	years
Zellner [3]	St. Jude	292	52	5.1	60	10	100	15	74	10	81	10	94	10
S. Carolina, USA					49	15			59	15	79	15	90	15
Santini [4]	Hancock I	331	49	6.3	46	10	67	10	82	10	96	10	72	10
Verona, Italy					30	15	32	15	74	15	91	15	36	15
					22	20								
Jamieson [5]	CE Porcine	501	56	9	51	10	70	10	85	10			65	10
Vancouver, Canada	(std)				24	15	21	15	78	15	n/a		19	15
					24	17							85	10
David [6] Toronto, Canada	Hancock II	310	65	8	30	15	66	15	87	15	n/a		69	15
Marchand [8] European Multi-center	CE Perimount	333	60.7	7.8	63	14	66	14	84	14	86	14	64	14
Fradet [7] Multi-center	Mosaic	366	68	4.1	97	5	100	5	92	5	100	5	96	5

CE = Carpentier-Edwards; n/a = not available; std = standard; SVD = structural valve degeneration; TE = thromboembolic events.

the elderly (patients >70 years old) because the likelihood for reoperation was thought to be lower. With newer technological advances in biologic valves, however, the age threshold for bioprosthetics may now be lower.

Current Status of Bioprosthetic Valves

The first bioprosthetic valves were stented porcine valves. First-generation porcine valves included the Hancock I (1971, Medtronic Inc., Minneapolis, Minn., USA) and the Carpentier-Edwards (C-E) Standard Porcine (1975, Baxter Health Care Corp., Edwards Div, Santa Ana, Calif., USA). Both were prepared with high-pressure glutaraldehyde fixation. Santini et al. [4] reported the disappointing long-term results with the Hancock I porcine valve in 331 patients. They observed a 15-year actuarial freedom from SVD of 32% and a freedom from reoperation of 38%. They did note a high degree of freedom from the complications of TE and bleeding: 74 and 91% respectively. Jamieson et al. [5] found similarly low 15-year actuarial rates of freedom from SVD (21%) and reoperation (19%) in 486 patients who received the C-E Standard Porcine valve.

Because of this limited long-term durability, improvements in tissue fixation as well as developments in anti-mineralization agents were implemented to design the second generation of porcine valves. These included the Hancock II and the C-E SupraAnnular Valve (SAV), both introduced in 1982. The C-E SAV utilized a completely low-pressure glutaraldehyde fixation while the Hancock II went to a two-staged technique with initial low-pressure followed by high pressure. The low-pressure fixation was thought to be more physiologic with zero pressure across the valve leaflets. In an effort to reduce mineralization deposition on the valves, the Hancock II was treated with sodium dodecyl sulfate and the C-E SAV with Polysorbate-80. In addition, the Hancock II was designed to minimize mechanical stress on the cusps, while the C-E SAV increased stent flexibility and reduced strut height. The performance of the second-generation Hancock II valve was evaluated in 310 patients by David et al. [6]. The 15-year freedom from SVD was 66% with a freedom from reoperation of 69%, both significant improvements from its first-generation predecessors. In addition, the 15-year freedom from TE remained high at 87%.

Further improvements in anti-calcification agents led to the development of the third-generation porcine valve. The Mosaic valve (1994, Medtronic) is prepared with low-pressure glutaraldehyde fixation, is mounted on a flexible polymer stent, and is treated with α-amino oleic acid to reduce tissue calcification. Due to its relatively recent introduction into clinical practice, there has been limited follow-up data on the third-generation mosaic porcine valve. In a study of 366 patients with 5-year follow-up, Fradet et al. [7] found 97% freedom from

SVD and 96% freedom from reoperation. Although this preliminary data is encouraging, it is important to note that in general there is a sharp increase in bioprosthetic failures seen after 7–8 years. Follow-up data at 10 and 15 years will be necessary for appropriate comparisons to the currently available bioprosthetic valves.

Bovine pericardial valves were developed as a bioprosthetic alternative to traditional porcine valves. The Ionescu-Shiley (1976, Shiley Inc., Irvine Calif., USA) and Hancock Pericardial Valve (Medtronic) were two initial attempts that were both withdrawn from the market by 1987 due to high rates of degeneration and failure. Currently, the most widely available pericardial valve is the C-E Perimount (1984). The valve design includes infra-stent tissue mounting, flexible and distendable struts, and improvements in tissue preservation from the earlier attempts. The C-E Perimount was analyzed in 333 patients by Marchand et al. [8]. They noted that, similar to the Hancock II porcine valve, the 14-year actuarial freedom from SVD was 66% and freedom from reoperation was 64%. Low rates of TE and bleeding complications were noted, with freedoms of 84 and 86% respectively at 14 years.

Historically, there has been an age-specific difference in the rate of SVD in bioprosthetic valves making these valves a less attractive option in patients below the age of 70. For example, Jamieson et al. [9] noted that in patients receiving the first-generation C-E Standard Porcine valves, the 10- and 15-year actuarial freedoms from SVD was 91 and 75% in patients 70 and older, but only 67 and 40% in patients aged 65–69. In contrast, Marchand et al. [8] noted in the second-generation pericardial (C-E Perimount) valves, that 10-year actuarial freedom from SVD was comparable between the >70-year-old group (100%) and the 61- to 70-year-old group (95%). Furthermore, Jamieson et al. [5] compared the second-generation pericardial to the second-generation porcine (C-E SAV) valves. The 10-year actuarial freedom from SVD in the 61- to 70-year-old age group was significantly higher in the pericardial valves (95%) compared to the porcine valves (75%). Additionally, the etiology and presentation of SVD were different with respect to these two valves. Whereas the pericardial valves typically presented insidiously with mitral stenosis secondary to calcification (70%), the porcine valves tended to present more acutely with mitral insufficiency secondary to leaflet tear (82%). Therefore, it appears that the bovine pericardial valve offers an acceptable level of durability at 10 years in the 61- to 70-year-old age group [10].

Nevertheless, there remains a higher risk of reoperation in bioprosthetic valves compared to mechanical valves despite the technological advances. However, the operative risks in these patients may not be as prohibitively high as once thought. In a comprehensive review assessing the risk of reoperative bioprosthetic valve replacements since 1986, Akins et al. [11] reviewed six

published series consisting of over 2,000 MVR patients. The average MVR mortality was 11.5% and ranged from 10.0–15.3%. In Akins' own series of 219 reoperative MVR for failed bioprostheses [1], he noted that the average age of the patient was 65.5 ± 10.0 years, the mortality was 6.8%, and 26% had a prolonged length of stay. This compares very favorably with the risk-adjusted operative mortality of 7% for an isolated first-time MVR according to the Society of Thoracic Surgeons database.

Conclusions

Thus, for the majority of patients with a history of a bioprosthetic valve, reoperative surgery can be performed safely. Moreover, the indications for bioprosthetic valve replacement is further expanding with a better understanding of the natural history of other co-morbid medical conditions with respect to lifespan. Peterseim et al. [12] noted that valvular surgery candidates with renal insufficiency (any age), lung disease (age >60 years), left ventricular ejection fraction <40% (any age), or coronary artery disease (any age), all have low 10-year survival rates ranging between 27 and 35%. As a result, these patients have a very high degree of freedom from reoperation at 10 years ranging from 90 to 100% in most published reports. Thus, in patients with other significant co-morbid conditions regardless of age, a bioprosthetic valve is a reasonable choice given the shorter lifespan and low likelihood for reoperation.

With continued refinements in anti-mineralization agents and valve design, the long-term durability of bioprosthetic valves will likely continue to improve. The decision to place a mechanical or bioprosthetic valve involves weighing the risk of bleeding and thromboembolism against the risk of SVD and reoperation. Patients already anticoagulated for chronic atrial fibrillation may be better suited for a mechanical prosthesis. However, in the remaining patients aged 61–70 years, bioprosthetic MVR should be considered a reasonable alternative. Recent studies support the pericardial valve as the better bioprosthetic option for this age group.

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Endocardial Cushion Defects: Embryology, Anatomy and Pathophysiology

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The atrioventricular (AV) canal defects are characterized by the deficiency or absence of septal tissue immediately above and below the normal level of the AV valves including the region normally occupied by the AV septum in hearts with two ventricles. The AV valves are abnormal to a varying degree. Whereas AV septal defects have a variety of terminologies, terms commonly used include AV cushion defect, AV canal defect, AV septal defect or endocardial cushion defect. Maude Abbott [1], in her atlas of congenital heart disease published in 1936, recognized the osmium primum atrial septal defect and the common AV canal. In 1948, Rogers and Edwards [2] subsequently recognized that these two defects were morphologically similar. Wakai and Edwards [3, 4] further elaborated the concept in 1956 and 1958 respectively, and introduced the terms partial and complete AV canal defects. Subsequently, Lev [5] described the position of the AV node and bundle of His in these malformations. Bharati and Lev [6] further categorized AV septal defects to include the intermediate and transitional types. Van Mierop et al. [7, 8] added to the overall understanding of the anatomic features of the various types of endocardial cushion defects. The first successful repair of the complete AV canal was performed by Lillehei and his colleagues in 1954. By the early 1960s, the surgical treatment of these defects provided a stimulus for further morphologic studies. In 1966, Rastelli et al. [9] developed a classification which is still currently used. Dr. Robert Anderson has emphasized that all variations of the defect are part of a spectrum. The overall incidence of this defect in congenital heart disease is 5%.

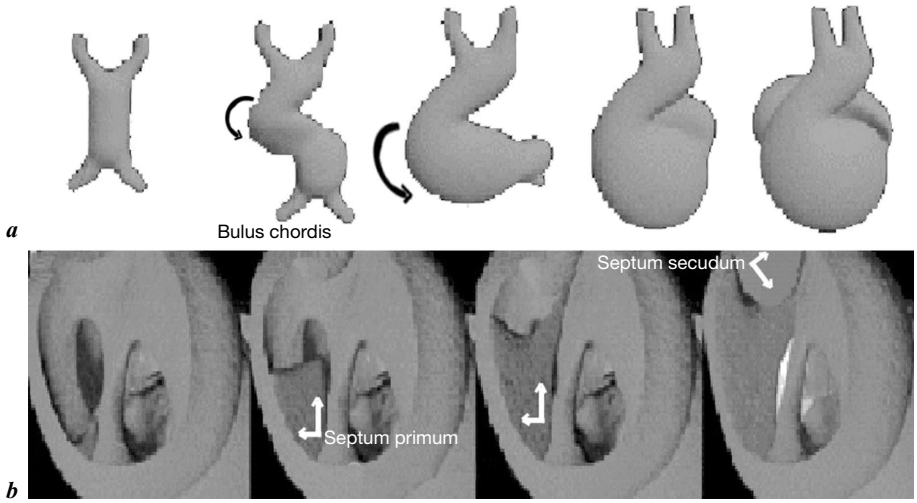


Fig. 1. Development of the heart. ***a*** The bulbus chordis becomes the right ventricle. ***b*** Formation of the interatrial septum.

Embryology

The heart develops as a tube and is fixed between two points. With rapid growth, the heart begins to bulge towards the right and forms the bulbus chordis, which is destined to become the right ventricle (fig. 1). Septation of the atria first starts with the septum primum, which begins inferiorly and moves in a superior direction. A septum secundum originates superiorly and moves inferiorly (fig. 1). Concurrently, there is septation of the ventricles with formation of the ventricular septum in an inferior to superior orientation. In addition, there is movement of the lateral endocardial cushions medially. These structures all meet in the center of the heart to form the four chambers of the heart.

The great vessels are derived from a common trunk, the truncus arteriosus, which septates, spirals and involutes to form the pulmonary artery and aorta. The truncal septum merges with the ventricular septum. Failure of the formation or a deficiency of the development of the septum primum results in an ostium primum septal defect (partial AV canal). Failure of the endocardial cushions to fuse with the ventricular septum results in a complete AV canal defect. In addition, this results in a deficiency of AV valve tissue as well (fig. 2).

The three types of AV septal defects described include complete, partial and transitional forms. From a surgical standpoint the key issues are: (1) the presence and size of the ventricular septal defect, and (2) the size of the right and left ventricles in relationship to each other (balanced or unbalanced).

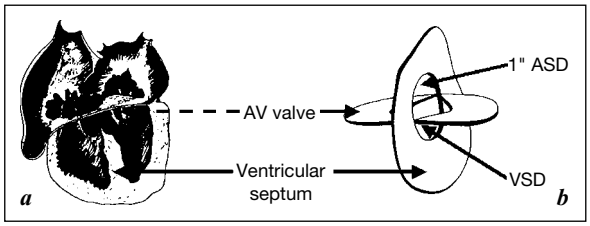


Fig. 2. a, ***b*** Atrioventricular (AV) canal defects. ASD = Atrial septal defect; VSD = ventricular septal defect.

All three forms of the AV canal defect have an ostium primum component atrial septal defect (ASD) primum and a cleft in the AV valve, which results in AV valve regurgitation. Figure 3 illustrates the anterior and posterior views of the AV canal. Note the common AV valve with its components, the anterior and posterior bridging leaflets, as well as the lateral leaflets.

Classification of the complete AV canal by Rastelli et al. [9] is illustrated in figure 4.

In the complete AV canal type A, the anterior bridging leaflet is divided with its chordal attachments to the crest of the ventricular septum. In type B, which is a rare form, the anterior bridging leaflet is still divided but its chordal attachments are to the medial papillary muscle of the right ventricle. In the more common type C defect, the free-floating type, the anterior bridging leaflet is non-divided, and without chordal attachments. These anatomic details are well defined by echocardiography and are important considerations for surgical repair.

Echocardiography also assesses the extent of AV valve regurgitation and overall ventricular function. An important echocardiographic clue to the diagnosis of this defect is the observation that in the apical four-chamber view, the AV valves are at the same level (fig. 5).

Right and left heart cardiac catheterization and angiography are certainly helpful in measuring pressures and saturations, in assessing valvular regurgitation (fig. 6), and in shunt calculation. Their current indication, however, is reserved for patients with suspected pulmonary artery hypertension. The purpose of cardiac catheterization, particularly in patients with trisomy 21, who generally have an earlier and greater predilection for developing pulmonary vascular disease, is to assess pulmonary vascular bed reactivity and the severity of pulmonary vascular resistance. Echocardiography can often non-invasively identify pulmonary artery hypertension by demonstrating the pancaking of the left ventricle by the right ventricle at systemic pressure (fig. 7).

The partial AV septal defect is an ostium primum defect with a cleft in the anterior leaflet of the mitral valve. There is no functional ventricular septal

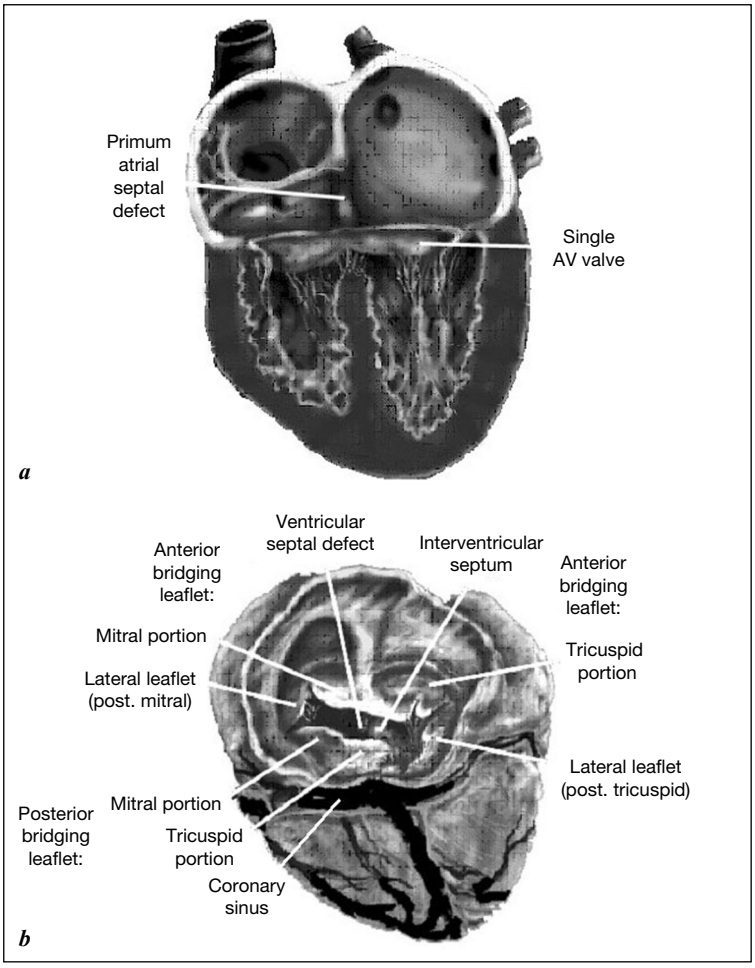


Fig. 3. a, ***b*** Views of the atrioventricular (AV) canal [from The Multimedia Encyclopedia of Congenital Heart Disease, courtesy of Scientific Software Solutions, Inc., with permission].

defect. Other conditions associated with AV canal defects include the double orifice mitral valve and tetralogy of Fallot.

Physiology

The physiology of AV septal defects will depend on whether the patient has an ASD alone (partial AV canal), or both an ASD and ventricular septal defect

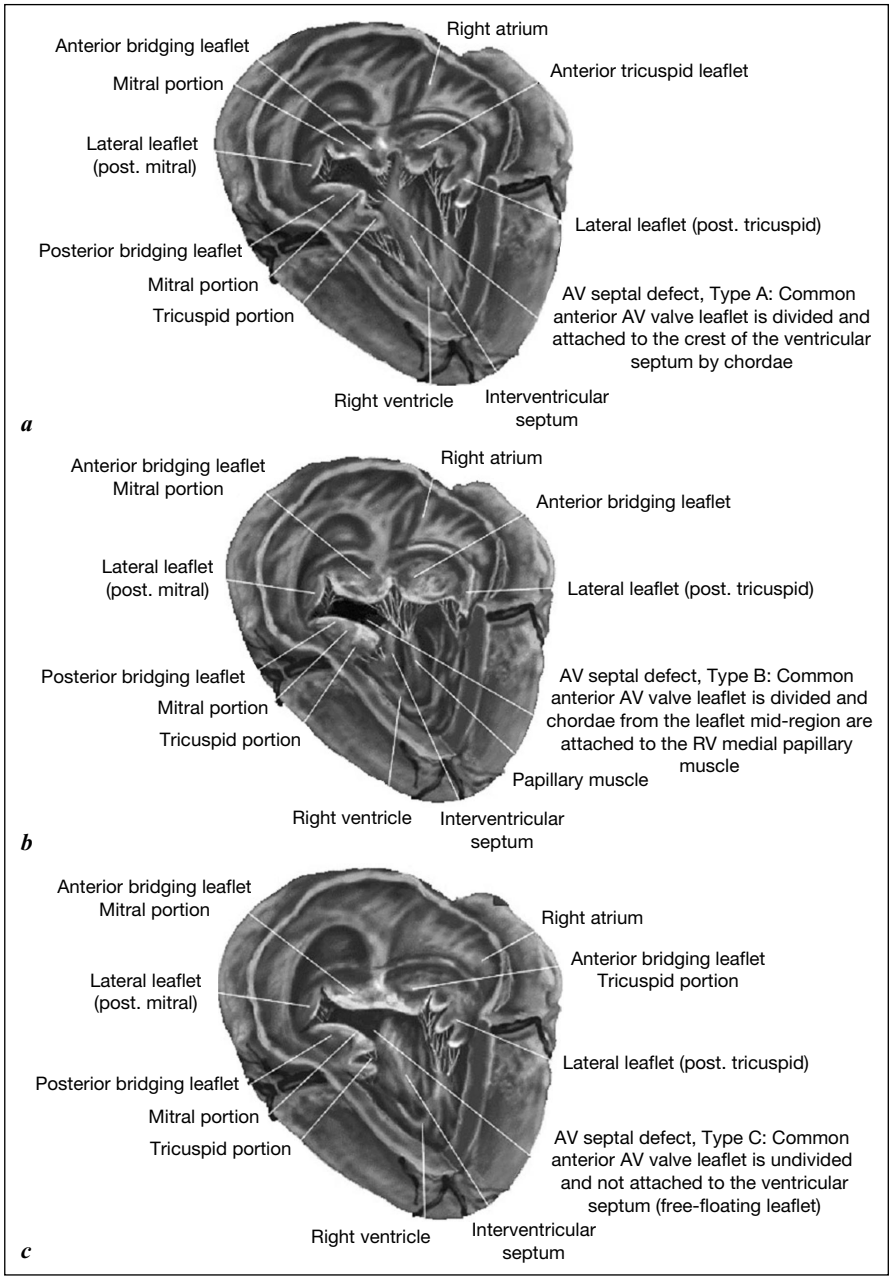
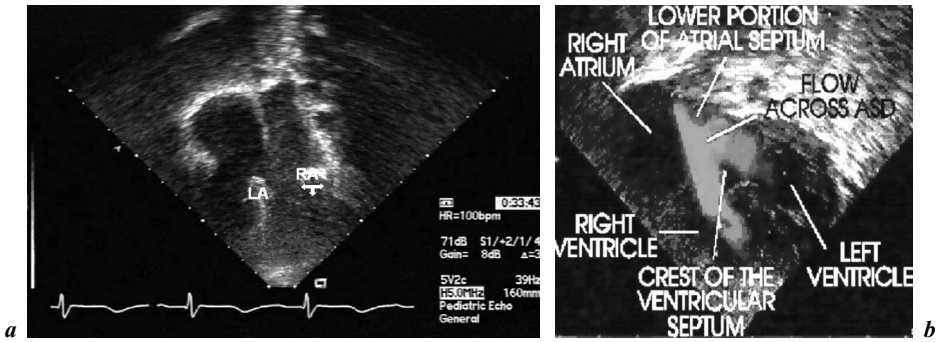


Fig. 4. a–c The complete atrioventricular (AV) canal classification of Rastelli [from The Multimedia Encyclopedia of Congenital Heart Disease, courtesy of Scientific Software Solutions, Inc., with permission].



a *b*

Fig. 5. ***a*** AV valves are at the same level. The 2-D echocardiogram resolves a defect in the lower portion of the interatrial septum. ***b*** Doppler echocardiography demonstrates left to right shunting. Echocardiographic assessment of atrioventricular (AV) valve regurgitation in AV canal defects. LA = Left atrium; LV = left ventricle; RA = right atrium; RV = right ventricle.

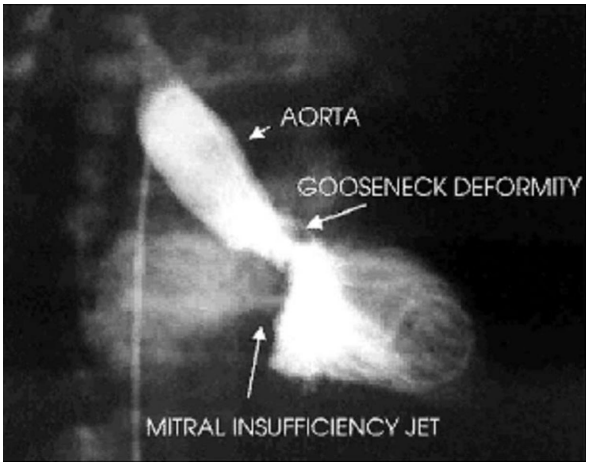


Fig. 6. The classic angiographic view of a complete atrioventricular (AV) canal with encroachment of the AV valve apparatus on the left ventricular outflow tract, referred to as a gooseneck deformity. AV valve regurgitation is also demonstrated.

(VSD), as occurs in the complete AV canal. With an ASD (ostium primum defect), the compliance of the right and left ventricles as well as the pulmonary vascular resistance and systemic vascular resistance are important. As left ventricular compliance decreases with age, the shunt at the atrial level should

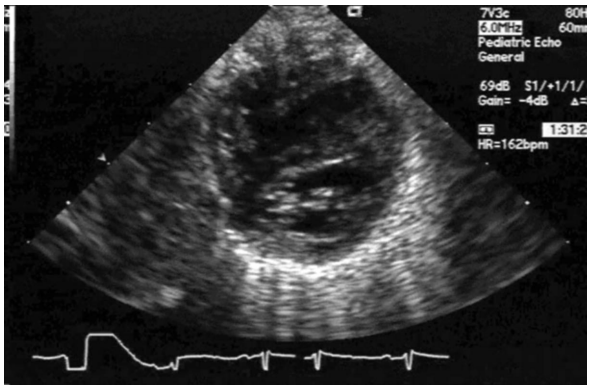


Fig. 7. Echocardiographic parasternal short axis view, demonstrating the pancaking effect of the right ventricle (RV) on the left ventricle (LV).

increase. In the presence of the combined atrial and VSD, the so-called complete AV canal, the right and left ventricular pressures are equal. Due to high pulmonary blood flow there will be pulmonary artery hypertension, which if untreated, will progress to irreversible pulmonary vascular disease known clinically as the Eisenmenger's syndrome.

As noted in figure 8, there is a step-up in oxygen saturation at the atrial level to 85%. The pulmonary veins are saturated at 95% and there is a step-down to 92% in the left atrium consistent with bi-directional shunting. The ventricular saturations are identical as are the pressures. There is a large pulmonary to systemic flow ratio ($Q_p/Q_s > 4{:}1$). The pulmonary artery pressure is at systemic level with a pulmonary to systemic resistance ratio ($R_p/R_s = 0.2$), which establishes the patient's operability. The large V wave in the left atrium reflects significant mitral valve regurgitation.

Left surgically untreated, the high shear velocities in the pulmonary vascular bed lead to pulmonary arteriolar damage. Pulmonary vascular changes in the extreme form result in histological grade V Heath-Edwards changes characterized by medial hypertrophy, and plexiform lesions. As a result, the pulmonary vascular bed becomes incapable of vasodilation.

As illustrated in figure 9, there is no step-up (increase in the oxygen saturation) at the atrial, ventricular or pulmonary artery level. In fact, there is right to left shunting (or step-down) at the atrial level. Notice there is a step-down from the normal pulmonary venous oxygen saturation of 98% to a left atrial oxygen saturation of 85% ($Q_p/Q_s < 1$). There is elevated pulmonary artery pressure and an abnormal pulmonary vascular resistance to systemic vascular resistance ratio, ($R_p/R_s > 1$), prohibiting surgical correction.

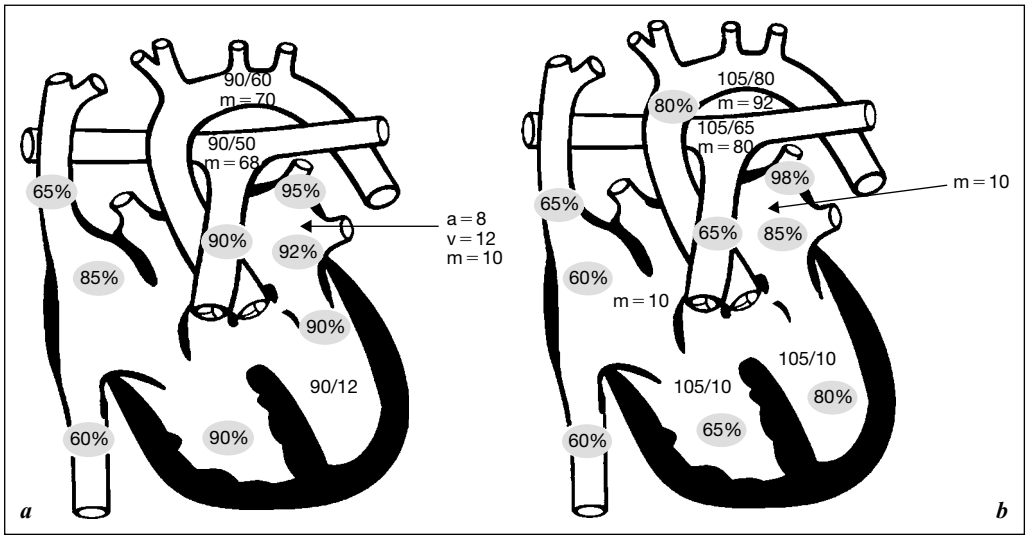


Fig. 8. Hemodynamics of a complete atrioventricular canal with (***a***) mitral regurgitation and with (***b***) Eisenmenger's physiology. Numerical values = pressures in mm Hg; a = a wave; m = mean; v = v wave; percentages = oxygen saturations.

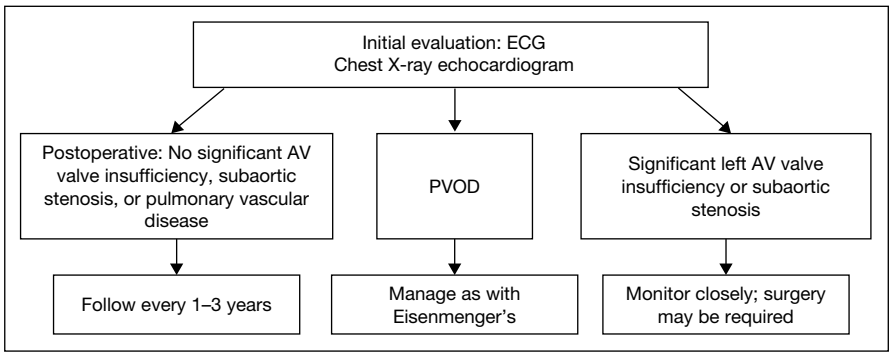


Fig. 9. Algorithm for the adult patient with atrioventricular (AV) canal. ECG = Electrocardiogram; PVOD = pulmonary valvular obstructive disease [from 10, with permission].

Finally, other problems that can develop after the surgical repair of an AV canal defect include the development of left ventricular outflow tract obstruction due either to accessory AV valve tissue or to the development of a subaortic membrane. Left ventricular outflow tract obstruction is more common with the partial AV canal defect.

Gersony and Rosenbaum [10], in their recent textbook, provide an excellent algorithm for the clinical management of these patients (fig. 9). Careful follow-up of the post-operative patient should be instituted in order to assess AV valve regurgitation, the possible development of left ventricular outflow tract obstruction, and/or the development of pulmonary vascular disease.

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Surgery for Atrioventricular Septal Defects

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Anatomic Considerations

Atrioventricular septal defects (AVSD) are characterized by the absence of AV membranous and muscular septum resulting in a deficiency both at the level of the atrium and particularly at the level of the inlet part of the ventricular septum. There is a high association with trisomy 21, which has a profound impact on the morphology of the AV valve, and the defect can either be complete or partial. The term transitional canal is not useful for the surgeon, as either a ventricular component exists or not. The canal is either balanced or unbalanced with right or left ventricular dominance. Heart defects with unbalanced AVSD are not discussed here. Figure 1 illustrates a left ventricular echocardiographic and cross-sectional view of the atrium, the AV junction, mitral valve, and the ventricular septum.

In the normal heart, the distance from the crux or inlet portion of the heart to the apex is almost equal to the distance from the apex to the aortic valve outlet portion (fig. 2a).

In an AV septal defect however, this is not the case. The inlet portion is foreshortened, and is much shorter than the outlet portion of the left ventricle (fig. 2b). The inlet part of the septum is scooped out, which results in the 'gooseneck' deformity, which may contribute to future development of subaortic stenosis. In the complete and balanced form of AVSD, very often there is only a minimal amount of mitral and tricuspid valve regurgitation pre-operatively. Also, infants without trisomy 21 tend to have more unusual AV valve anatomy and are more difficult to repair. The severity of AV valve incompetence is greater in older patients. Figure 3 illustrates a normal mitral valve and normal tricuspid valve.

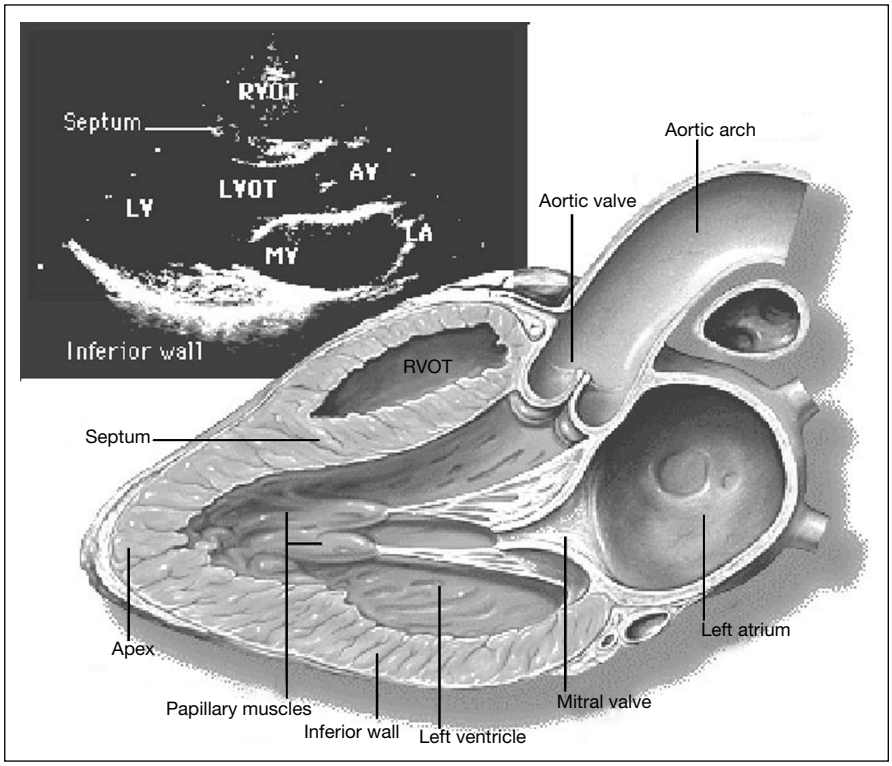

Fig. 1. Normal anatomy. AV = Aortic valve; LA = left atrium; LV = left ventricle; LVOT = left ventricular outflow tract; MV = mitral valve; RVOT = right ventricular outflow tract [copyright 2003, Yale University School of Medicine, with permission from Patrick Lynch, illustrator].

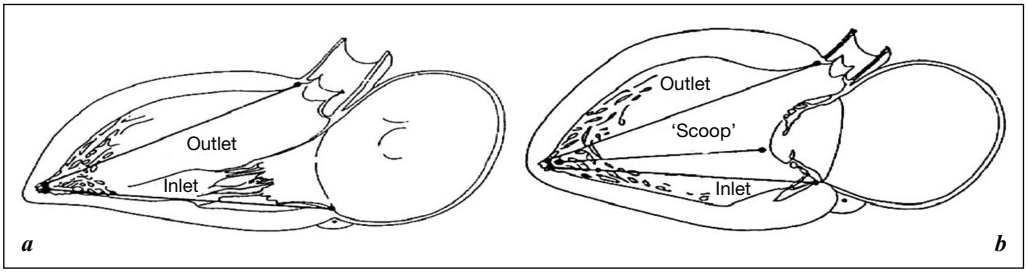

Fig. 2. Hearts with normal atrioventricular (AV) septation (***a***) and AV septal defects (***b***).

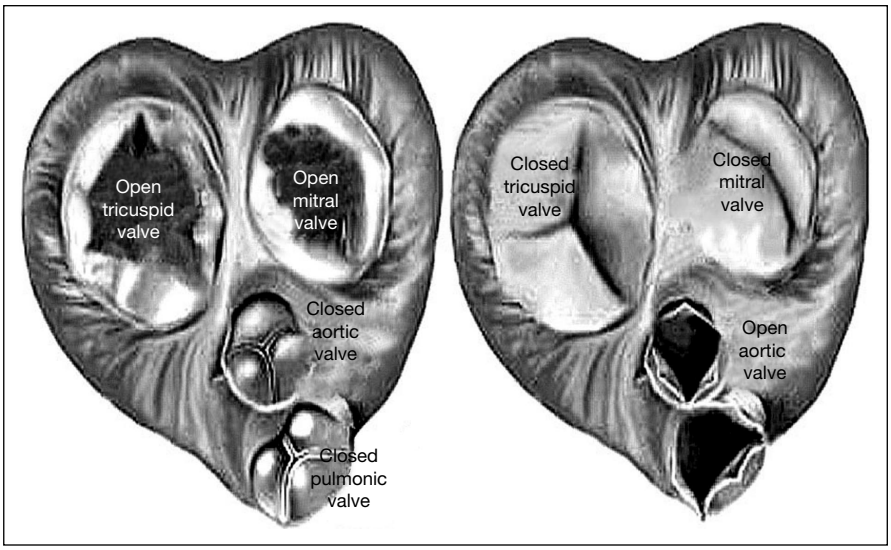

Fig. 3. Normal mitral and tricuspid valve anatomy.

In the partial AVSD canal, the mitral valve morphology is different. The left side of the AV valve is trifoliate and one can distinguish a lateral leaflet, a left superior leaflet, and a left inferior leaflet (fig. 4).

In the complete AVSD, there is a communication between the right ventricle and left ventricle underneath the bridging part of the superior and/or inferior leaflets. In all forms of AVSD the AV valve on the left side is trifoliate and can either be attached to the septum or can be free-floating. This has important implications for the surgical repair. In addition, another aspect of this condition with potential surgical consequences is the location of the conduction system. The AV node in AVSD is not located in the triangle of Koch. Instead, the AV node is located posteriorly more toward the AV valve junction. In addition, the non-divided bundle of His runs underneath the AV valve tissue in the partial form and runs on the crest of the ventricular septum in the complete form. The bundle is longer than in a normal heart. This information is vital so as to avoid creation of surgical AV block during repair.

The AV septal defects are known to be associated with other conditions: such as a small left ventricle, hypoplasia of the aortic arch, tetralogy of Fallot, and subaortic stenosis which can be present even before surgery. Other complex forms of congenital heart defects, which may be associated with this condition, include transposition of the great vessels, total anomalous pulmonary venous connection and single ventricle.

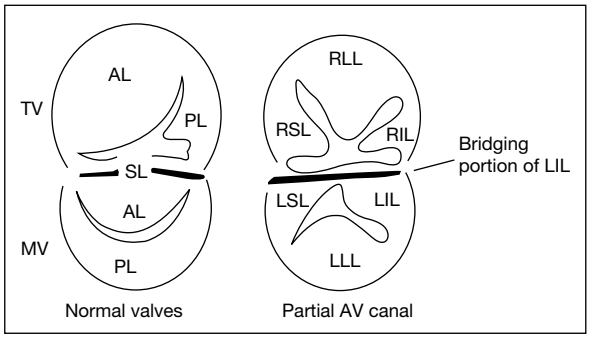

Fig. 4. Trifoliate AV valve. AL = Anterior leaflet; AV = atrioventricular; LIL = left inferior leaflet; LLL = left lateral leaflet; LSL = left superior leaflet; MV = mitral valve; PL = posterior leaflet; SL = superior leaflet; TV = tricuspid valve; RIL = right inferior leaflet; RLL = right lateral leaflet; RSL = right superior leaflet [reprinted from Pediatric Cardiac Surgery (E. Arciniegas, ed.), Fig. 11C-1, with permission].

Surgical Technique

Interestingly, many of the earlier operations for complete AV canal repair used a two-patch technique. Lev and Bharati's description of the location of the bundle of His in 1958 provided the basis for repair techniques to avoid heart block. The two-patch technique uses pericardium for the atrial patch and Gortex for the ventricular patch. In order to expose the entire rim of the ventricular septum, careful retraction – rather than division of leaflets – is preferable. A semilunar Gortex patch is cut to the appropriate size and shape and sewn along the right ventricular aspect of the septum. Again, careful attention must be paid to the conduction system running along the crest of the septum. After the ventricular component is closed, the valve leaflets are then 'sandwiched' between the ventricular patch and the atrial patch, which prevents disruption of these very friable structures. This principle is used whether there are attachments between the leaflets and the crest of the septum or not. The cleft in the AV valve is sutured closed over most of its distance, depending on the presence of chordal attachments supporting the leaflets. Sometimes, chordal shortening maneuvers are employed to enhance AV valve competence. When appropriate, annuloplasty sutures are used to decrease the size of the AV valve annulus. Annuloplasty rings are not used in children for their obvious inability to grow.

More complex AV valve morphology (like double orifice mitral valve or parachute mitral valve) do occur, and are more difficult to repair. Moreover, there is a higher degree of post-repair mitral incompetence in infants with deficient

AV valve tissue. Generally, these patients present themselves with severe regurgitation before the operation.

Echocardiography has been extremely useful in pre- and post-operative assessment of AV valve regurgitation and the quality of the surgical repair. Unfortunately, some patients require second or third operations for mitral valve malfunction. At the second operation, one is often able to repair the mitral valve again. Few patients do require mitral valve replacement. Fortunately, as they outgrow their mitral valve, one is always able to implant a larger sized valve in a growing child.

Surgical Results for Partial AV Septal Defects

In the last decade we have performed 120 repairs of partial AV septal defects. The majority of the patients are in the older age group, since it is often not necessary to operate on these children as neonates or during the first year of life. The surgical results have been good with low mortality. In a group of 52 patients with follow-up of at least 5 years, there has been no hospital mortality or reoperation for residual shunt. Three patients required reoperation for persistent mitral valve regurgitation; 1 had a repair, and 2 had mitral valve replacement. In addition to mitral valve replacement, both these patients also developed subaortic stenosis. The reoperation rate for subaortic stenosis is 5.7%.

Surgical Results for Complete AV Septal Defects

In complete AV septal defects, which constitute a larger patient group, the operation is generally performed in the first 6 months. This timetable minimizes the development of pulmonary vascular disease. Older patients generally have other associated conditions but their mortality has nevertheless been quite low. Between 1990 and 2000, 202 patients underwent repair of AVSD. Long-term survival has been stable with a low mortality of 1.3%. There were 4 late deaths. One death was related to pulmonary hypertension; another was attributable to respiratory insufficiency requiring extracorporeal membrane oxygenator for respiratory support post-operatively; 1 patient who developed subaortic stenosis and also had coarctation of the aorta at the time of the repair, died of chronic congestive heart failure. Lastly, 1 patient died following mitral valve replacement.

Reasons for reoperation included: residual shunt, mitral valve incompetence and development of subaortic stenosis. One patient underwent repair of a residual ventricular septal defect; 7 had mitral valve repair, and no one required

mitral valve replacement. The reoperation rate for subaortic stenosis in both complete and partial AV canal defects was 5.8%.

Conclusion

In general the results of repair of both partial and complete AVSD can be performed with very low risk and quite good outcomes with regards to survival and mitral valve function. Left AV (mitral) valve regurgitation, subaortic stenosis and AV block may be sequelae, which develop, or progress [1–6]. In general, late results after 'mitral' valvuloplasty for these patients have been excellent with the need for surgical revision in about 5% of patients. Occasionally, repair of an abnormal left AV ('mitral') valve may result in a stenotic valve, which will usually necessitate reoperation. The likelihood of residual left-to-right shunt from left atrium or left ventricle to right atrium is very small. Subaortic stenosis will develop or progress in up to 5% of patients after repair, particularly in patients with primum atrial septal defect as well as in some complete AV septal defects, especially if the left AV (mitral) valve has been replaced.

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When Should Tricuspid Valve Replacement/Repair Accompany Mitral Valve Surgery?

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The purpose of this review is to consider the problems associated with tricuspid valve disease as it relates to multivalvular cardiac surgery.

The scope of the surgical procedures we are going to review is a combined tricuspid valve procedure, particularly in the setting of aortic valve disease, mitral valve disease, coronary disease or congenital heart disease. The type of the procedure may be a tricuspid reconstruction or a valve replacement. The nature of the pathology that we are dealing with can be primary, in the form of acquired congenital or degenerative disease. It can also be secondary in the form of a myopathy or associated with pulmonary hypertension, aortic or mitral valve disease [1–18].

Tricuspid Anatomy

It is important to recall that the tricuspid valve does not exist totally isolated from the other cardiac valves. It is particularly important to recognize the concept of the fibrous skeleton of the heart in which the aortic valve, the mitral valve and the tricuspid valve are all imbedded in a fibrous network of connective tissue. Changes in the mitral valve and the aortic valve are very intimately related to what happens to the tricuspid valve. The tricuspid valve is also very intimately related to the right ventricle, which, by nature, is a low-pressure, high-volume ventricle. As a result the right ventricle tends to be a very compliant. Not only is the ventricle compliant, but the valve annulus is also compliant. Anatomy of the right atrium is also important for many reasons, including the location of

the conduction system lying at the base of the triangle of Koch. If one looks at a simplistic diagram of the anatomy, there are three leaflets of the tricuspid valve. An anterior leaflet which is clearly the largest and represents well over half of the circumference of the valve, a posterior leaflet, and the septal leaflet. The conduction system typically lies immediately subjacent to the septal leaflet at the base of the triangle of Koch, which is outlined by the coronary sinus, the tendon of Todaro and the septal leaflet of the tricuspid valve. One needs to be knowledgeable about the conduction system and the anatomy of the right bundle branch. There is one major papillary muscle along with multiple mural leaflets, papillary muscle connections, and septal connections. Unlike the mitral valve which has a fairly fixed and defined papillary muscle anatomy, the tricuspid valve is quite variable.

Diseases of the Tricuspid Valve

The etiology of tricuspid stenosis is most commonly rheumatic but there are other etiologies, including carcinoid disease, tumor, and collagen vascular disease. In addition, tricuspid stenosis may be the result of intervention which may have overly narrowed the valve or annulus at a previous time. Tricuspid insufficiency is far more common and is usually secondary to aortic or mitral valve disease, myopathy of the ventricle, and, sometimes occurs in the setting of isolated pulmonary hypertension. The primary causes of tricuspid insufficiency include rheumatic, infectious and traumatic etiologies.

Ischemic heart disease, carcinoid disease and myxomatous disease can selectively affect the tricuspid valve. Collagen vascular disease as well as certain types of iatrogenic injury, produced either in the operating room or sometimes caused in the hands of the interventional cardiology team, can produce the need for surgical intervention for tricuspid insufficiency. This is particularly true as it relates to the placement of transvenous pacemaker leads.

The clinical diagnosis of tricuspid insufficiency is usually clear. Peripheral edema, ascites, hepatomegaly, jugular venous distention and a pulsatile liver are typical findings that we see. These are not specific, however, as they are common findings, particularly the peripheral edema, as manifestations of secondary pulmonary hypertension from left-sided heart failure from due to left-sided valvular or other heart disease.

Echocardiography can be diagnostic of many these lesions and to quantify the severity of most forms of valvular insufficiency. In particular, to quantify the severity of tricuspid insufficiency lesions, it is far better done on a preoperative, alert patient than it is in the operating room where, in the hands of a cardiac anesthetist, one can make almost any degree of tricuspid insufficiency

disappear by hemodynamic manipulation. There are quantification techniques based upon the width and velocity of the jet, the anatomy of the leaflets, the chordae, the papillary muscles, etc. A number of centers believe in cardiac catheterization and hemodynamics as an important way of diagnosing the severity of tricuspid insufficiency. They base their assessment on the presence of an A-wave in patients in sinus rhythm, on the presence or absence of a gradient in the setting of insufficiency, and on angiographic contrast quantification.

In our center we rely more on transesophageal and transthoracic echocardiography, which are key. It is important to know what the status of the tricuspid valve is in the operating room and to determine this before we go to the operating room. We attempt to repair these valvular lesions and want to be very sure that we have rendered the tricuspid valve just as competent as we have rendered the mitral valve.

Surgery for Tricuspid Valve Disease

Let us now consider what to do, when to do it, how to do it, and what long-term results to expect. In order to address these issues we need to consider a surgical procedure known as 'triple valve surgery'. This construct focuses on the role of approaching the tricuspid valve surgically in the setting of operable left-sided valvular heart disease. There are several studies that address this. In one study of 59 such cases, 8% of patients were lost to long-term follow up t during an average follow up of 82 months. The Montreal Heart Institute study was somewhat smaller but similar in many ways in reporting a 77-month follow-up. Our colleagues at the Mayo Clinic have reported a series of 109 patients that they followed for up to 66 months. These were all analyzed slightly differently.

If one specifically considers aortic valve and mitral valve surgery (be it repair, or replacement) plus tricuspid valve operation (be it repair or replacement), the so called 'triple valve', it is seen that tricuspid valve procedures were required in 20–35% of patients in these combined series b of patients otherwise being subjected to double valve surgery. Much of the decision making was based upon the clinical signs and symptoms. Tricuspid stenosis was rare and structural tricuspid malfunction was relatively uncommon as well. Echocardiographic findings, cardiac catheterization data, and operative findings were all determinants of patient selection. In these combined series approximately 35% of the patients with tricuspid valve insufficiency had to come back for surgery or died during the follow-up period because of right-sided heart failure, if only the operable left-sided heart disease was treated. Thus, in one

third of patients in whom we might do the most perfect left-sided heart operation for, we really have not done that patient adequate service if we don't address the right-sided heart pathology.

A review of these populations shows that 80% were female, 10% had pure aortic stenosis as their aortic lesion, 52% had pure aortic insufficiency, 65% of the mitral lesions were stenosis, and 74% had associated mitral regurgitation. Of these patients, 27% were NYHA Class IV, 57% NYHA Class III, 15% had ascites, 60% had hepatomegaly, and 33% had pulsatile livers. Peripheral edema was very common and jugular venous distension was present in 66% percent of them. Furthermore, 34% of patients had one prior valve operation and 8% had two previous operations. Three quarters of them were in atrial fibrillation. Thus, these are relatively seriously ill patients.

In these series the tricuspid valve was replaced in 12 to 31% of the cases. The indications for replacement were failed attempts at repair (the surgeon attempted to repair the tricuspid valve and it didn't work), or failed previous repair (that is to say the patient had a previous tricuspid valve operation that was repaired to the satisfaction of the surgeon at that time but came back with a persistent or recurrent disease). The overwhelming majority, especially in the later series, underwent successful tricuspid valve reconstruction.

The results showed that 13% of these patients who underwent the triple valve operations did not survive the hospitalization, with half of the deaths being from cardiac related causes. The risk factors for in-hospital death in the setting of the triple valve operation included female gender, hepatomegaly, and previous valvular heart surgery. If the aortic valve had previously been replaced there was a greater risk than if the previous surgery involved the mitral valve. In the patients that succumbed to late death during the course of follow up, pulsatile liver, ascites, and jugular venous distension persisting after operation were all predictors of late death. This was independent of the severity and the reversibility of left-sided heart failure. The presence of concomitant coronary artery disease and the related need for coronary artery bypass surgery was also risk factors. However, late death was not predicted by repair versus replacement of the tricuspid valve, whereas it is predicted by repair versus replacement of the mitral valve. After 12 months of follow-up in these combined series, 87% of patients were alive, with 70% alive at 60 months. After 120 months or 10 years, less than half of these patients undergoing this complex operation were still alive. The loss of follow-up information was approximately 1%, so these are remarkably complete series. Freedom from reoperation was 94% at 12 months and about 66% at 5 years.

The issue of biological versus mechanical valve replacement in the tricuspid position is important. A group of 129 patients who failed repair of the tricuspid valve and, thus, required a replacement, were followed. In this series,

32% of the valve replacements were biological and 67% were mechanical prosthesis. Although early mortality was high, late mortality was very low. The 20-year actuarial follow-up of the mechanical valve was good as 68% of the patients with mechanical valves were alive at the end of the follow-up period compared to 54% of those with biological valves. The biological valves had a 10% incidence of tissue degeneration, whereas the patients with mechanical valves had a 3% incidence of embolization and degeneration of the valve, with a 7% incidence of pulmonary embolization.

The overwhelming majority of tricuspid valves are repaired. The basic techniques for repair include bicuspidization, annular plication and various types of annuloplasty, i.e., ring annuloplasty, linear reduction annuloplasty, and so-called suture annuloplasty. The most common repair is likely the DeVega suture annuloplasty in which a continuous monofilament suture is run from the base of the junction of the septal leaflet, pledged on each end circumferentially, and the annulus is reduced. The ring-type annuloplasty places a ring structure into the non-septal portion of the tricuspid valve annulus. The technique we have applied in our center is called a multi-pledget technique, which was very much like the DeVega technique except instead of a single set of pledgets at either end, we ran the same suture through multiple pledgets to keep it from cutting though the fragile annular tissue. We had an opportunity to review some of the late results. There were no incidents of heart block. We analyzed recurrent tricuspid valve insufficiency with ring technique were in our facility, and 77% of patients were completely free of tricuspid regurgitation. Only 6% had more than 1+ tricuspid regurgitation and the techniques in both of these groups were equivalent. The Beck's technique, which is a linear reducing technique, when compared to the DeVega, is also very similar. Twenty-seven patients were followed for 4 years, with no incidents of heart block, and 66% were completely free of insufficiency in late follow-up. If one considers the DeVega suture techniques (41 patients followed for 10 years) 81% were completely free of recurrent tricuspid insufficiency and 7% had 2–3+ tricuspid regurgitation and 2% had more. With the Beck's linear reducer the results were also excellent, with no heart block, no new tricuspid stenosis, and with 80% completely free of recurrent tricuspid insufficiency at late follow-up. With our pledgeted suture technique there was not really much difference. We reviewed 74 patients with a 66-month follow-up. It took us an average of 10 min to do the repair. We adjusted the tension simply to the dimension of the annulus. There was no late pull through of the sutures, there was no new incidence of tricuspid stenosis, and there was no incidence of heart block, either transient or permanent. At the end of our follow-up period, 93% of patients had 0–1+ tricuspid insufficiency, with 5 and 2% in the more severe (2+ and 3+ TR) groups.

Conclusions

Tricuspid valve disease, particularly tricuspid insufficiency associated with mitral and aortic valve disease, is common. The threshold for combined surgery should be low because the incidence of death, readmission, and reoperation is otherwise substantial. Whereas a reinforced suture repair, if at all possible, is preferable to the replacement of the valve, if tone must replace the valve, mechanical and biological prosthesis seem to have excellent long-term results. Repair techniques are safe, rapid and reliable, and the morbidity and mortality of residual or untreated tricuspid valve disease is high. When in doubt, don't 'roll the dice', fix the valve.

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Strategies for Management of Postcardiotomy Cardiogenic Shock following Valvular Heart Surgery

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Despite vast improvements in the field of cardiac valve surgery in the areas of surgical technique, cardiopulmonary bypass, and myocardial protection, postcardiotomy cardiogenic shock (PCCS) remains a potential complication. We define PCCS as cardiac failure that results in an inability to wean a patient from cardiopulmonary bypass or as cardiac failure that occurs in the immediate postoperative period. From a purely hemodynamic perspective, it may also be defined as systolic blood pressure <100 mm Hg, mean pulmonary artery blood pressure >25 mm Hg, central venous pressure >15 mm Hg, and cardiac index (CI) $<2.01 \cdot \text{min}^{-1} \cdot \text{m}^{-2}$ [1]. This syndrome results from myocardial insult associated with stunning, infarction, or poor preservation. As a result of poor cardiac and/or end-organ recovery, this syndrome is associated with significantly high morbidity and mortality [2]. Approximately 2–6% of all postcardiotomy patients develop cardiogenic shock following their elective cardiac procedures [3–5]. Traditional management of PCCS was largely medical, comprised of inotropes, pressors, and intra-aortic balloon pump (IABP) support. The ventricular assist device (VAD) is the most recent addition to the armamentarium available to treat these patients. This chapter will focus on support strategies that are commonly implemented at our institution for postcardiotomy failure following valvular heart surgery.

Types of Support

The first-line treatment in combating PCCS is high-dose inotropic support. High-dose inotrope can be defined as twice the normal dose of a center's usual

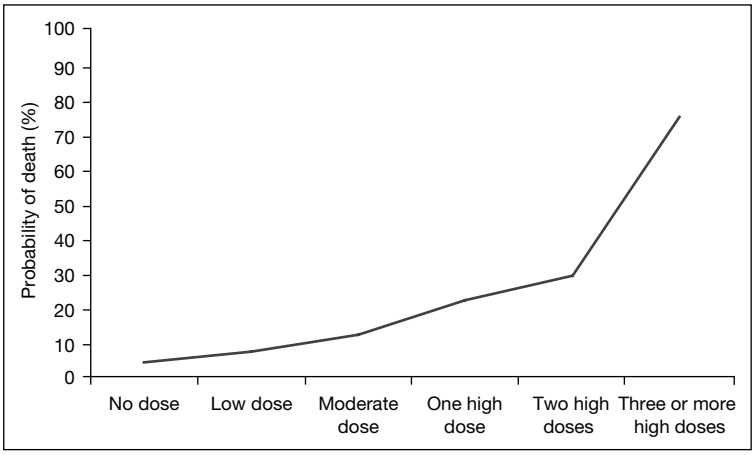

Fig. 1. Probability of death based on postoperative inotropic support. *Low dose:* epinephrine 1–4 μg/min, dobutamine 1–4 μg/kg/min, dopamine 1–4 μg/kg/min, milrinone 0.125–0.24 μg/kg/min. *Moderate dose:* Epinephrine 5–9 μg/min, dobutamine 5–9 μg/kg/min, dopamine 5–9 μg/kg/min, milrinone 0.25–0.49 μg/kg/min. *High dose:* Epinephrine ≥10 μg/min, dobutamine ≥10 μg/kg/min, dopamine ≥10 μg/kg/min, milrinone ≥50 μg/kg/min [from reference 6, with permission].

drug of choice (i.e., epinephrine, milrinone, dobutamine, or dopamine) [6]. Figure 1 illustrates the rapid increase in mortality rates after more than one high-dose inotrope is initiated. Drawbacks of high-dose inotropic support include increased workload for an already stressed heart, and compromised perfusion of end-organs with subsequent prolonged dysfunction. In our center, we have noted that the majority of our chronic terminal intensive care unit (ICU) patients have recovered cardiac function with end-stage renal, hepatic or pulmonary failure.

The next line of assault against PCCS is an IABP. This method of support was first introduced in the 1960s. It is a commonly used rescue device in the cardiac surgeon's armamentarium because it is easily inserted, easily removed, and relatively inexpensive. Although IABP theoretically provides afterload reduction and enhances coronary perfusion, important advantages in the setting of cardiac ischemia, a major observed disadvantage of IABP is its lack significant ventricular unloading. The survival rate for postcardiotomy heart failure when an IABP is necessary is 40 to 60% [7]. The mortality rates for IABP in the treatment of PCCS are high for several reasons. The first and most important is that IABP requires a stressed heart to continually expend energy, due to the lack of significant ventricular unloading. The afterload-reducing effect is often mitigated by the increased myocardial oxygen demand of inotropic support that is required to maintain an adequate CI. Finally, IABP alone cannot provide a profoundly

insulted heart with the support it needs to maintain adequate end-organ perfusion. Utilizing an IABP to increase the cardiac output from 2.2 to 2.45 l/min often does not positively impact the patient's ICU course.

These dilemmas led surgical innovators to focus on developing a device that would address PCCS while also ameliorating most of the shortcomings of both pharmacologic therapy and IABP. The VAD provided some answers and was appropriately embraced by physicians whose patients could not be adequately treated with IABP. The VAD provides complete unloading of the ventricle, thereby allowing a failing ventricle time for recovery or evaluation for transplantation. In addition, with VAD support, the need for inotropic support and its accompanying increase in myocardial oxygen consumption are eliminated. The VAD also attenuates the extent of end-organ damage, thereby further decreasing morbidity in this gravely ill patient population.

Patient Selection for VAD/Timing of Mechanical Support

According to data from the Society of Thoracic Surgeons, the average cardiothoracic surgery program in this country performs approximately 600 cases annually. Of these patients, 93% tolerate surgery well with a predicted mortality rate below 1% (fig. 2). Of the remaining patients, 6% are weaned from cardiopulmonary bypass (CPB) on inotropic support with an IABP. Twenty percent of these patients have normal hemodynamics and a 2% or lower mortality rate. The patients we continue to struggle with are those with marginal hemodynamics or cardiogenic shock. Although we manage to get these patients to the ICU, they have a significantly higher mortality compared to the others. So the fundamental question remains of defining the correct time to intervene with mechanical support after valvular surgery.

Traditionally, consideration for insertion of a VAD into patients with PCCS was undertaken only after the patient failed to respond to high-dose inotropic therapy and IABP. In response to the previously discussed high mortality rates and lack of consensus associated with the use of high-dose and/or multiple inotropes, Samuels et al. [6] proposed early VAD insertion. His group developed a formula to assist surgeons in the decision-making process and takes into account the patient's hemodynamics, the number and dosages of inotropic therapy, and the length of time that has elapsed since the initiation of weaning from CPB.

Aside from pharmacologic therapy, other factors that influence VAD insertion include heart rate >100 beats/min, CI $<2.01 \cdot \text{min}^{-1} \cdot \text{m}^{-2}$, the presence of an IABP that provides only marginal benefit, decreased urinary output, mixed venous oxygen saturation $<50\%$, pulmonary capillary occlusion pressure

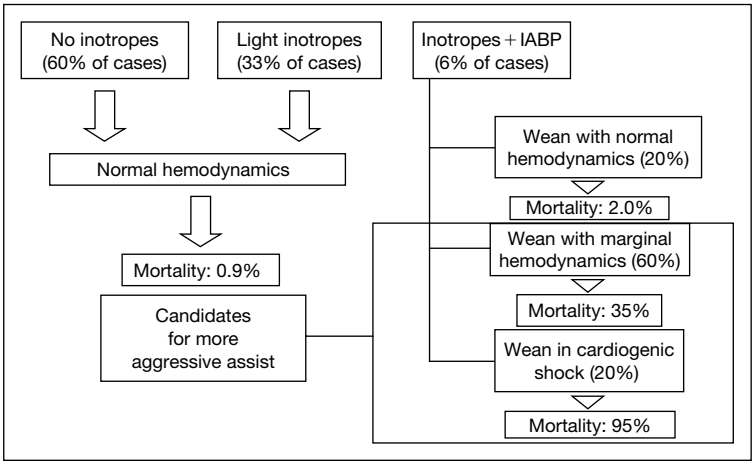

Fig. 2. Cardiopulmonary bypass weaning and associated mortality (based on 600 cases with 2.4% mortality). CPB = Cardiopulmonary bypass; IABP = intra-aortic balloon pump; STS = Society of Thoracic Surgeons [from Society of Thoracic Surgeons database, with permission].

>25 mm Hg, and arrhythmias. At our institution, no patient with a mixed venous oxygen saturation below 50% leaves the operating room without a VAD, unless there is a congenital condition that explains such a depression. Extensive data supports the observation that patients who require a VAD fare better when the device is implanted in the operating room, rather than after they decompensate in the ICU [7].

We also recommend early intervention with a VAD in technically unsuccessful operations, after which there is reason to believe that the patients may have trouble in the long term. Combining the early postoperative mortality rate with the 1-year complication rate of these patients yields a value high enough to warrant mechanical support. Perioperative infarction and biventricular failure, independent predictors of postoperative complications, are particularly common in high-risk valve cases and also warrant early VAD insertion.

With Americans living longer, there has recently been a significant increase in the number of elderly patients undergoing cardiac surgery. Historically, published reports have suggested that this patient population may have higher mortality rates and lower recovery rates following PCCS [4, 8]. However, more recent work by Wareing and Kouchoukos [9] suggests that there is no appreciable difference in outcome between the elderly population and a younger cohort after each has undergone implantation of mechanical circulatory support. This information has great implications, because if the surgeon knows that elderly

patients with valvular pathology are candidates for a VAD, it may influence their operability.

Selecting the Appropriate Device

Selecting a suitable device is primarily determined by the clinical scenario, particularly the length of time the surgeon estimates will be necessary for the patient to regain adequate cardiac function. Irrespective of the device chosen, the ultimate goal of postcardiotomy support is twofold. First, it allows the myocardium time to declare its recoverability (stunned vs. necrosed); additionally, and possibly more importantly, postcardiotomy support maintains adequate end-organ perfusion.

Centrifugal Pumps

With the exception of the IABP, centrifugal pumps are the most commonly used cardiac assist devices [2]. These pumps represent a first-line VAD and are designed for short-term support. Centrifugal pumps are widely available and very surgeon-friendly because they are easily implanted and operated. Additionally, these devices are suitable for all sizes of patients who experience either uni- or biventricular failure. The initial financial burden on the patient for this device is considerably less when compared with more sophisticated systems. The limitations of centrifugal pump support include frequent pump malfunction, non-pulsatile flow, hemolysis, the need for full-time bedside personnel, and lack of proper reimbursement. Additionally, patients with this device have an increased risk of hemorrhage from cannulation sites as their blood pressure rises. This typically occurs during recovery as the patient becomes more aroused. As a result, patients with centrifugal pump support should be kept sedated. In turn, these requirements place additional restraints on ambulation and early postoperative rehabilitation. The need for full-time support personnel and periodic complications resulting from use of a technology not designed for postcardiotomy support often make this technology more expensive in aggregate compared to customized systems discussed in the remainder of this chapter.

Abiomed System

The Abiomed BVS 5000 was approved by the Food and Drug Administration (FDA) to support all etiologies of recoverable cardiac failure. Like centrifugal pumps, this system is a short-term cardiac support device that is widely available, easy to insert and remove, and capable of providing both uni- and biventricular mechanical support. This device delivers pulsatile flow

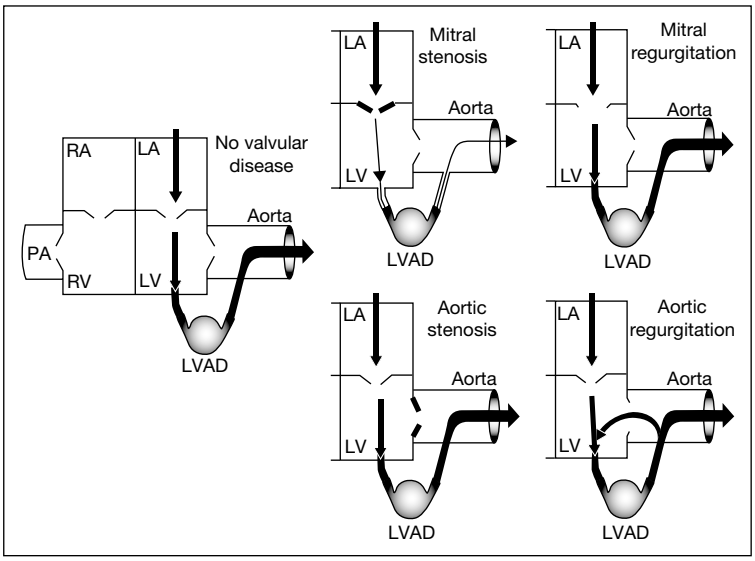

Fig. 3. Effects of valvular pathology on left ventricular assist device function. LA = Left atrium; LV = left ventricle; LVAD = left ventricular assist device; PA = pulmonary artery; RA = right atrium.

and requires minimal bedside monitoring. The limitations of the Abiomed BVS 5000 are similar to those of centrifugal pumps, which include minimal mobility and rehabilitation, and the necessity for systemic anticoagulation.

Implantable Systems

The Novacor (World Heart, Ottawa, Canada) and HeartMate (Thoratec, Pleasantville, Calif., USA) VADs are implantable pulsatile devices. These devices are FDA approved and an excellent source of longer term support. Anticoagulation is not necessary with the HeartMate system. Possibly the most important advantage of these devices is the opportunity for early rehabilitation of the patient. Disadvantages of implantable devices include a complex implantation process, risk of bleeding from cannulation site, and requirement for patients to have a body surface area $\geq 1.5\ m^2$.

Tackling the Valvular Pathology

Valvular pathology in the setting of heart failure can complicate VAD insertion (fig. 3). For example, diagnosis of aortic insufficiency in patients with

end-stage left ventricular failure is difficult because the left ventricular end diastolic pressure (LVEDP) is high, the aortic diastolic pressure is low, and subsequently a very low gradient remains across the aortic valve. Aortic insufficiency is often unmasked after insertion of a VAD, when the valve is exposed to systolic pressure and the LVEDP is reduced to <10 mm Hg. Several techniques have successfully addressed this problem. If the patient has a native or tissue valve, we often suture the dysfunctional cusp to the adjacent cusp. Usually this creates a normally functioning valve that is capable of withstanding increased aortic pressures after VAD insertion. This repair prevents a vicious cycle that would otherwise occur, allowing blood ejected through the outflow graft from re-entering the left ventricle. If this fails, the entire valve can be oversewn. A mechanical valve in the aortic position during VAD insertion can also be of concern. Small thrombi may develop on the pivot guards of the valve and when the patient performs a Valsalva maneuver, he may experience a thromboembolic event. To address this potential complication, we suggest placing a patch on the aortic aspect of the valve to prevent any opening of the mechanical aortic valve.

The management of mitral valve pathology to allow the VAD to function efficiently is relatively simple. In the setting of mitral regurgitation, we recommend an edge-to-edge repair of the valve. This procedure is less challenging and time consuming compared to mitral valve replacement. For patients with mitral valve stenosis, we recommend commissurotomy. Replacement of the valve is generally not warranted and removal of a pre-existing valve exposes the pulmonary system to intolerable pressures when the ventricle ejects against an already ejecting VAD.

Technical Considerations

The amount of times the surgeon attempts to wean from CPB influences whether patients with PCCS will ultimately develop uni- or biventricular failure. The protocol at our institution is to attempt CPB wean, and if initially unsuccessful, wait 15 min and then initiate a second attempt. If the second attempt fails, wait 1 h before a third attempt. After the third unsuccessful attempt, we customarily insert a VAD. There are two reasons for being so aggressive. The first is that the longer one waits before inserting a VAD, the more likely the need for both left and right ventricular support. Secondly, the depletion of adenosine triphosphate, which is believed to be the most common etiology of reversible cardiogenic shock, may require 72 h for normalization. Thus, spending significant time in an operative suite repeating multiple attempts to wean from CPB may not be the most efficient strategy. In addition, this prolonged

bypass time may also lead to increased risk of postoperative bleeding complications.

Right ventricular function typically improves with adequate left ventricular unloading. Nevertheless, both ventricles sometimes fail and biventricular support will be necessary. We prefer this option when substantial end-organ dysfunction is expected or the patient was in shock preoperatively. Biventricular VAD support should also be encouraged in the setting of elevated right atrial pressure coupled with low pulmonary artery pressure, hepatic failure with continued bleeding, and progressively decreasing urine output. Nevertheless, the initial approach is to obtain left heart support and wait. Close monitoring of right heart function is essential. Right heart failure in the ICU can be initially inconspicuous, but often swift and devastating. If right heart failure occurs, the initial treatment is pulmonary vasodilators.

When implanting a VAD into a patient with a mechanical valve in the mitral or aortic position, we recommend avoiding left atrial cannulation. This is important for several reasons. First, a mechanical mitral valve will serve as a nidus for thrombus if adequate blood flow across the structure is not ensured. Second, if implantation follows an acute myocardial infarct, there is an increased risk of endocardial thrombus formation in the ventricle due to stasis at the site of infarction. This may lead to thromboembolic events following removal of the VAD. Finally, apical cannulation results in increased VAD flow and the left ventricle ejects blood, even at a low pressure, into the system. For these reasons, we routinely cannulate the apex of the heart for the inflow in these patients. Cannulating the apex affords easy accessibility for implantation and removal.

Conclusion

The keys to success include early VAD insertion, early biventricular support when appropriate, adequate time for recovery, and identification of a regional transplant center for inter-hospital transfer if needed. Early VAD insertion minimizes complications of prolonged CPB, and survival approaches 50% when VAD insertion occurs within 60 min of the first attempt to wean CPB. Allowing adequate time for recovery refers to return of relatively normal ventricular as well as end-organ function. Regeneration of adenosine triphosphate stores can take as long as 5 days, allowing 90% of PCCS survivors to be weaned from support with 7 days. Although many centers have devices capable of temporarily supporting patients with PCCS, they do not offer long-term assistance or cardiac transplantation. These centers should become part of a network that allows patients to be transferred to a tertiary facility that offers implantable devices and cardiac transplantation (fig. 4).

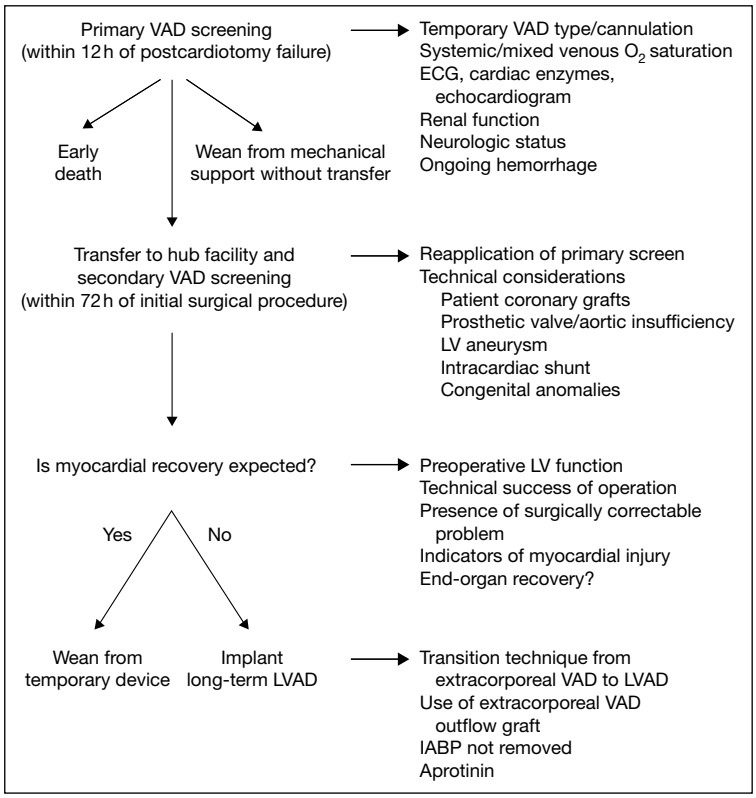

Fig. 4. Algorithm for the management of postcardiotomy shock. ECG = Electrocardiogram; IABP = intra-aortic balloon pump; LVAD = left ventricular assist device; O_2 = oxygen; VAD = ventricular assist device [from 2, with permission].

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Neurological Dysfunction after Coronary Artery Bypass Surgery: Facts vs. Fiction

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Coronary artery bypass grafting (CABG) surgery is an effective treatment of angina and coronary artery obstruction. Each year approximately 300,000 Americans undergo this form of surgery with excellent results and a low risk of mortality. With this success, indications for surgery have broadened; patients in their 8th and 9th decades and patients with complex medical history, e.g. diabetes mellitus, chronic renal failure, and hypertension, are being routinely sent to surgery. Although these patients generally do well, and concerns about loss of life are not as great as in years past, they are at risk for central nervous system dysfunction. Two types of injury are encountered. Stroke is the most serious with an incidence of 1–5% in most studies. Patients with a history of vascular disease, diabetes and hypertension are at particular risk and new techniques to further isolate patients at highest risk will be outlined in this paper.

Cognitive dysfunction, the second type of neurological injury, is more difficult to define and is frequently seen in the early post-operative setting. Causes may include residual anesthesia effects, pain and sedative medication, psychological trauma, depression, and emotional upset as well as organic causes. These types of dysfunction usually resolve several weeks after surgery and it is long-term cognitive changes that this paper will address. These changes are seen in patients who report they are ‘different’ or ‘not the same’ months after their recuperation from CABG. ‘My memory is not as good as before surgery’ and ‘I can’t do my job as well as I should’ are commonly heard expressions from patients. The family may report that the patient experiences ‘mood swings’ or is emotionally labile. Other patients complain of being ‘emotionally flat’.

Relationship between CABG and Neurological Dysfunction

In 2001, researchers at Duke University reported that when they tested patients post-operatively after CABG with a sophisticated battery of neurocognitive tests, 24% of their patients demonstrated significant neurocognitive decline 6 months after surgery and this number increased to 42% at 5 years [1]. This article published in the *New England Journal of Medicine* shook the medical community and was widely quoted in key newspapers and journals including the *New York Times*. Patients who had undergone CABG read this report and immediately called their surgeons and cardiologists asking about these results. They asked questions like, 'Was I injured during my operation?' or 'Will I have brain damage if I have bypass surgery?' An alarm had been sounded and many physicians and patients wanted more information and some answers to pointed questions. Some lay articles implied that the 'dark secret' of cardiac surgery, 'cognitive dysfunction' had just been defined.

At the Weill Cornell Medical Center we have been studying the relationship between neurological injury and CABG since 1990. We have been documenting and testing strategies to improve neurological outcomes and to understand the complex relationship between bypass surgery, central neurological injury and cognitive dysfunction. Specifically, we have completed two NHLB-1-funded trials and enrolled over 650 patients to study the effects of mean arterial pressure during cardiopulmonary bypass (CPB) on four outcomes, including neurological and cardiac complications, neurocognitive dysfunction, and quality of life. We hypothesized that as our patient population grew older with more comorbidity, the incidence of carotid and intracerebral vascular disease would also increase and that cardiopulmonary perfusion pressure during the CPB period would need to be increased.

For years, mean arterial pressure during the CPB operation had been maintained between 50 and 60 mm Hg. It had been previously believed that with calculated flow rates of >2.2 l/min/m^2, mean arterial pressure during CPB was not a key variable and a relatively low mean blood pressure of 50–60 mm Hg was adequate. However, we hypothesized that flow-limiting lesions in the carotid and intracerebral circulation could compromise brain circulation leading to organic injury, and that these changes might be prevented by increasing the mean blood pressure to 80 mm Hg while on bypass.

Our first trial (1991 through 1994) demonstrated that maintaining a patient at higher mean arterial pressure (80 mm Hg) during CABG dramatically reduced the rate of cardiac and neurological complications, including stroke and myocardial infarction [2]. Among 248 non-emergent patients undergoing CABG, those randomized to the high-pressure group (80 mm Hg) had a combined neurological and cardiac complication rate of 4.8% compared to 12.9%

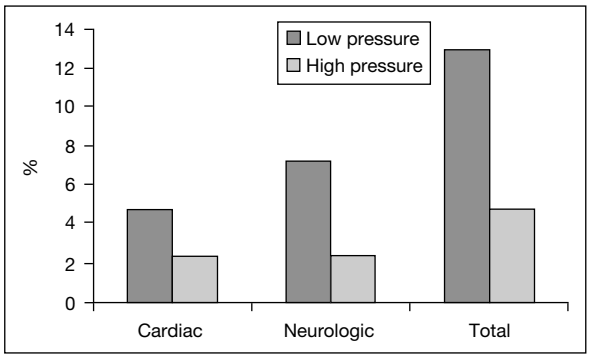
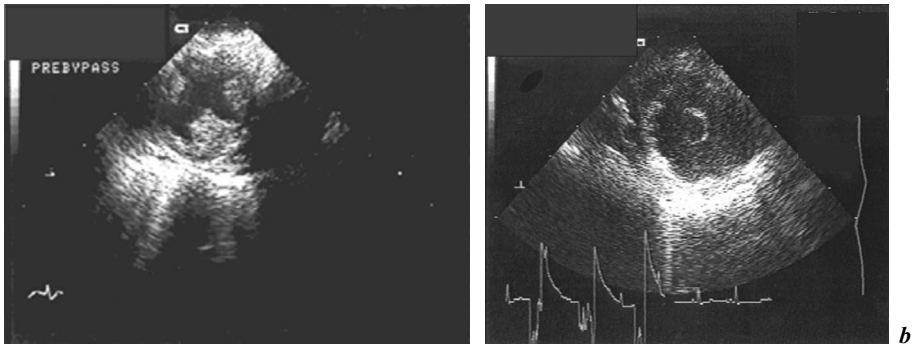


Fig. 1. Influence of mean arterial pressure on neurological and cardiac complications during coronary artery bypass surgery.



a ***b***

Fig. 2. Grading of the severity of atheromatous aortic disease by TEE. ***a*** Grade IV: >5 mm atheroma; ***b*** grade V: mobile atheroma.

in the low-pressure group (50–60 mm Hg) (fig. 1). Neurocognitive decline in the high-pressure group at 6 months was 11%.

A second critical finding of the study was that we could also predict patients at greatest risk of developing neurological injury by doing routine transesophageal echocardiography (TEE) on the descending aorta. In addition, we showed that atheromatous disease in the aorta could be reproducibly assessed on a scale of 1–5. Grades I–III were an aorta with atheroma <5 mm thick, grade IV was an aorta with disease >5 mm in thickness (fig. 2a), and grade V aortas contained mobile atheroma (fig. 2b). We observed that nearly all strokes occurred in patients with grade IV and grade V atheroma in their descending aortas (fig. 3). More importantly, as shown in figure 4, stroke rates

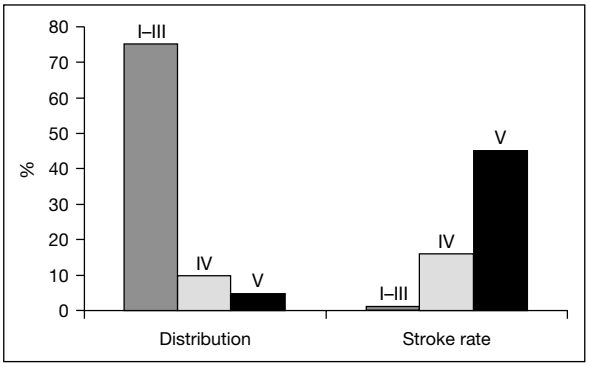


Fig. 3. Relation of strokes to atheroma grade.

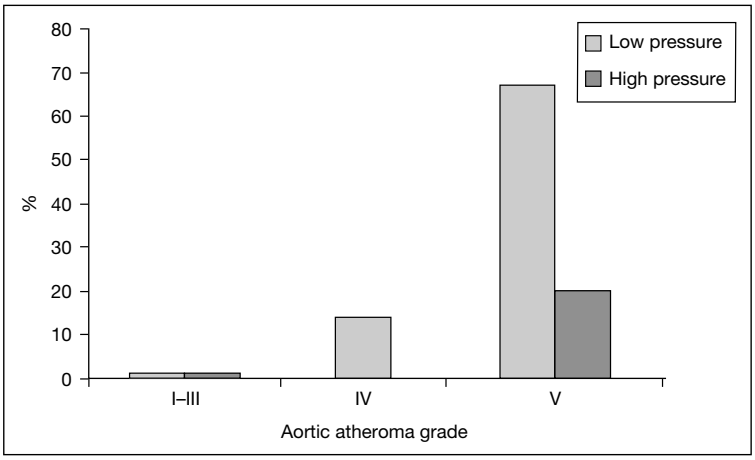


Fig. 4. Relation of strokes to atheroma grade and mean arterial pressure.

were dramatically decreased among patients with atheroma who had higher pressures during bypass. Thus, we could both predict patients at high risk for neurological injury and as a result could treat these patients with higher mean arterial pressures during surgery. Stroke rate in patients with grade V atheroma (highest risk) fell from 67% in the low-pressure group to 20% in the high-pressure group.

To further investigate these dramatic results, we initiated a second trial comparing mean arterial pressure during bypass at 80 mm Hg to a 'customized' mean arterial pressure determined by patients' usual pre-operative mean arterial

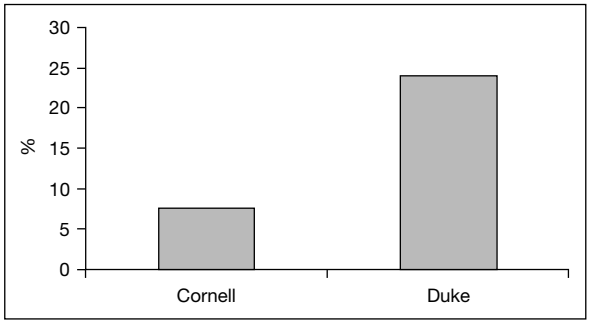


Fig. 5. Cognitive complication rates at 6 months after CABG.

pressure. A total of 412 elective CABG patients were studied and, results are pending.

Defining cognitive dysfunction is complex. As a result, testing techniques and definitions of cognitive dysfunction are not standardized at all medical centers, which may explain observed variations in published results. At our center, we use a 10 test battery, comprised of 3 memory tests, 5 tests of motor function, and 2 tests of linguistic function performed. The long-term (6-month) cognitive dysfunction rate of 24% at Duke seems high when compared to our Cornell experience of 11 and 4.9% (fig. 5). Careful review of the operative protocol during the bypass procedure of the CABG operation at Duke does not reveal that specific attention was paid to mean arterial pressure during CPB. Non-pulsatile perfusion of 2–2.4 l/min/m^2 of body surface area was maintained throughout CPB [1]. No mention of mean arterial pressure was made and no quantification of atheromatous disease in the aorta was recorded. Perhaps more attention to these two critical parameters might have impacted on their relatively high incidence of cognitive dysfunction at the 6-month mark.

Cognitive complications after any type of surgery may be difficult to define and may be present regardless of the type of surgery. In one study, postoperative cognitive deterioration in cardiac versus non-cardiac surgical patients was compared in 262 patients undergoing total knee replacements (TKR) with 248 patients undergoing CABG [3]. Although the group of CABG patients showed a greater mean impairment in cognitive function at 1 week after surgery (worse on ≥3 tests: CABG 12% vs. TKR 11%), there was no detectable difference at 6 months between the two groups. Dr. Mary Charlson, Chief of the Division of General Internal Medicine at Weill Medical College of Cornell University, who conducted the CABG follow-up studies, points out that cognitive impairment post-CABG is ‘widely over reported’ and may be ‘no more common’ than after hip or knee replacement. She emphasizes that patients

should not avoid life-saving cardiac surgery because of fears of post-operative cognitive dysfunction. Cardiologists and internists need to be aware of the power of such myths and must help their patients sort out facts from widespread fictions.

Dr. Charlson's studies have emphasized the important impact of depression on post-operative recovery and cognitive determination. Her studies document that significant depressive symptomatology is found in 43% of CABG patients pre-operatively and 23% post-operatively [4]. Depression may lead to lower scores on cognitive tests and is also associated with higher long-term mortality and morbidity [5]. Dr. Charlson notes that depressive patients are more likely to believe that they have cognitive deterioration as a result of surgery. This complex picture makes their post-operative care difficult and adds to the myth that cognitive defects are a result of CABG. She notes that it is most important that depression be recognized as a common occurrence both pre- and post-operatively and that it be appropriately treated.

Conclusion

When evaluating any body of research or series of clinical studies, it is important to ask 'Has this research impacted on the way we think about medical care or practice medicine?' or 'Has it changed our operative protocols?' or 'What do we do differently because of this new information?' We are really asking 'Is this research so compelling or convincing that it will make you change time-honored techniques and guidelines for something new?' The answer in our medical center is an emphatic *YES*. In our CABG operations, TEE is now part of a standard protocol. Since all patients have TEE, we know patients with grade V atheroma have an extremely high risk of stroke and their clinical indications and surgical management may change when this problem is diagnosed. These patients may be treated with off-pump bypass surgery or with alternative forms of therapy. If CPB is required, higher pressures are mandatory. Elderly patients and patients with known peripheral vascular disease are now routinely maintained at mean arterial pressure that approximates their age. We are careful to evaluate the ascending aorta with an epicardial Doppler probe in all patients where we have documented descending atheroma on the TEE. This allows us to cannulate the aorta and place the side-biting clamp in an area free of atheromatous disease and, thereby, decrease the chances of releasing emboli. Alternatively, we may decide not to use a side-biting clamp and complete the proximal anastomoses with the aorta cross-clamped. The cumulative efforts have been very effective in our medical center in decreasing neurological complications and in improving overall patient outcomes.

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Robotic Valve Surgery: How Does the Future Look?

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Over the last 7–8 years there has been an effort to create a less invasive operative approach in cardiac surgery. This has involved techniques that either avoid a conventional sternotomy or minimize it, gaining access to the chest cavity via a minithoracotomy. Many authors, including Cohn, Cosgrove, Gundry, and Arom have shown favorable results using a ministernotomy or parasternal incision for aortic and mitral valve surgery [1–5]. The next logical step in this progression of minimization has been the establishment of port access surgery. With this approach, incisions are reduced to 1 cm in size, through which endoscopic instruments are placed. The surgeon controls these instruments by telemanipulating handles, which translates into movement by robotic arms.

By reducing incision size and overall operative trauma to the patient, it may be possible to improve postoperative quality of life (QOL). The hope is that patients will have less pain and a hastened recovery, as measured by intensive care unit (ICU) stay, hospital stay, ability to resume preoperative activities, and number of days until return to work after surgery. Little data exists, however, comparing open, minithoracotomy, and robotic approaches, and further studies are necessary to adequately address this issue.

Robotic Technology

The Da Vinci robotic system (Intuitive Surgical, Mountain View, Calif., USA) consists of a master console with viewing capability and surgical arms that control detachable instruments (fig. 1). The surgeon is typically seated several feet away from the operating table at the console. From the console, the

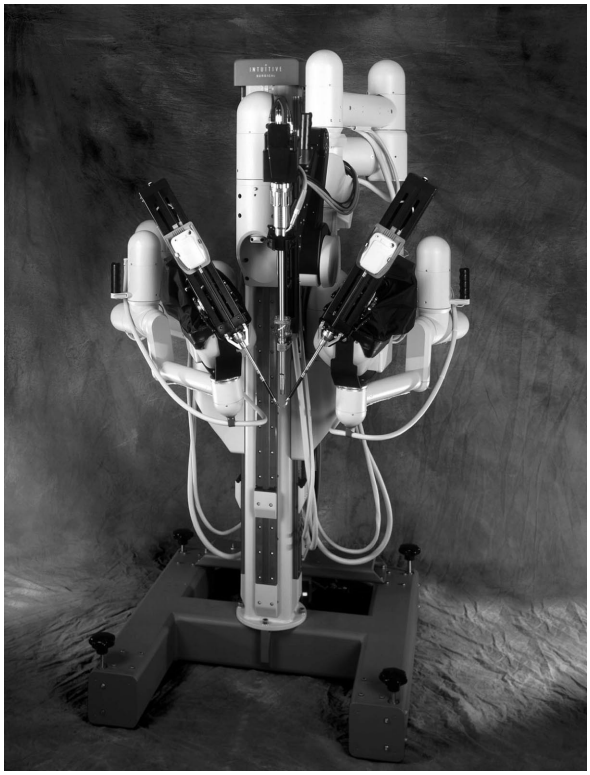

Fig. 1. Da Vinci robotic system [from 6, with permission].

surgeon has a high-definition, full-color, magnified, three-dimensional image of the surgical site provided by the endoscope. There are two 'master' handles positioned beneath the console. The physician moves his hands and this movement translates into action by the robot [6]. The system provides the surgeon with 7 degrees of freedom.

Robotic Experience with Mitral Valve Repair

We are involved in a multicenter trial evaluating robotic mitral valve repair and have currently performed 15 mitral valve repairs via a robotic approach. The trial requires that patients have simple posterior leaflet pathology. Exclusion criteria are anterior leaflet pathology, calcification, and age >80 years. Unlike a robotic atrial septal defect closure, which can be performed via a totally endoscopic approach, mitral valve repair requires a minithoracotomy.

Table 1. Intraoperative times for mitral valve repair

	Minithoracotomy	Robotic	p
BP time, min	146 ± 36	234 ± 53	0.000
XCl time, min	93 ± 26	157 ± 43	0.000

BP = Cardiopulmonary bypass; XCl = cross-clamp.

Table 2. Length of stay for mitral valve repair

	Minithoracotomy	Robotic	p
ICU, days	2 ± 1	2 ± 1	0.360
Hospital stay, days	7 ± 3	7 ± 4	0.217

In the 15 patients who underwent robotic mitral valve repair at our institution, 13 (87%) were male and 2 female (13%) with a mean age of 55.4 ± 10.5 years (range 37–71). Cross-clamp and bypass times averaged 157 ± 43 (range 96–240) and 234 ± 53 (range 140–316) min, respectively (table 1). Stays in the ICU and hospital were 2 ± 1 and 7 ± 4 days, respectively (table 2).

Minimally Invasive Approach – Mitral Valve Repair

A robotic approach avoids a sternotomy and requires four incisions. The first is a 4- to 5-cm minithoracotomy incision made along the 5th rib, lateral to the midclavicular line. The second is a stab wound in the right axilla, through which a transthoracic aortic cross-clamp (Chitwood) is passed and applied to the ascending aorta. Small (8-mm) incisions are made in the 3rd and 4th intercostals spaces, lateral to the minithoracotomy incision. The right and left robotic arms are passed through these port sites, and the robotic endoscopic camera is positioned in the medial aspect of the minithoracotomy incision [6, 7].

Surgical Procedure

Using the robotic instrument arms, under endoscopic video assistance, annuloplasty sutures (2-0 Tevdek) are placed and passed individually through a

Cosgrove ring. Selection of the appropriate ring size is based on preoperative transesophageal echocardiographic measurement of the free anterior leaflet and by intraoperative endoscopic measurement. The sutures are tied, and needles and suture fragments passed out of the minithoracotomy incision with the assistance of a patient-side surgeon. After the valve is tested with cold saline injection into the left ventricle, the robotic arms are removed from the patient and the system is pulled away from the table. The left atriotomy is closed with running 3-0 prolene, and the patient is de-aired in standard fashion. The aortic pressure is temporarily reduced to 50 mm Hg. The aortic cross-clamp is removed and the patient is ventilated and de-aired once again. Upon completion of de-airing maneuvers, the left ventricular vent is removed and the left atriotomy closed. The retrograde coronary sinus catheter is also removed and closed as is the Bentley needle site. The patient is weaned from cardiopulmonary bypass.

The ribs are then approximated with #2 Vicryl pericostal sutures and the muscular and subcutaneous tissues are approximated with absorbable sutures. The skin is closed with 4-0 subcuticular Vicryl sutures.

Quality of Life Assessment

We are currently in the process of evaluating QOL in patients who have undergone minimally invasive mitral valve surgery via a robotic or minithoracotomy approach. QOL was measured by the administration of the Medical Outcomes Study Short Form Survey that consists of 36 questions (SF-36). This form covers eight basic health concepts: bodily pain, physical function, social function, general health, mental health, vitality, physical role function, and emotional role function. A score of 0–100 is calculated for each of the eight variables, with higher scores corresponding to a better QOL. The SF-36 has been used and validated in patients undergoing heart surgery.

Robotic patients showed improved SF-36 scores in all eight scoring categories as compared to minithoracotomy patients (table 3). The difference was statistically significant for bodily pain and mental health. This was seen despite an increase in both cross-clamp and bypass times for robotic procedures ($p = 0.000$).

Although we have been unable to show a significant difference in ICU or hospital stay when comparing robotic to minithoracotomy, as stated above, we do believe that as time progresses and surgeons become more familiar with robotic technology, we may begin to see a shorter stays in the ICU and the hospital stay associated with the robotic approach.

Table 3. Quality of life analysis by the Medical Outcomes Study Short Form Survey following minimally invasive mitral valve surgery

	Minithoracotomy	Robotic	p
Day 30 PF	56 ± 24	61 ± 32	0.749
Day 30 PRF	18 ± 31	53 ± 47	0.117
Day 30 BP	54 ± 16	79 ± 24	0.038
Day 30 GH	57 ± 20	65 ± 20	0.504
Day 30 VT	42 ± 12	51 ± 24	0.403
Day 30 SF	52 ± 27	59 ± 36	0.660
Day 30 ERF	38 ± 45	71 ± 45	0.184
Day 30 MH	56 ± 9	78 ± 24	0.040

BP = Bodily pain; ERF = emotional role function; GH = general health; MH = mental health; PF = physical function; PRF = physical role function; SF = social function; VT = vitality.

Review of Literature on Robotic Mitral Valve Surgery

Much has been written about minimally invasive mitral valve surgery. Mohr et al. [9] reported a series of 129 patients with nonischemic mitral valve disease who underwent mitral valve surgery via a port access approach. Of these patients, 72 underwent a repair and 57 underwent valve replacement. Only 4 patients required conversion to an open technique because of retrograde aortic dissection.

Mohr et al. [10] subsequently reported on 17 patients undergoing robotic mitral valve repairs, in whom 14 were completed successfully and 3 required conversions to open procedures. At 1- to 6-month follow-up, all 17 patients were alive and free from recurrent myocardial insufficiency.

Reichenspurner et al. [11, 12] reported on 26 mitral valve repairs and 24 mitral valve replacements using a port access technique and had 2 required conversions to open procedures. In the last 20 patients in this series, a voice-activated robotic arm (Aesop) was used instead of the patient-side assistant, and there were no deaths and a 2% incidence of reoperations.

Vanermen et al. [13] reported on 41 mitral valve repairs and 33 mitral valve replacements performed via port access with two conversions to open procedures. Finally, Chitwood [14] reported on 85 patients who underwent robotic mitral valve surgery with a 1.2% surgical mortality.

Future Development within Robotic Technology

There are several modifications that can be made to improve robotic technology. Firstly, a fourth operating arm may be useful. Currently, with two robotic arms and one port for the assistant, there is often a need for further access ports. Secondly, changes in the configuration of the robotic system, such as suspending the apparatus from the ceiling as opposed to a mobile floor unit, are being considered.

The real challenge and goal of robotic technology with regard to valvular surgery is to be able to perform the procedure totally endoscopically, as is currently possible for closure of an atrial septal defect. The addition of the robot to a minithoracotomy will probably not impact outcome very significantly. A totally endoscopic approach via complete port access, however, is likely to yield more major improvements in postoperative QOL. The future of robotic valvular surgery, therefore, is dependent on continued miniaturization of the access approach.

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Selection of Techniques for Combined Valve Surgery and Coronary Artery Bypass Grafting: The Impact of Combined Procedures Involving the Aortic or Mitral Valve

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The operative therapy of patients with combined valvular and coronary artery disease has evolved significantly since the early 1970s when the first cases were performed and routine coronary angiography was advocated for all patients with valve disease. Operative mortality has decreased significantly for combined mitral valve/coronary artery bypass grafting (CABG) procedures from 20% in the early 1980s to near 2–4% in many centers, results that are now compatible with primary mitral valve repair or replacement. However, many longitudinal series at our unit and others have confirmed that the combination of valve and coronary disease negatively impacts long-term survival following surgery. In addition, the incidence of combined valve and coronary artery disease is increasing, likely related to an aging population. In our experience over the past 10 years, 47% of patients with aortic valve disease had concomitant coronary artery disease while 44% of mitral valve patients required at least one coronary bypass graft.

Thus, in patients with valve and coronary artery disease, there are a host of judgmental questions, which the surgeon must consider related to the procedure to be performed. This discussion will explore the problems surrounding valve selection in the context of combined valve and coronary disease.

Aortic Valve Disease

Aortic valve surgery and concomitant CABG is extremely common. Over the past 10 years at our institution, 2,889 aortic valve replacements were

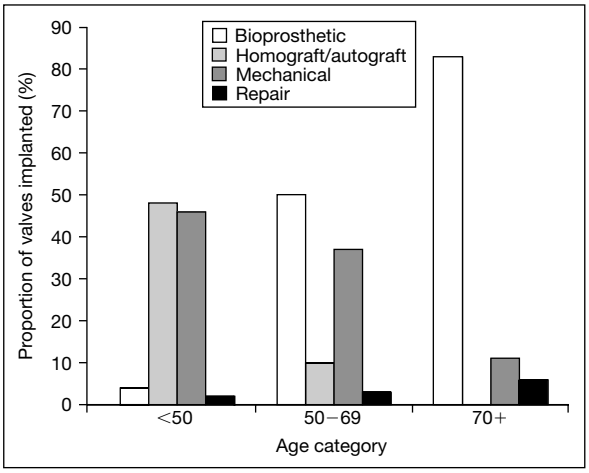

Fig. 1. Selection of operative techniques for combined aortic valve and coronary artery disease. Data represent BWH aortic valve usage from January 1 through December 31, 2001 (n = 380). BWH = Brigham and Women's Hospital; n = number of patients.

performed, of which 1,525 were primary aortic valve replacements while 1,364 were combined aortic valve/CABG. It was once thought that left ventricular hypertrophy resulting from aortic valve disease, particularly aortic stenosis, was a contraindication to the use of the internal mammary artery bypass for left anterior descending coronary disease. Data from the Northern New England Cardiac Surgical data bank, however, has shown that the internal mammary is protective and more beneficial than a vein graft in every setting including the hypertrophied left ventricle.

A number of factors determine the type of aortic valve implanted. In calendar year 2001 at the Brigham and Women's Hospital, the choice of procedure in almost all 380 cases was based on age categories (fig. 1). The vast majority of patients in the 70 and over age group had a bioprosthetic valve inserted, while only a few received homografts (because of the presence of endocarditis). Relatively few had a prosthetic valve implanted because of the well-known complications of anticoagulation in the aged. In the middle-aged group (50–69 years), there was a slight preponderance toward bioprosthetic valves and homografts. This new trend is likely the result of good long-term results, particularly with the pericardial valve, in this age group. Additionally, the inconvenience and concern about loss of balance and traumatic injury in this population mitigates against anticoagulation management. These considerations undoubtedly have supported the increased use of tissue valves in this population. In the age group <50 years old, there was a predominance of homografts and a few autograft

(Ross operation) replacements, with a high incidence of St. Jude valve replacements in our particular series. In younger patients, biologic valves are less successful in terms of structural degeneration because of rapid calcium turnover.

How does co-existent coronary artery disease affect valve choice, tissue or prosthetic? Both the Emory and Tampa series demonstrated that patients with combined coronary artery and valve disease do not survive as long as patients with only a primary valve pathology [1, 2]. In elderly patients with normal sinus rhythm, a tissue valve is an excellent choice. Often, however, younger people will choose a biologic valve to avoid the need for anticoagulation. However, data similar to that noted above would argue for the use of tissue valves in younger patients with concomitant coronary disease since in this setting, the patient may not outlive the valve. On the other hand, patients with extensive coronary disease of a diffuse nature requiring an endarterectomy in addition to CABG may benefit from a prosthetic valve. In this situation, long-term anticoagulation, with or without aspirin, may be helpful in maintaining patency of grafts with limited outflow.

A homograft valve is an increasingly popular choice in patients 40–60 years old because of the perception that there is longer viability of this valve as opposed to a stented biologic valve. The complexity of the homograft operation, which is now performed as a total root replacement with reimplantation of both right and left coronary arteries, takes twice as long to implant as the stented biologic valve (45 vs. 90 min of cross-clamp time). Thus, myocardial preservation techniques must be precise and meticulous to achieve good results in the homograft root replacement group. Currently, the homograft valve is used for two indications: (1) endocarditis of the aortic valve and the aortic root (since this is natural tissue without prosthetic material), and (2) elective operations in patients under 60 years of age with no other cardiac lesion, such as coronary artery disease. In our experience of 178 aortic homograft root replacements, *elective* primary root replacement with a homograft was carried out with an operative mortality of 0 in 138 patients. However, once there is increased complexity of the operation related to the length of the operation or multiple coronary artery bypass graft CABG procedures, the operative mortality increases.

Recently, the Ross operation (pulmonary autograft) has gained popularity as a particularly attractive option for very young patients. In this operation, the pulmonary valve trunk is transposed to the aortic trunk, both coronary arteries are re-implanted, and a homograft is placed in the pulmonary valve position, essentially a two-valve operation for single valve disease. This is an excellent operation for the young adult 18–40 years of age. The Achilles heel of this operation is the pulmonary homograft, which has recently been associated with a certain amount of stenosis in the pulmonary artery trunk. Concomitant CABG is not advised with this operation since the present state of myocardial

protection cannot yet support the extent of this surgery. Although this is an attractive procedure to use, the surgeon's judgment and careful selection of the operation must be based on the specific disease of the patient actually and not the attractiveness of the procedure.

The minimally invasive approach to aortic valve procedures through a mini-sternotomy has become standard for most cases. Multiple series confirm that minimally invasive valve surgery results in less pain and trauma, fewer blood transfusions, potentially less atrial fibrillation, and less cost, while maintaining the same quality of operation compared to traditional valve surgery [3]. Most importantly, there is definitely more patient satisfaction, which translates into faster recovery and return to work. This approach has been used in a wide range of ages, up to 93 years. The elderly, particularly if they have no or only moderate coronary disease which can be intervened upon, do far better than similar patients with full sternotomies. Occasionally, but increasingly, a hybrid procedure is utilized in order to reap the benefits of minimally invasive valve surgery. For a patient with moderate coronary disease, either one-vessel or even two-vessel disease, rather than perform a sternotomy, we might first ask our interventional colleagues to insert a stent into a coronary lesion and then proceed with a minimally invasive aortic valve replacement. As of March 2002, 836 patients have undergone such a procedure at the Brigham and Women's Hospital (including 3 robotic mitral valve cases). The scope of minimally invasive aortic valve surgery has even been broadened to include 48 re-operative aortic valve replacements, many of who had failed tissue valves. We have been able to utilize virtually every operation in the mini-aortic valve series including homograft root replacement.

Mitral Valve Disease

During calendar year 2001 at our institution, mitral valve surgical procedures totaled 359 cases, the vast majority being mitral valve repair. Repair is justifiably the superior approach for the vast numbers of patients who have either ischemic or floppy mitral valves. In the younger age group, there were some St. Jude valve implants, but very few bioprosthetic valves because these tend to wear out faster in the younger patients. In the elderly patients undergoing valve replacements, the choice of valve is usually the Medtronic mosaic or the Carpentier-Edwards pericardial valve (fig. 2).

Patients with coronary artery disease and concomitant mitral regurgitation usually develop this lesion because of left ventricular dilatation and a dilated annulus. In the vast majority of instances, an annuloplasty ring is effective at reducing the mitral regurgitation with concomitant CABG. Debate exists as to

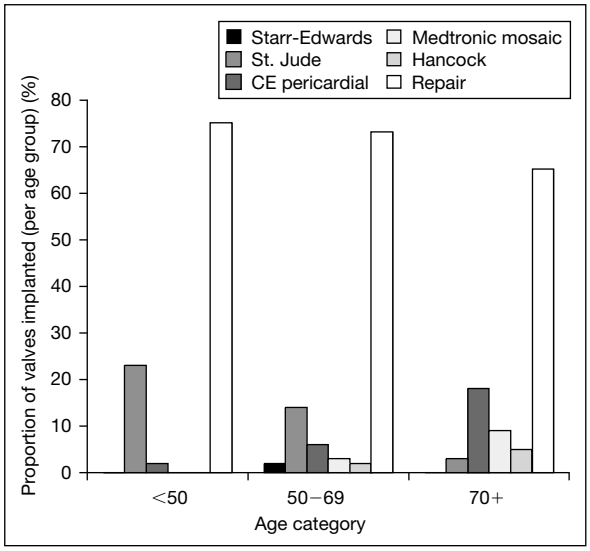

Fig. 2. Selection of operative techniques for combined mitral and coronary artery disease. Data represent BWH mitral valve usage from January 1 through December 31, 2001 (n = 359). BWH = Brigham and Women's Hospital. CE = Carpentier-Edwards; n = number of patients.

the aggressiveness one should use particularly related to moderate and moderately severe mitral regurgitation [4, 5]. In these patients, as long as the mitral regurgitation is chronic and is evaluated preoperatively with a decision made to correct the mitral regurgitation at that time, the operation should proceed since the majority of these patients only require an annuloplasty ring.

In non-ischemic mitral valve disease, i.e., floppy myxomatous valves, when the issue of concomitant CABG is introduced, the additional risk in this group is much less. We have shown that the operative mortality in this group has fallen considerably. In our series of approximately 3,000 mitral valve operations over the past 10 years, the operative mortality is less than 2% for non-ischemic mitral regurgitation, including patients ≥70 years of age. In non-ischemic mitral valve disease with CABG, the operative mortality is slightly higher, but over the past 5 years the operative mortality has fallen to under 2% even in this group.

The question that arises if one has coronary disease is, 'Should a mitral valve repair or replacement be carried out?' The more skilled the mitral valve repair surgeon, the lower the threshold for operative intervention, but, preservation of the left ventricle's normal physiology is more important in those with coronary artery disease. In almost every series of patients comparing mitral valve replacement to repair, patients undergoing repair seem to fare better in

terms of operative risk than those having replacement [6]. However, as pointed out by our group in 1995, the patient's left ventricular function is perhaps the most important factor in determining long-term survival regardless of operation [7]. With depressed left ventricular function, it is most desirable to obtain the most physiologic repair. Should repair be impossible, particularly in patients with a cardiomyopathic ventricle, preservation of the entire papillary muscle-chordal interaction is still possible with a mitral valve replacement. This involves preservation of the posterior leaflet, which is commonplace now, but also preservation of the anterior leaflet chordae by reefing the anterior leaflet to the annulus. If this is not done, interference with left ventricular outflow tract may occur. After reefing and preserving all of the papillary muscles, a smaller sized valve can be implanted because of the excess tissue around the annulus. To this point, implantation of a size 25 or 27 mitral valve may be contraindicated if the person has a large body surface area.

Similar to aortic valve surgery, mitral valve repair or replacement can be adequately performed through a lower mini-sternotomy. Cardiopulmonary bypass is necessarily miniaturized, and vacuum-assisted suction with 24-French cannulas in the superior and inferior vena cavae is employed. In the 361 repairs and approximate 50 valve replacements through these incisions (age range 17–90 years old) operative mortality has been remarkably low with zero operative mortality in the mitral valve repair group and only 1 death (in a 90-year-old patient) in the replacement group. This has been the procedure of choice for almost 400 patients at the Brigham and Women's Hospital, with only 14 re-operations over the 6-year period, suggesting that operative results are good and are similar to that done through the open sternotomy. Therefore, if a patient has a moderate stenosis in a coronary artery, a hybrid procedure with the use of a stent followed by minimally invasive mitral repair would likely be the option of choice.

Valve Surgery Long after CABG

There are increasing numbers of patients who have had a previous triple CABG procedure and have an intact mammary artery graft who return with senile aortic stenosis, or there are those who have had a prior aortic valve procedure plus CABG and the aortic valve has failed for some reason. These patients can be managed with minimally invasive re-operative valve surgery providing care is taken in terms of perfusion status [8, 9]. These patients are all cannulated peripherally either through the femoral or axillary artery. In our patient series at the Brigham and Women's Hospital, no patient has had perioperative bleeding and the blood transfusion rate, though higher than in the regular

mini-valve surgery, is not excessive. The operative mortality is 5%. An example of the kind of patient who dramatically benefits from this approach is provided by a man who is a 93-year-old retired physician who had an aortic valve/triple CABG in 1987. He returns about 10 years later with a leaking aortic valve. On cardiac catheterization, two of the three bypass grafts are open and he has a failed right graft with a totally occluded right coronary artery. Does this 93-year old man who is suffering from severe heart failure from a failed valve really need that extra CABG? Is perfection going to be the enemy of the good here? No. We performed a re-operation mini-aortic valve repair cannulating his right axillary artery and femoral vein. He did quite well with no blood transfusions and was discharged on the sixth postoperative day. This is just the type of judgment that we are increasingly called upon to make, and we must make use of different techniques available to us to improve our results. Importantly, vacuum-assisted suction, which has been popularized by the Cleveland Clinic, allows minimally invasive valve surgery to be performed safely with the same results as a complete sternotomy.

Conclusions

Considerable judgment must be exercised in planning the valve and CABG operation in patients with combined disease. The long-term survival is affected by the combination of the two diseases. Survival curves are improving and the operative risk has certainly decreased dramatically. The patient's quality of life and long-term functional status are extremely important and may be determined by the type of operative decisions made in patients with combined diseases.

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Aortic Valve and Non-Ischemic Mitral Valve Surgery in Patients Undergoing Coronary Artery Bypass Grafting

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The indications for primary valve surgery are well established [1]. Controversy persists as to whether patients with less severe valvular disease should undergo 'prophylactic' valve surgery as an adjuvant to coronary artery bypass grafting (CABG) [2]. In patients undergoing CABG, this decision must weigh the risks of disease progression leading to a high late re-operative risk (10–18%) versus the increased risk of combined valve CABG. Additionally, the potential of performing unnecessary valve surgery in patients who may never develop disease progression exists. This chapter reviews pertinent literature on this topic and develops a logical framework for making this difficult surgical decision.

Aortic Valve Disease

Severe Aortic Valve Disease

The indications for valve replacement are clearly established in patients with severe aortic stenosis (AS) and severe aortic insufficiency (AI). It has been well established that patients with symptomatic AS have high mortality rates without valve replacement. After the onset of symptoms, average survival is 2–3 years. It has been shown that the pressure gradient in AS progresses at a rate of 5–10 mm Hg/year, and that aortic valve area decreases approximately 0.1 cm^2/year.

Similarly, asymptomatic patients with a mean gradient of >50 mm Hg or with a valve area of <0.8–1.0 cm^2 are likely to develop symptoms or need

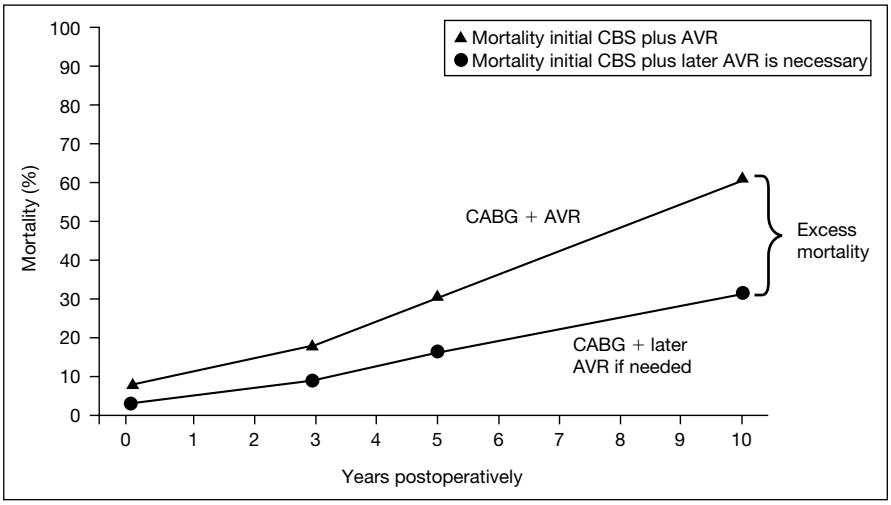

Fig. 1. Projected outcomes in patients with severe coronary artery disease and mild aortic stenosis undergoing aortic valve replacement (AVR) and coronary artery bypass grafting (CABG) surgery [from 2, with permission].

surgery. An echocardiographic study by Otto et al. [3] demonstrated that asymptomatic patients with a peak trans-valve flow velocity of >4.0 m/s (peak gradient >64 mm Hg) had a 70% risk of developing symptoms and requiring aortic valve replacement (AVR) within 2 years. Thus, early valve replacement is clearly indicated in these patients. Similarly, no controversy exists in patients with severe AI, where 'prophylactic' AVR is indicated even in the absence of symptoms [4].

Mild to Moderate Aortic Valve Disease

The need for concomitant AVR in patients with less severe aortic valve disease is more controversial, but guidelines do exist, based on the predictability of disease progression. The progression of AS is more rapid in elderly patients, in the presence of coronary artery disease (CAD), and in patients with a calcific degenerative etiology. In contrast, patients with congenital bicuspid valves or rheumatic pathology demonstrate slower progression of disease. Progression of AS may necessitate, within a short time, subsequent AVR, which carries an increased perioperative risk [5].

Evidence clearly supports avoidance of concomitant AVR in patients with mild AS. Patients with mild AS (mean gradient <15 mm Hg or aortic valve area >1.5 cm^2) are extremely unlikely to develop disease progression over 10 years. Therefore, AVR is not indicated in these patients (fig. 1). One study demonstrated

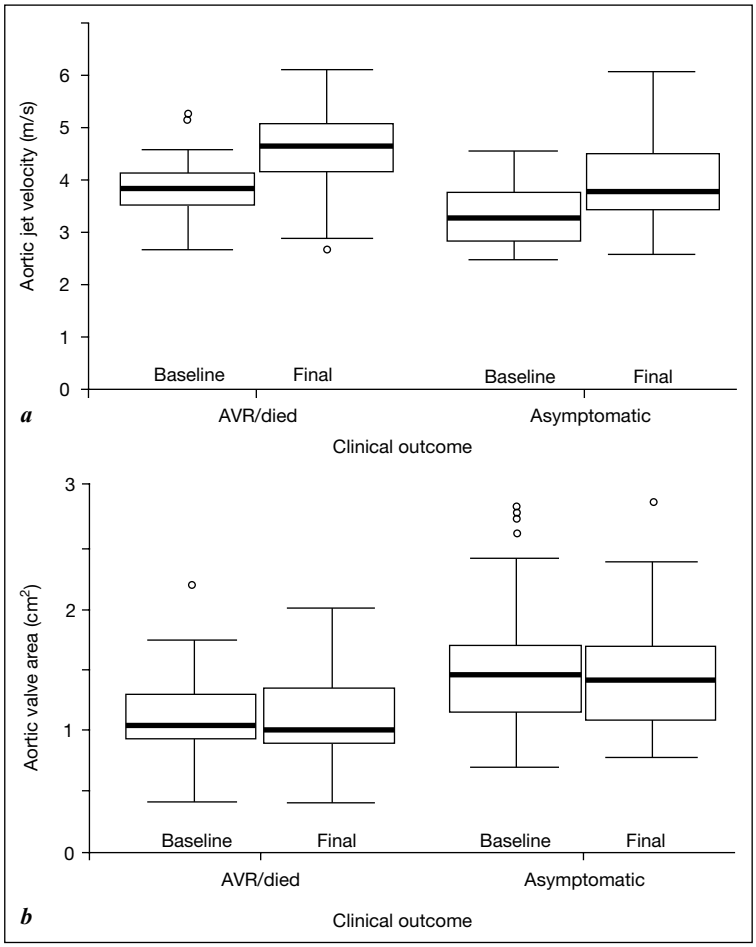

Fig. 2. Aortic jet velocity (***a***) and aortic valve area (***b***) in subjects who developed symptoms requiring aortic valve replacement or died (AVR/died) are compared with those who remained asymptomatic for the baseline and final studies. Values plotted are mean ± SD ($p < 0.001$ for asymptomatic versus those with an endpoint for both baseline and final values) [from 3, with permission].

that only 8% of such patients developed significant AS over 10 years [6]. Similarly, Otto et al. [3] demonstrated that late symptoms or subsequent surgery were infrequent when the peak echocardiographic trans-valve flow velocity was <3.0 m/s (peak gradient <36 mm Hg) (fig. 2).

In contrast, Otto [3] has shown that with more moderate disease (peak aortic valve flow velocity 3–4 m/s or peak gradient 36–64 mm Hg), 36% of patients

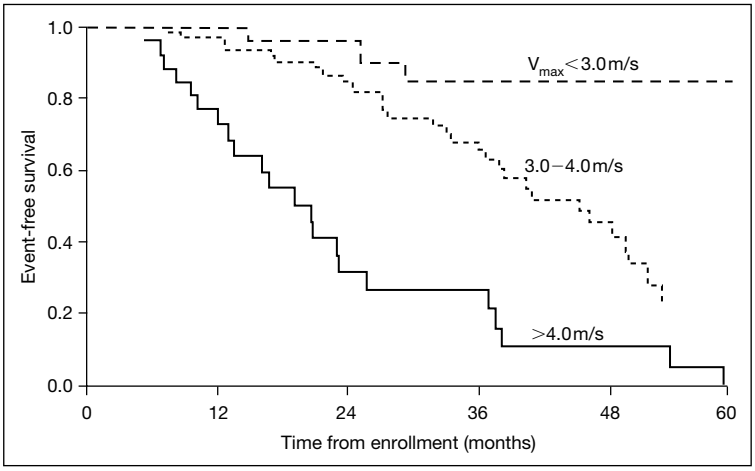

Fig. 3. Cox regression analysis showing event-free survival in groups defined by aortic jet velocity at entry ($p < 0.0001$ by log-rank test). m/s = Meters per second [from 3, with permission].

developed symptoms, died, or required surgery over 2–3 years (fig. 3). Severity of leaflet calcification and leaflet mobility are factors that should be taken into account when deciding to perform AVR/CABG for intermediate gradients. Kennedy et al. [7] demonstrated that the annual risk of AVR or death was 10% in patients with an initial aortic valve area of 0.7–1.2 cm^2. Thus, 'prophylactic' AVR may be indicated in patients with peak gradients of 36–64 mm Hg, with mean gradients of 20–40 mm Hg, or with aortic valve areas of 0.8–1.2 cm^2. This is particularly true in patients 60–75 years of age, who have a reasonable life expectancy.

These patients may now receive a new third-generation bioprosthesis with a low subsequent risk of re-operation, without the need for long-term anticoagulation. Importantly, Herlitz et al. [8] reported that AVR in combination with CABG is not a predictor of increased early or late postoperative mortality. This is different from prior surgical eras. Currently, the operative risk is probably not significantly increased by adjuvant AVR in patients with well-preserved left ventricular function who require CABG.

Patients with mild AI, who have normal left ventricular function, seldom develop disease progression or symptoms over the following 10 years. However, surgical valve replacement for moderate AI in combination with CABG is less clear. Valve replacement in this setting should be reserved for patients with both significant left ventricular diastolic volume overload and systolic dysfunction. Valve surgery should be performed if these patients have a decreased ejection

fraction or increased end-systolic diameter on echocardiography. Additionally, patients whose ejection fractions decrease or who develop significant ventricular arrhythmias in response to exercise are more likely to benefit from valve replacement. In contrast, patients with normal left ventricular size and function and a normal response to exercise are unlikely to benefit from AVR.

The guidelines for concomitant AVR and CABG obviously must take into consideration patient age, co-morbidities, and specific operative and survival goals of any particular patient.

Non-Ischemic Mitral Valve Disease

In the current surgical era the vast majority of patients with mitral regurgitation (MR) from mitral prolapse can be treated with valve repair rather than with valve replacement. This treatment strategy has been shown to result in durability that is equal to valve replacement, but with fewer late valve-related complications (fig. 4). These include thromboemboli, anticoagulant-related hemorrhage, and endocarditis. Late cardiac function and overall survival are also improved after valve repair [9, 10]. Thus, most patients with severe MR are now offered a primary mitral valve repair procedure earlier in the course of the disease, prior to the onset of severe symptoms, significant left ventricular dysfunction, or pulmonary hypertension [11].

The indications for primary mitral valve repair surgery include severe MR with symptoms, or severe MR in asymptomatic patients with early left ventricular systolic dysfunction (ejection fraction <0.60 or echocardiographic left ventricular end systolic dimension >45 mm) [11]. Increased left atrial size and recent onset of atrial fibrillation are considered relative indications. In symptomatic patients the mortality rate is approximately 5% per year without treatment, with survival rates as low as 33% at 8 years [12, 13]. Although Rosen et al. [14] reported that only 28% of asymptomatic patients with severe MR with good ventricular function required surgery within 5 years, Ling et al. [15] reported that 90% of asymptomatic patients with 'flail' leaflets required surgery within 10 years.

It is well known that combined mitral valve repair and CABG has an increased operative risk in patients with ischemic etiology and in patients who have significantly reduced left ventricular ejection fractions. However, the operative risk of combined repair and CABG is not increased in patients who are NYHA functional classes I or II and who have normal left ventricular function [16]. Since the incidence of late valve-related complications is quite low after valve repair, and the late functional status and survival are excellent if repair is performed when the left ventricular ejection fraction is still normal, a strong

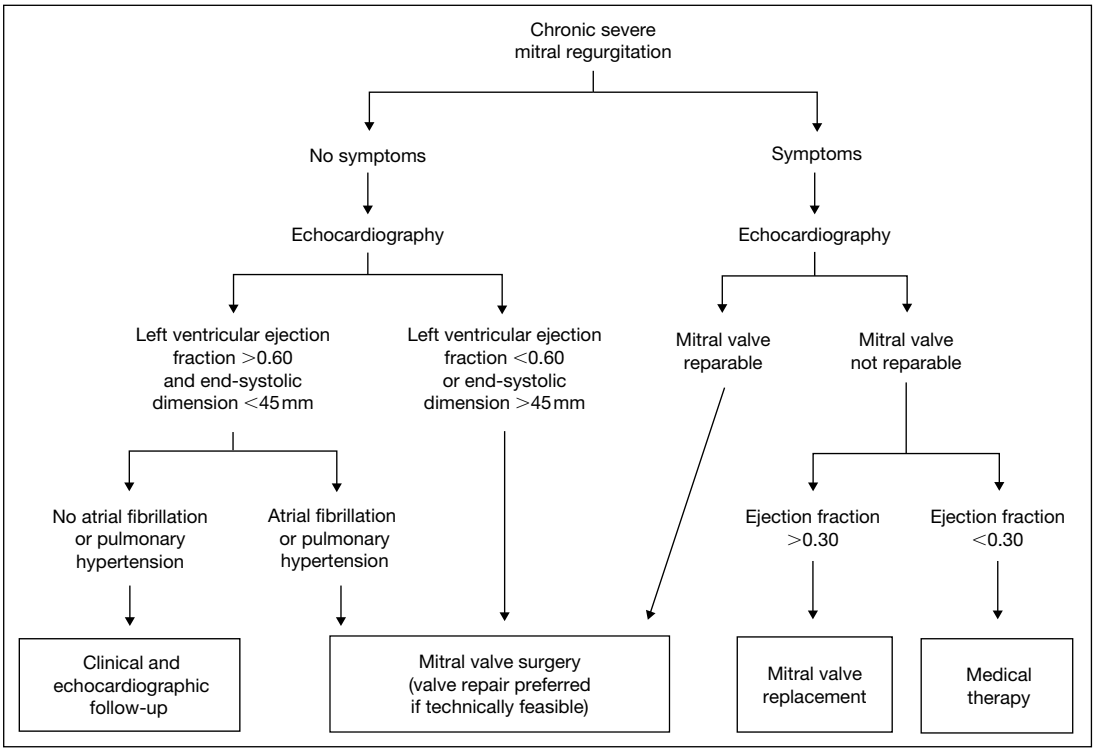

Fig. 4. Evaluation and management of chronic mitral regurgitation [from 11, with permission].

case can be made for performing concomitant mitral valve repair in most patients undergoing CABG who have moderate or severe MR.

This treatment should improve late survival and decrease the likelihood of late functional disability without significantly increasing the operative risk. If only mild insufficiency is present, however, and the left atrial and left ventricular dimensions are normal, valve surgery should not be performed. Finally, in patients whose pathology makes valve repair unlikely, the threshold for addressing the valvular pathology should be higher, since the late valve-related complications are more significant after valve replacement than after valve repair [9]. Every patient must be individualized according to age, predicted survival, and by the degree of coronary-related cardiac dysfunction and other risk factors. In general, patients who have a predicted survival of more than 5–7 years and who have severe MR should undergo concomitant valve repair surgery with CABG.

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Echocardiographic Doppler Evaluation of Prosthetic Valve Function and Dysfunction

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Prosthetic valves can be visualized, hemodynamics measured, and flow patterns assessed by comprehensive echocardiography (ECHO) with Doppler examination. Prosthetic valve dysfunction can be readily determined, i.e., various mechanisms of stenosis (including tissue valve calcification, thrombus, pannus ingrowth) valvular regurgitation, paravalvular regurgitation, endocarditis, dehiscence, structural deterioration, and hemolysis.

There are several different prosthetic valve types and each has its own distinct normal imaging patterns and potential problems [1–3]. One of the older prosthetic valves still seen in patients, though rarely implanted today, is the Starr-Edwards 'ball-in-cage', which, when functioning properly, causes blood flow to circumnavigate around the ball creating turbulence that is destructive to the red cells and causes hemolysis. Though very durable, with valves implanted in the early 1960s still functioning, this valve is large (potentially obstructing left ventricular outflow if in the mitral position) and highly thrombogenic. These valves require close monitoring of anticoagulation with INR in the range 2.5–3.5. The next generation of metallic prosthetic valves was the single disc valve which opens like a 'hinged lid.' The most serious problem was strut fracture allowing the disc to escape and lodge downstream. Currently, the most widely used prosthetic metallic valve is the bicuspid, double disc or bi-leaflet, St. Jude's valve in which each strut is a half moon, opening to create three channels of flow with a larger central and two smaller lateral jets. The Carbomedics is a supra-annular double disc valve. The most physiological of the metal valves is the St. Jude's. Its 2 discs open like a butterfly's wings and when it opens the wings are up and there are actually 3 flow jets, 1 central and 2 lateral jets which create part of a Doppler artifact.

The tissue prosthetic valves, obtained from an animal (heterograft) or human (homograft) native aortic valve or designed from tissue from an animal, are probably the most physiological because they have only central flow.

Bioprosthetic valves have excellent flow dynamics. However, the flow velocity in a bioprosthetic valve is not equal to that of the native valve because, by their nature, the prostheses are always smaller than the valve that was replaced. Importantly, the ECHO imaging of the bio-prosthetic valve is easier than that of metal valves because there is tissue and less metal. The artificial mechanical prosthetic valves, regardless of their material, pyrolytic carbon, or steel, create shadowing and the transvalvular pressure gradients are going to be inherently higher than in tissue valves [4].

Clinical Assessment of Prosthetic Valves

How do we clinically assess prosthetic valves? Initially, the clinical presentation of congestive heart failure, central or peripheral emboli or rapid change in clinical status, could be an indication of prosthetic valve dysfunction. Auscultation may be valuable. Each metal prosthesis has a distinctive sound or vibration perceived by the patient and audible on auscultation. A high-frequency holosystolic or holodiastolic murmur may indicate that the valve is not well seated and is closing poorly. Abnormal blood tests such as anemia with damaged red cells and elevated lactic dehydrogenase (LDH) may indicate hemolysis. The ECHO may demonstrate spontaneous microbubbles, thought to be microcavitation and destruction of red cells going through a paravalvular leak or dysfunctional prosthetic valve. Actually, a minimal number of microbubbles may be found in 99% of bi-leaflet and 40% of monoleaflet valves. Thus, a small rise in LDH may be physiological for mechanical prosthetic valves. However, many bubbles accompanied by high levels of LDH, decreased haptoglobin, and the presence of many schistocytes on a peripheral smear may be pathological.

Echocardiographic Assessment of Prosthetic Valves

The most effective method for evaluation of prosthetic valve function is ECHO. Though fluoroscopy is still used in the cardiac catheterization laboratory to identify valve 'rocking,' ECHO provides a more comprehensive evaluation. Regardless of prosthesis type, ECHO images the anatomy and Doppler measures the hemodynamics to assess valve stability, dehiscence, abnormal masses on the valve, excessive regurgitation, or gradients.

There are some important prosthetic valve artifacts such as 'ring down' and 'masking.' These ECHO artifacts are due to the slow speed of sound transmission through the prosthetic material or to rapid reflection from its leading surface. The metal prosthetic material is very dense, causing reflection and decreasing the resolution as well as increasing reverberation and attenuation of the sound waves. A typical 'ball-in-cage' valve produces rapid reflection so the leading edge appears closer than reality and the reverberations, which slow transmission through the valve produce a trailing edge, which appears farther away than reality. If one considers the flow parameters, the color flow Doppler demonstrates 2 jets which circumnavigate the ball, seen best in the apical 4-chamber view, and which generates some hemolysis. The St. Jude's valve, a single disc valve has a fairly central turbulent jet. The disc motion itself may be difficult to visualize unless imaged in the plane of motion, but the flow through the valve is usually central.

Transesophageal ECHO (TEE) has certain advantages over transthoracic ECHO (TTE). The TEE uses a higher frequency (7 vs. 3–4 mHz) and images at a closer proximity to the heart with fewer interposed structures than TTE [5, 6]. Since TEE images from behind the left atrium, the atrial surface and annulus of the prosthesis are better seen. With TEE, valve opening and closing are better appreciated than by TTE. In the open position a St. Jude's valve has 3 distinct inflows, 2 side and 1 central jet. When the valve is closed 3 distinct jets of physiological 'backwash' regurgitation, which are inherent to prevent thrombosis on the valve, can be seen.

ECHO-Doppler imaging of a normal tissue valve demonstrates the 3 metal struts and the 3 leaflets moving well. The metal struts generate artifact and shadowing, but the leaflets are usually seen very well with low turbulent central flow through the valve as observed by color Doppler. M-mode color Doppler is very useful for timing of prosthetic valve movements and for documenting regurgitation. Physiological 'backwash' regurgitation is very brief. Opening and closing clicks envelop and delineate normal or abnormal flow patterns.

A few important principles for ECHO-Doppler imaging of prosthetic valves are worth noting:

(1) Prosthetic valves are *inherently smaller* than native valves and therefore *relatively stenotic*. Thus, the implanted valve type and size need to be identified even before imaging.

(2) Mechanical valves may be more difficult to assess than tissue valves.

(3) Transvalvular gradients by continuous wave Doppler will vary with the cardiac output, gradient between interrogated chambers, hematocrit, and blood viscosity.

(4) The *continuity equation* can be used to calculate function of aortic and mitral prosthetic valves.

For a mitral prosthesis:

$$\text{Mitral prosthesis area} = \frac{[\text{LVOT area}]\,[\text{LVOT velocity}]}{[\text{Mitral prosthesis velocity}]}$$

where LVOT = left ventricular outflow tract.
For an aortic prosthesis:

$$\text{Aortic prosthesis area} = \frac{[\text{LVOT area}]\,[\text{LVOT velocity}]}{[\text{Aortic prosthesis velocity}]}$$

Changes in cardiac output should not affect the valve area calculated by the continuity equation [7]. Pressure half-time calculation, which was developed for mitral stenosis, utilizes a fixed numerator of 220 divided by the measured pressure half time. But that 220 constant was derived for native valves, not for prosthetic valves, and pressure half-time analysis may overestimate the areas of prosthetic valves.

(5) *The smaller the implanted valve size, the higher the gradient:* The St. Jude's valve has a higher aortic gradient at small sizes. However, depending upon the way the measurement is made, this can be in part artifactual ('pseudo-stenosis'). Thus, the highest gradient measured by catheter occurs within the central orifice; the measured gradient decreases rapidly when the catheter is moved further downstream from the central orifice. This is called the 'pressure recovery phenomenon.' Potential etiologies of prosthetic valve stenosis include: small implanted prosthesis, St. Jude 'pseudo-stenosis'; tissue valve degeneration, pannus ingrowth, thrombus, vegetation, and abscesses.

(6) *Tissue valves:* The older the patient, the slower the valve deterioration. The valve deteriorates faster in younger patients probably because of higher calcium turnover, more stress on the valve from higher cardiac output, and greater force of contraction. Both stress on the valve and hemodynamic factors cause calcification of the cusp, leading to valve failure, which can cause both regurgitation and stenosis. Tissue valves, especially the newer Carpentier and mosaic tissue valves, may last 15 years or longer with innovative anticalcification preservation technique, but regurgitation as well as stenosis can develop.

Specific Prosthetic Valve Problems

Why is the valve gradient so variable with a St. Jude's valve? There are 1 central and 2 side jets as the 2 discs open and close. When the valve opens with the 1 central and 2 side jets there is a greater gradient through the central orifice

than through the 2 lateral jets because of the pressure recovery phenomenon. Since Doppler interrogation cannot differentiate between the side and the central flow jets, the continuous wave Doppler records the highest jet velocity which may yield a high gradient, especially if there is high cardiac output and small orifice size, creating 'pseudo-stenosis' [8]. Early in the history of implantation of St. Jude valves, some were taken out for high Doppler gradients, but were actually non-stenotic. Suggested guidelines to differentiate a normal from an abnormal St. Jude's prosthesis in the aortic position include assessment of the size of the St. Jude's valve and assuming a normal cardiac output. If the peak velocity is >4.5 m/s or the mean gradient is >50 mm Hg, and the calculated valve area is <0.8 cm^2, be suspicious of significant stenosis. For a mitral prosthesis, if the pressure half time is >160 cm/s, the mean area <1.5 cm^2 and there is a high peak gradient (>10 mm Hg) with potential pulmonary hypertension, suspect significant stenosis.

Prosthetic Valve Thrombosis. In patients with prosthetic valves, prosthetic valve thrombosis can occur in 0.2–1.8% per year. These prosthetic thrombosis can be clinically silent, an incidental echo finding, present as central or peripheral embolization, or can present with obstruction of disc movement generating valve stenosis and/or regurgitation. The treatment alternatives are surgery or thrombolytic therapy which is associated with a potential 6% mortality and total embolic risk of 12–17%. For diagnosis, TEE may be able to differentiate between pannus and thrombus [9].

Prosthetic Valve Regurgitation. Metal prostheses have an inherent small degree of regurgitation to prevent thrombosis and improve opening inertia. The St. Jude's valve has three 'backwash' jets, which are physiological. Tissue valves really should show minimal or no regurgitation, whereas stentless tissue homografts in the aortic position may demonstrate a small degree of regurgitation. Physiological backwash closure jets have certain characteristic parameters in either the mitral or aortic position, including short jet length, small area, and relatively low velocity. Hemodynamic factors determining the transvalvular driving forces of gradient may affect the jet size. Technical ECHO equipment factors, such as gain and filter settings, can affect the relative regurgitant jet size and shape.

Regurgitation can also be due to physiological features, tissue valve degeneration, pannus ingrowth, thrombosis, vegetation, abscess, dehiscence of the valve, or paravalvular leaks.

Prosthetic Valve Endocarditis. Endocarditis can cause relative stenosis or precipitate regurgitation depending on whether the leaflets are opening or closing abnormally. The AHA/ACC guidelines for surgery for prosthetic valve endocarditis include the following as class I categories: (1) early prosthetic valve endocarditis; (2) heart failure; (3) fungal endocarditis; (4) *Staphylcoccus aureus* infection, and (5) significant paravalvular leak.

The following clinical algorithm is suggested for suspected prosthetic valve endocarditis: (1) Clinical history, physical examination and electrocardiogram may be helpful. (2) Higher suspicion if the LDH is high. (3) Positive blood cultures. (4) TTE as a screening examination may not be very helpful with metal prosthetic valves. If a thrombus or a vegetation is detected, further definition with a TEE may be desirable. (5) Cardiac catheterization and an angiogram may be needed to assess the coronary arteries, although crossing a thrombosed or infected valve is relatively contraindicated. (6) Because prosthetic endocarditis is difficult to sterilize, consider surgical therapy for large vegetations (especially fungal), abscess, dehiscence, heart failure, or embolization.

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