MAYO CLINIC

CARDIOVASCULAR UPDATE

CLINICAL CARDIOLOGY AND CARDIOVASCULAR SURGERY NEWS

volume 1
number 2
2003

Myectomy Still "Gold Standard" Treatment for Severe Hypertrophic Cardiomyopathy

Dual-chamber pacing, septal ablation may help selected patients

Rick A. Nishimura, MD
Joseph A. Dearani, MD

Hypertrophic cardiomyopathy (HCM) has fascinated clinicians for more than 40 years. In the late 1950s, Teare and colleagues performed autopsy studies on a number of young patients who died suddenly. They speculated that the severe increase in the size of the ventricular septum might be attributable to a hamartoma or benign tumor of the heart. Sir Russell Brock subsequently operated on several patients with the clinical findings of aortic stenosis and found no significant valvular disease but rather subvalvular obstruction. A unique disease entity was identified by Braunwald and colleagues in the 1960s when they described a constellation of findings consistent with what was termed "idiopathic hypertrophic subaortic stenosis" or "IHSS," subsequently renamed "hypertrophic cardiomyopathy."

We now know that HCM is a genetic cardiac disorder caused by a missense mutation in 1 of at least 10 genes that encode the proteins of the cardiac sarcomere. "The pathophysiology is complex, consisting of a dynamic left ventricular outflow tract obstruction, mitral regurgitation, diastolic dysfunction, myocardial ischemia, and cardiac arrhythmias," according to Rick A. Nishimura, MD, codirector of the Mayo Clinic Hypertrophic Cardiomyopathy Clinic. Treatment strategies have focused on improvement of symptoms, specifically in those patients with left ventricular outflow tract obstruction greater than 50 mm Hg (at rest or during provocation). A separate area of evaluation in all patients with HCM is risk stratification and prevention of sudden cardiac death.

Medical Therapy

Medical therapy should be considered the initial approach to alleviating symptoms in all patients. Therapy is directed at 1) decreasing the obstruction caused by catecholamine stimulation and 2) slowing the heart rate to enhance diastolic filling. Although medical therapy does usually not abolish a resting left ventricular outflow tract gradient, it may prevent increases that occur during exercise.

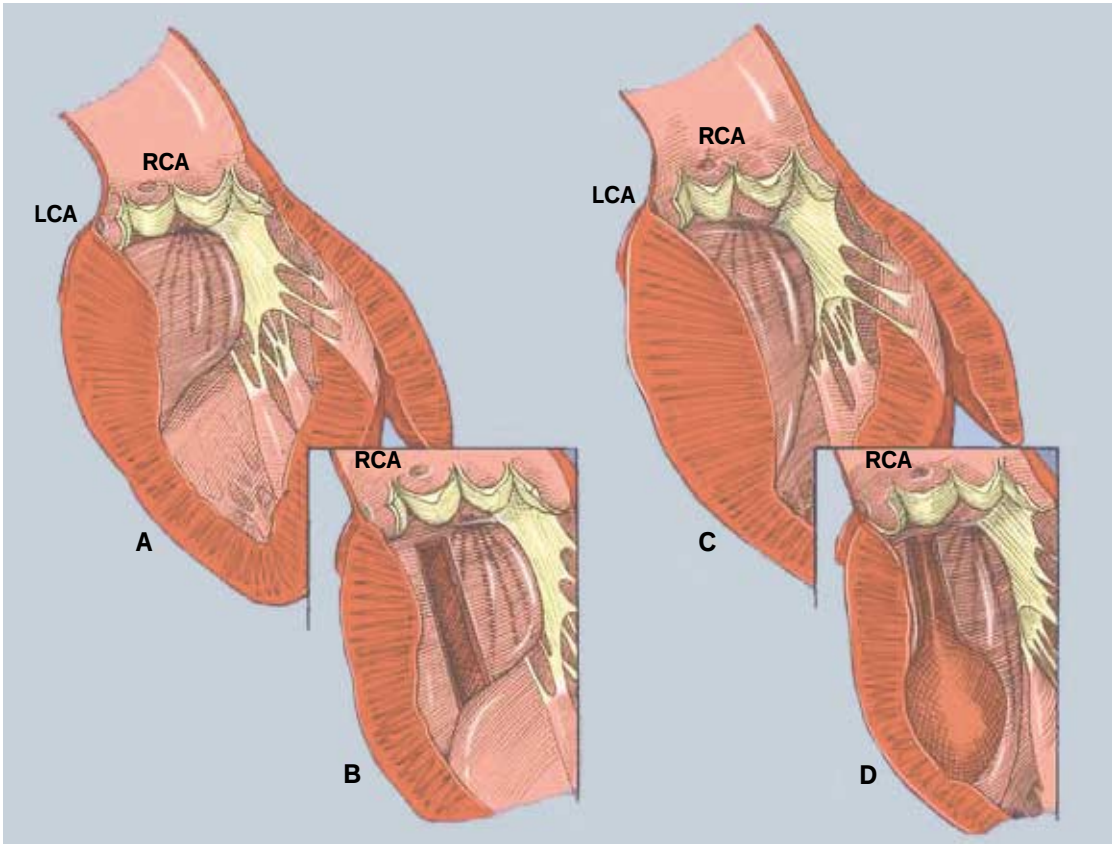
Although optimal medical therapy is initially effective in the majority of patients, some continue to have severe limiting symptoms, and less than 50% of patients who do respond have long-term relief. For these patients, additional therapy should be considered.

Surgical Myectomy

Surgical septal myectomy (surgical resection of the basal septum) is considered the "gold standard" for the treatment of symptomatic patients in whom medical therapy has failed. The operation is performed via median sternotomy with the patient on cardiopulmonary bypass, and a relatively large amount of muscle is resected from the proximal septum through a transaortic approach to relieve outflow tract obstruction.

This approach was first developed in the 1960s. Since then, more than 2,000 patients have undergone septal myectomy in North America and Europe. "The operative mortality for septal myectomy has steadily decreased over the last 2 decades and is less than 2% at experienced

Inside This Issue



Surgical resection of the basal septum. A, Prominent basal septum; B, standard septal myectomy; C, prominent basal septum with midventricular obstruction; and D, extended septal myectomy. LCA, left coronary artery; RCA, right coronary artery.

Hypertrophic Cardiomyopathy Clinic Consultants

Rick A. Nishimura, MD, Codirector
Steve R. Ommen, MD, Codirector
A. Jamil Tajik, MD
Bernard J. Gersh, MD
Kyle W. Klarich, MD
William K. Freeman, MD
Allison Cabalka, MD
Douglas J. Kocer, RN

Cardiovascular Surgery Consultants

Hartzell V. Schaff, MD, Chair
Richard C. Daly, MD
Joseph A. Dearani, MD
Christopher G. A. McGregor, MD
Charles J. Mullany, MD
Thomas A. Orszulak, MD
Francisco J. Puga, MD
Thoralf M. Sundt III, MD
Kenton J. Zehr, MD

centers," according to Joseph A. Dearani, MD, Mayo Clinic cardiovascular surgeon. "At Mayo Clinic, more than 400 patients underwent myectomy between 1993 and 2001, and the overall mortality for isolated myectomy was 1%," he says.

The results of a successful operation are complete abolition of the gradient, significant reduction in secondary mitral regurgitation, and marked improvement in symptoms. Nearly 90% of patients are free of serious symptoms after the surgery.

Variations of the myectomy procedure have been developed (Figure above). A more extensive septal myectomy is performed in patients who have evidence of midventricular obstruction, in which resection extends to the level of the papillary muscle. In addition, there are many abnormalities of the mitral valve apparatus, such as attachment of the papillary muscles directly into the anterior leaflet or chordae insertions directly into the ventricular septum, which also may be addressed at the time of operation. In some patients, a "fixed" obstruction from scarring and fibrosis of the outflow tract area may require circumferential resection of the fixed obstruction.

Current complications of the surgery are rare. "Complete heart block and ventricular septal perforation now occur in less than 1% of patients undergoing surgery at experienced centers," says Dr Dearani. These results not only depend on surgical experience but also relate to the use of intraoperative transesophageal echocardiography, which can guide the surgeon in resecting an optimal amount of muscle.

Long-term follow-up of more than 30 years shows that patients who undergo this procedure have persistent improvement in symptoms and exercise capacity. If the outflow tract obstruction is relieved after surgery, obstruction recurs rarely in adult patients. Some evidence from cohort studies suggests that mortality *may* be improved after septal myectomy, particularly in younger patients with severe outflow tract obstruction.

Dual-Chamber Pacing

Implantation of a dual-chamber pacemaker (DDD pacing) has been proposed as a less invasive therapeutic modality for treatment of symptomatic patients. The mechanism by which DDD pacing may improve symptoms and hemodynamics is not completely understood. "Although many patients' symptoms improved after pacemaker implantation, up to 50% claimed symptomatic improvement even when the pacemaker had been turned off, indicating a placebo effect," says Dr Nishimura. Objective improvement in exercise performance and decrease in gradient were far less with DDD pacing than after septal myectomy.

Despite these less than optimal results, a select subset of patients (10%-20%) respond to DDD pacing. Since no uniform standards have been established to identify patients who will respond, this therapy should be limited to those patients who are not candidates for other therapeutic modalities or those who have severe bradycardia.

If pacing is used, the ventricular lead should be placed as far apically as possible. The device should be programmed to pace or track the atrium to maintain A-V synchrony, and the A-V delay should be short enough so that mandatory ventricular pacing occurs. Dynamic A-V delay should be considered so that mandatory ventricular pacing continues with the physiologic A-V shortening seen in exercise.

Septal Ablation

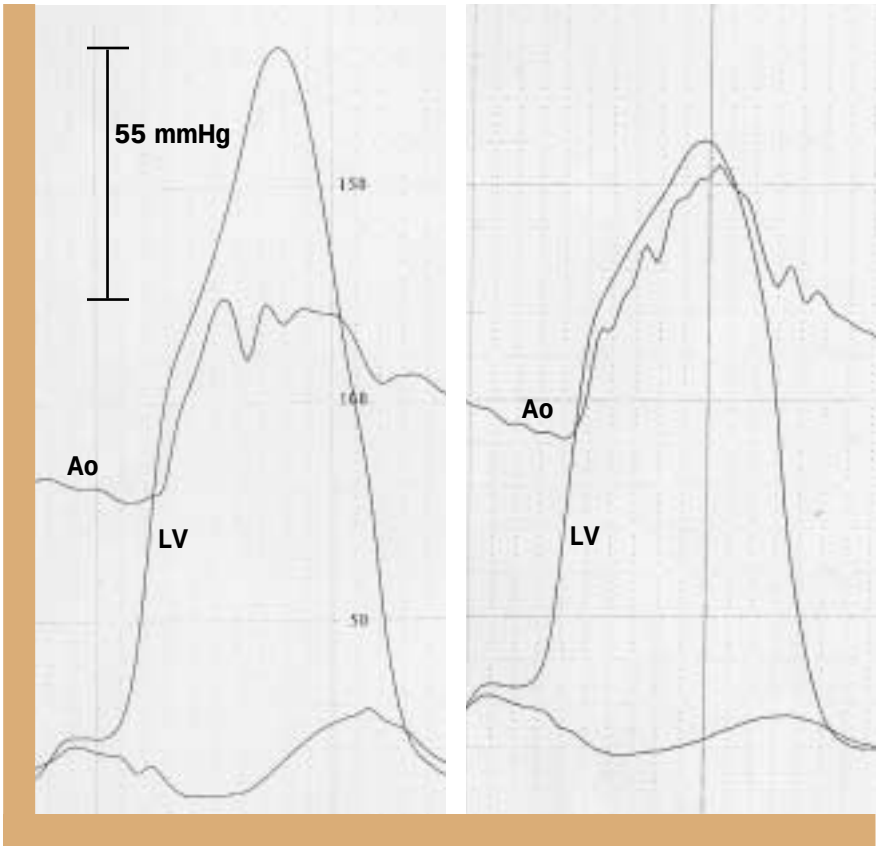
Alcohol septal ablation is an investigative therapeutic modality in which 100% alcohol is infused selectively into a septal perforator artery, which perfuses the proximal septum. "This infusion produces a controlled myocardial infarction, and the subsequent thinning and remodeling of the basal septal region results in reduction or even abolition of the outflow obstruction," according to Dr Nishimura. The procedure consists of placing a small percutaneous transluminal coronary angioplasty (PTCA) catheter in the first septal perforator artery. With either radiographic contrast or contrast echo guidance, the region of the septum supplied by the first septal perforator artery can be identified. If either the watershed region of the first septal perforator artery corresponds to the mitral valve–septal contact or if balloon occlusion results in a hemodynamic drop in gradient, then 100% alcohol is slowly infused distal to an inflated PTCA catheter. The alcohol itself results in necrosis and infarction of the affected septal muscle, which constitutes from 3% to 10% of the left ventricular mass.

The initial results from several centers have shown impressive short-term subjective and objective results after septal ablation (Figure below); however, the results of septal ablation may not be comparable to those of septal myectomy. Overall, fewer patients obtain complete abolition of gradient with septal ablation versus septal myectomy. This may be caused by 1) the highly variable anatomic course of the septal perforator arteries; 2) the inability to identify and cannulate the correct septal perforator artery; and 3) comorbid conditions such as intrinsic mitral valve disease that may not be corrected by the alcohol-induced infarction.

The most common complication of septal ablation is complete heart block requiring a permanent pacemaker, which may occur in 10% to 40% of patients (the outcome is highly dependent on the experience and technique of the operator). "Other complications, such as large myocardial infarction, ventricular septal defect, myocardial perforation, coronary artery dissection, and ventricular fibrillation, have also been reported," according to Dr Nishimura. "Late complications may occur up to 2 weeks after the procedure and include complete heart block and ventricular arrhythmias."

There has been concern that production of a myocardial infarction may have a detrimental long-term outcome; the susceptibility to arrhythmia is especially unclear. Adverse remodeling from the myocardial infarction is another potential concern.

Overall, the ultimate role of septal ablation in the treatment of patients with HCM is unclear. It should not be considered for those patients who have other pathophysiologic abnormalities that make septal ablation ineffective, such as fixed subvalvular obstruction, anomalous papillary muscle attachments, and primary mitral valve disease. Health centers that perform septal ablation should be able to interrelate echocardiographic and catheter procedures and also be committed to study the long-term outcome of the procedure. Nonetheless, in experienced centers with expertise in the technique and a foundation of knowledge about the disease, this catheter-based procedure may become an option in selected patients.



Hemodynamic tracings: Aortic (Ao) and left ventricular (LV) pressure tracings before (left) and after (right) septal ablation, demonstrating near resolution of the 55 mm Hg gradient.

Conclusions

A number of therapeutic modalities can be used to treat HCM patients with outflow tract obstruction. However, these therapies should be reserved only for those patients who have severe, limiting symptoms unresponsive to medical management. Treatment of outflow tract obstruction is only a part of the comprehensive therapy that should be instituted. Arrhythmia management and sudden cardiac death risk assessment will be addressed in upcoming issues.

ACC Late Breaker: Highlights and commentary on the clinical implications of key studies presented at ACC '03 are available on our Web site. "The State of the Stent" with analysis of the latest data on drug-eluting stents will be included in the summer edition of *Cardiovascular Update*.

Earlier Valve Repair Yields Survival Improvements

Morbidity, mortality much lower with repair versus replacement

Kenton J. Zehr, MD
Thomas A. Orszulak, MD

More than 40 years ago, Mayo Clinic cardiovascular surgeon Dwight C. McGoon, MD, described a simple plication technique to correct mitral regurgitation. Since this pioneering event, more than 3,200 mitral valve repairs have been performed at Mayo Clinic, including more than 400 in 2002. Initially, procedures were reserved for symptomatic patients with declining left ventricular function. "As we have become more comfortable with repair techniques and repairs have shown long-term durability, more complex repairs have been conceived," says Kenton J. Zehr, MD, a cardiovascular surgeon at Mayo Clinic in Rochester. "These techniques allow 85% of patients with regurgitation secondary to degenerative valve disease to undergo valve repair with excellent long-term results."

Operative mortality has decreased to less than 1% in patients younger than 75 years undergoing isolated mitral valve repair. Mayo Clinic data confirm the significantly improved 10-year survival afforded by mitral repair in patients with normal left ventricular function (72%±4% survival) compared with those with an ejection fraction of less than 50% (32%±12% survival) or with even moderate reduction in left ventricular function (ejection fraction of less than 60%) (53%±9% survival). "The results infer that repair should be performed in patients who are good candidates for successful mitral valve repair before their left ventricular function decreases," according to Dr Zehr. "Many of these patients are asymptomatic or have class I symptoms. This approach contrasts greatly with the previous practice of waiting for more debilitating symptoms or left ventricular dysfunction."

Results from Mayo Clinic in Rochester show much lower morbidity and mortality rates, both early and late, in patients undergoing mitral valve repair versus replacement. Repair avoids the need for long-term anticoagulant therapy required after valve replacement. Long-term anticoagulant therapy results in a small but ongoing risk of life-threatening bleeding. Mechanical valves have a low but persistent risk of infection and stroke. Overall survival at 10 years in 195 patients undergoing valve repair was 68%±6% compared with 52%±4% in 214 patients undergoing valve replacement. "Our findings suggest that early intervention should be standard in patients with severe mitral regurgitation," says Dr Zehr.

Many of the repair techniques were first applied to regurgitant valves with degenerative disease, and the largest percentage of repairable versus nonrepairable valves occurs in patients with regurgitant valves. However, these techniques can be applied to mitral disease of ischemic, congenital, infectious, and rheumatic origins as well.

The most common technique of valve repair focuses on the posterior leaflet (Figure at right). Techniques include resection of flail segments with suture reapproximation of supported adjacent leaflet edges. Smaller unsupported areas can be plicated instead of resected. A posterior annuloplasty is then performed with a strip of Dacron. The annuloplasty relieves stress on the repaired area and downsizes the dilated valve annulus.

Anterior leaflet repair techniques usually require supporting prolapsing or flail segments with shortened, transferred, or artificial chordae tendineae. Triangular resection or plication can be performed on patients with redundancy of the anterior leaflet. However, removal of anterior leaflet tissue can result in inadequate mitral valve tissue to achieve coaptation of the leaflets. Therefore, supportive techniques are preferred. An important study performed at Mayo Clinic showed that anterior mitral leaflet repairs with artificial chordae tendineae of ePTFE (expanded polytetrafluoroethylene) proved more durable than shortening or transferring existing chordae tendineae. In a comparison of 121 patients undergoing chordae replacement with artificial chordae and 75 patients undergoing chordae shortening, the risk of reoperation in the chordae replacement group was 1.4% versus 14.8% in the chordae shortening group at 3.5-year follow-up.

Repair of native mitral valves in patients with acute endocarditis may be associated with better survival and lower reoperative rates than valve replacement. In a 13-year period at Mayo Clinic, 45 patients with acute endocarditis underwent valve repair (17 patients) or valve replacement (28 patients). Nine patients had complex repairs—replacement of a portion of the leaflet with a prosthetic patch, placement of artificial chordae tendineae, or partial resection of both leaflets with remodeling of a commissure. In the replacement group, 6 in-hospital and 6

Cardiovascular Surgery Consultants

Hartzell V. Schaff, MD, Chair
Richard C. Daly, MD
Joseph A. Dearani, MD
Christopher G. A. McGregor, MD
Charles J. Mullany, MD
Thomas A. Orszulak, MD
Francisco J. Puga, MD
Thoralf M. Sundt III, MD
Kenton J. Zehr, MD

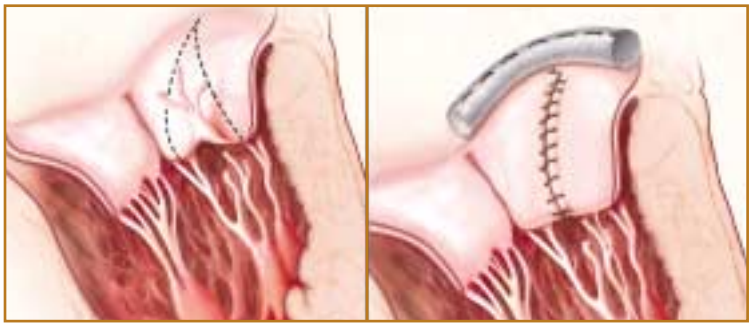
Mitral valve repair vs replacement, 2000 and 2001 (Mayo Clinic Rochester)

	Repair	Replace
Degenerative	371	61
Rheumatic	13	141
Endocarditis	19	10
Other	98	52
Total	501	264

late cardiac deaths occurred; the repair group had no deaths. Reoperation was necessary in 5 patients in the replacement group but none in the repair group.

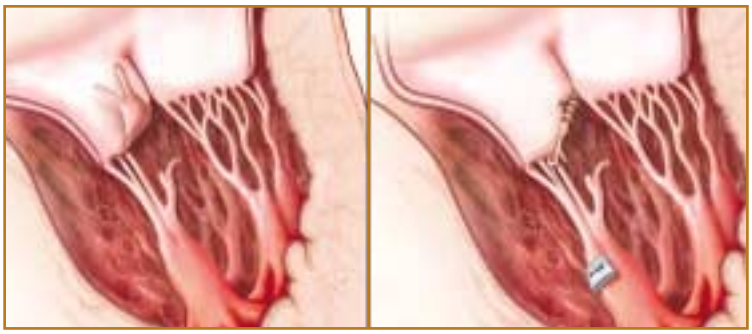
The position of the tricuspid valve mirrors the location of the mitral valve. "Infrequently, the adult tricuspid valve is primarily diseased; more commonly it is involved secondary to other cardiac disease," according to Mayo cardiovascular surgeon Thomas A. Orszulak, MD. The most frequent finding is tricuspid regurgitation secondary to dilation of the annulus. The greatest portion of the circumference of this annulus is unsupported—it makes up the free wall of the right atrium and right ventricle—rendering it susceptible to regurgitation. Dilation is a compensatory response to anatomic or physiologic abnormalities of the right ventricle, pulmonary arteries, or left-sided disease increasing the left atrial pressure, which is then transmitted to the pulmonary circuit. "This results in a structurally normal valve with poor or no coaptation centrally," says Dr Orszulak.

This category of regurgitation responds to repair via a direct approach to the annulus. Tightening or reducing the circumference of the annulus brings the valve leaflets back into the normal relationship and allows leaflet edge overlap and thus competence of the valve. The critical point in constructing this annuloplasty is to avoid the conduction system, located at the base of the posterior leaflet in the triangle of Koch. This arc of the circumference is within the "rigid" or nondilating part of the annulus, and thus no sutures are necessary. Most suturing starts above or anterior to this location and ends posterior to it.



Flail section of the posterior leaflet caused by rupture of chordae tendineae.

Final repaired posterior leaflet after resection of flail segment and suture reapproximation.



Flail section of the anterior leaflet caused by rupture of chordae tendineae.

Final repaired anterior leaflet after resupport of the flail segment with artificial ePTFE chordae tendineae.

The 2 most common types of repair are the DeVega suture annuloplasty and the Carpentier-Edwards rigid annuloplasty ring. The DeVega technique is a running suture involving 290° of the annulus avoiding the conduction area. The Carpentier-Edwards system involves the same amount and location of the annulus but applies a rigid, elliptical, incomplete ring to the annulus. Interrupted sutures are placed along the dilatable portion of the annulus. Ring size is based on the size of the anterior leaflet of the tricuspid valve, which reduces the circumference of the annulus to the normal area to support the leaflets. No randomized studies have been conducted to determine whether one approach is better than another, and the choice of technique has been left to the surgeon's discretion.

More important than which type of tricuspid annuloplasty to perform is when to perform it. The timing has progressed recently from surgeon preference to graduated indications. Tricuspid regurgitation of grade II or more should probably be repaired when encountered with left-sided valve disease at operation. This is especially true when pulmonary artery pressure is higher than normal. A caveat is to avoid tricuspid repair with high pulmonary artery pressure and decreased right ventricular function; tricuspid regurgitation in this situation acts as an afterload reducer for the right ventricle.

The need to repair the tricuspid valve at the time of left-sided repair is attributable to the high-risk status of patients who present later with worsening tricuspid regurgitation, right ventricular dysfunction, and ascites. "If tricuspid correction is performed then, the symptoms and clinical state may not improve," says Dr Orszulak. Ruptured chordae to the tricuspid valves are infrequent, but when ruptures occur, the best course is to follow the same criteria and techniques used to repair the mitral valve.

Endocarditis of the tricuspid valve is most frequent in patients with a history of intravenous drug use. Generally, because of the young age of these patients and their lack of structural heart disease, either a repair with autologous tissue (pericardium) is performed, or the valve is totally excised. When the infection is eradicated and measures are implemented to prevent recurrent infections, a valve replacement can be planned.

Other abnormalities that may be acquired on the tricuspid valve are those involving tumors or systemic diseases, eg, systemic carcinoid. Every attempt is made to preserve all native valvular tissue, but frequently these maladies require valve replacement.

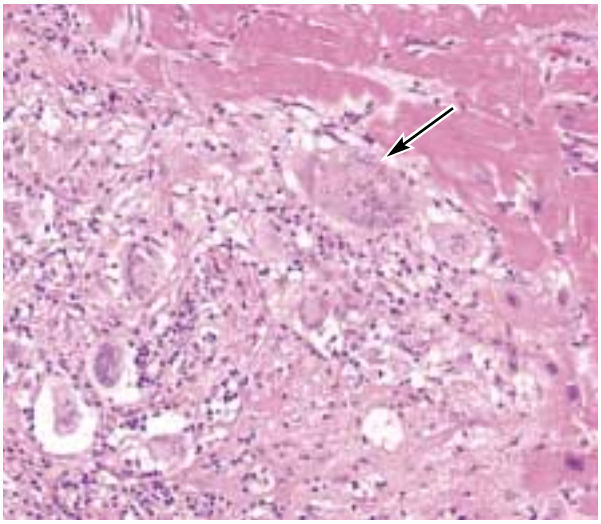
Familiarity and experience with a variety of repair techniques, both simple and complex, and an understanding of the fundamentals of valve anatomy and function enable the surgeon to intervene early, safely, and effectively to correct regurgitation and still save the native valve and preserve its function, agree Dr Zehr and Dr Orszulak.

Mayo Clinic Cardiologist Heads Multicenter Giant Cell Myocarditis Study

Leslie T. Cooper, MD

Giant cell myocarditis (GCM) is a highly lethal disorder that generally affects young, otherwise healthy individuals, although a minority of cases occur in association with autoimmune disorders. From Saltikow's classic description in 1905 until 1987, all cases were described at autopsy after a short illness. The first prolonged transplant-free survival was described in 1993, raising the possibility that prolonged survival might even be possible. "Because GCM is so uncommon, no one medical center has gathered sufficient cases to characterize the natural history and estimate the effect of various treatments," according to Leslie T. Cooper, MD, a cardiologist at Mayo Clinic in Rochester. "Current knowledge of GCM derives from 1 multicenter registry and numerous case reports." The diagnosis of GCM should be considered in patients with subacute heart failure of unknown cause, particularly if accompanied by ventricular arrhythmias or heart block. Of the 63 Multicenter Giant Cell Myocarditis Registry cases, 75% presented with congestive heart failure, 14% had ventricular arrhythmias, and lesser percentages presented with a syndrome mimicking acute myocardial infarction, heart block, or arterial embolization. The median age was 42 years, with equal sex predilection. Up to 20% of cases occur in individuals with other inflammatory or autoimmune disorders.

The diagnosis of GCM can be confirmed only by pathologic examination of heart tissue from endomyocardial biopsy, explant, or postmortem specimens. Endomyocardial biopsy ought to be considered for patients with heart failure or ventricular arrhythmias of less than 3 months' duration whose condition fails to improve or deteriorates after 1 to 2 weeks of optimal medical care. GCM is usually progressive and frequently requires the concurrent management of congestive heart failure, arrhythmias, and renal and hepatic insufficiency. "We usually avoid the use of digoxin because of the risk of heart block or worsening ventricular arrhythmias," says Dr Cooper. Despite aggressive and timely care, a majority of patients require cardiac transplantation or die within 1 year. Survival of GCM patients after heart transplant is comparable to survival for patients who receive transplants for idiopathic cardiomyopathy.



Diagnostic findings are diffuse or serpiginous myocardial infiltrate, usually composed of lymphocytes and eosinophils. Multinucleated giant cells (arrow) often cluster at the margins of the inflammatory process, and myocyte necrosis or damage is present.

Data from the multicenter registry suggest that treatment with cyclosporine and corticosteroids (sometimes combined with azathioprine, muromonab-CD3, or both) improves transplant-free survival from 3 months to more than 12 months. The Multicenter Giant Cell Myocarditis Treatment Trial, a federally funded study led by Dr Cooper, seeks to confirm the GCM registry results and estimate the safety of aggressive immunosuppression for GCM. This study is a randomized, open-label trial of muromonab-CD3, cyclosporine, and corticosteroids compared with usual care without specified immunosuppression for GCM diagnosed by endomyocardial biopsy.

Detailed information about the trial may be obtained from Dr Cooper or from www.clinicaltrials.gov.

Forms of Myocarditis

(see web site for additional information)

Disorder	Associated Findings and Diagnostic Studies	
Lymphocytic myocarditis	Often presents as asymptomatic ECG changes after a flulike illness. Symptomatic cases usually present with heart failure with decreased left ventricular contractility. Sustained ventricular arrhythmias and heart block are uncommon. A considerable minority of cases progress to dilated cardiomyopathy. Endomyocardial biopsy reveals lymphocytes, histiocytes, and associated myocyte damage.	Most patients give a history of antecedent upper respiratory tract infection.
Giant cell myocarditis	A rare but usually rapidly progressive disorder characterized by heart failure, frequently with ventricular arrhythmias and variable degrees of heart block. Biopsy reveals multinucleated giant cells and myocyte damage in the absence of granulomas.	Associated disorders include thymoma, inflammatory bowel disease, and thyroiditis.

Upcoming Courses

Continuing Medical Education, Mayo Clinic

To register for or obtain information about programs, visit www.mayo.edu/education or call 800-323-2688.

Medical and Surgical Controversies in Cardiovascular Disease: The Aorta and Peripheral Vessels
Jun 14-15, 2003, Rochester, Minn

8th Annual Mountain Course: Success With Failure: New Strategies for the Evaluation and Treatment of Congestive Heart Failure
Aug 10-12, 2003, Whistler, BC

Internal Medicine Review for Nurse Practitioners and Physician Assistants
Aug 25-26, 2003, Rochester, Minn

Mayo Cardiovascular Review Course for Cardiology Boards and Recertification
Sep 20-25, 2003, Rochester, Minn

Echocardiography for the Sonographer
Sep 21-23, 2003, Rochester, Minn

19th Annual Echocardiography in Pediatric and Adult Congenital Heart Disease
Oct 12-15, 2003, Rochester, Minn

Harold W. Siebens Conference: Genetic and Cell Therapies for Cardiovascular Disease
Oct 24-26, 2003, Rochester, Minn

Update in Cardiovascular Diseases: A Case-Oriented, Interactive Approach
Oct 30-31, 2003, Rochester, Minn

American College of Cardiology Programs

To register for or obtain information about programs, visit www.acc.org or call the ACC Resource Center at 800-253-4636, ext 694. Outside the United States and Canada, call 301-897-2694 or fax 301-897-9745.

The 17th Annual Echocardiographic Symposium on 2-D and Doppler Echocardiography at Vail
Jul 27-31, 2003, Vail, Colo
Directed by George M. Gura, Jr, MD, FACC; Fletcher A. Miller, Jr, MD, FACC; Jae K. Oh, MD, FACC

Cardiac Device Therapy—2003: Update in Pacemaker, ICD, and Cardiac Resynchronization Therapy
Aug 7-9, 2003, Chicago, Ill
Directed by David L. Hayes, MD, FACC

Cases in Echocardiography: TEE, Doppler, and Stress—Interpretation and Clinical Decision Making for the Advanced Echocardiographer
Oct 30-Nov 1, 2003, Seattle, Wash
Directed by Rick A. Nishimura, MD, FACC; Fletcher A. Miller, Jr, MD, FACC

Other Education Opportunities

Clinical Decision Making in Cardiology: Role of Diagnostic Techniques
Sep 18-20, 2003, Madrid, Spain

Mayo Alliance for Clinical Trials Education Conference—Clinical Trials Research
Sep 25-26, 2003, Rochester, Minn
For information call 800-541-5815 or 507-266-3074.

1st Annual Echocardiography: From Pictures to Information
Oct 24-26, 2003, Phoenix, Ariz

Stephen C. Hammill, MD, is scientific program chair for the North American Society of Pacing and Electrophysiology (NASPE) 24th Annual Scientific Sessions, May 14-17, 2003, in Washington, DC.

ACC National Award Recipients: Samuel J. Asirvatham, MD, W. Proctor Harvey Young Teacher Award; Horng H. Chen, MD, Career Development Award; A. Jamil Tajik, MD, Distinguished Fellow Award; Douglas L. Wood, MD, Distinguished Service Award.

Mayo Clinic Cardiovascular Update

Medical Editor: Margaret A. Lloyd, MD
Surgical Editor: Christopher G. A. McGregor, MD
Editorial Board: David L. Hayes, MD, Hartzell V. Schaff, MD, Rick A. Nishimura, MD, Lee A. Aase, Marjorie G. Durhman
Managing Editor: Jane C. Lantz, MLA, ELS
Art Director: Marjorie G. Durhman
Media Support Services Contributing Artists: Randy J. Ziegler, Michael A. King, Aimee L. Unverzagt, Joseph M. Kane

Cardiovascular Update is written for physicians and should be relied upon for medical education purposes only. It does not provide a complete overview of the topics covered and should not replace the independent judgment of a physician about the appropriateness or risks of a procedure for a given patient.

MAYO CLINIC

200 First Street SW
Rochester, Minnesota 55905
www.mayoclinic.org

C-Reactive Protein: A New Adjunct to Predicting Cardiovascular Risk

Iftikhar J. Kullo, MD

Atherosclerosis is a complex process and not just a disease of lipid deposition in the arterial wall. "Evidence increasingly suggests that inflammation plays a key role in the initiation, progression, and eventual complications of atherosclerosis," according to Iftikhar J. Kullo, MD, a cardiologist at Mayo Clinic in Rochester, Minnesota. There is considerable interest in circulating markers of inflammation as predictors of cardiovascular risk.

One such marker, C-reactive protein (CRP), has been studied the most intently. Several prospective studies have shown that CRP levels (measured with a high-sensitivity assay) are related to future occurrence of cardiovascular events such as myocardial infarction and stroke. Most of these studies examined risk in subjects with CRP levels in the highest quartile or quintile (top 25% or 20%, respectively). Independent of other risk factors, the relative risk for these subjects is about twice as high as that for subjects in the lowest quartile or quintile. CRP is elevated in the presence of known risk factors such as diabetes, smoking, low high-density lipoprotein (HDL) cholesterol, and obesity, but levels may also increase because of as yet unknown or unmeasured risk factors. Whether CRP levels reflect inflammation in the arterial wall remains to be proven. Also not established is a role for CRP in the pathogenesis of atherosclerosis. "An agent that specifically lowers CRP would be useful in answering some of these questions, but such an agent is not currently available," says Dr Kullo.

Statins lower CRP in addition to modifying the lipid profile, but whether this reduction independently results in reduced cardiovascular risk is not yet known. Other agents that may lower CRP include the fibrates, fish oil, and modest alcohol consumption. The effect of aspirin on CRP levels has not yet been established.

Steps in the use of "novel" risk factors to assess cardiovascular risk. TRF, traditional risk factors; CRP, C-reactive protein; LDL, low-density lipoprotein; Lp(a), lipoprotein (a).

The American Heart Association and the Centers for Disease Control and Prevention recently issued guidelines for CRP testing and interpretation. The expert panel recommends initial assessment of patient risk by conventional methods such as the Framingham risk equation. People at low risk or high risk may not benefit from further testing. In patients at intermediate risk or those with the metabolic syndrome, CRP measurement may be helpful to decide further treatment options. If CRP is elevated, then lifestyle changes should be the initial approach, including weight reduction, low-fat diet, smoking cessation, and regular exercise. In certain settings, initiation of lipid-lowering therapy may be appropriate. The panel cautions that the benefit of such a strategy is not proven at present. "Widespread screening of CRP is not currently recommended nor is serial testing to monitor the effects of treatment," notes Dr Kullo.

Additionally, the panel recommends use of an average of 2 CRP measurements performed 2 to 3 weeks apart. When levels are checked, the patient should be free of any intercurrent illness, injury, or increased stress, and levels should be measured at least 2 to 3 weeks after any such event. The following cut points have been suggested to interpret CRP levels:

Risk	CRP level
Low	<1.0 mg/L
Average	1.0-3.0 mg/L
High	>3.0 mg/L

The enthusiasm about use of CRP measurement as a diagnostic tool needs to be tempered by recognition of its limitations. "It's a nonspecific marker of inflammation, and there is no convincing evidence to proclaim elevated CRP as a risk factor; rather, it appears to be a risk marker," cautions Dr Kullo. No prospective, randomized clinical trial data are available to demonstrate the benefit of treatment based on CRP testing. Also lacking are data about the cost-effectiveness of such a strategy. Evidence for its utility as an indicator of risk in several ethnic groups is not available. Many other questions about CRP as a risk marker also remain unanswered.

What is the temporal relationship of elevation of CRP to the occurrence of cardiovascular events? Why do women have higher levels of CRP than men and yet are not at higher risk? Is the increased incidence of cardiovascular events in women started on hormone replacement therapy related to elevated CRP? Further research is needed to clarify some of these issues and to develop more sensitive and specific tests of inflammation of the arterial wall. The possible utility of combining serum markers for inflammation and thrombosis also needs to be evaluated (Figure). "The results of such investigations may eventually help us become better at something we are not able to do very accurately at the present time: predict risk," concludes Dr Kullo.