

CLINICAL THERAPEUTICS

Mitral-Valve Repair for Mitral-Valve Prolapse

Subodh Verma, M.D., Ph.D., and Thierry G. Mesana, M.D., Ph.D.

This Journal feature begins with a case vignette that includes a therapeutic recommendation. A discussion of the clinical problem and the mechanism of benefit of this form of therapy follows. Major clinical studies, the clinical use of this therapy, and potential adverse effects are reviewed. Relevant formal guidelines, if they exist, are presented. The article ends with the authors' clinical recommendations.

A 55-year-old man with a holosystolic murmur of increasing intensity has been seen regularly by his family physician for the past 3 years. He is referred to a cardiologist. The patient reports no shortness of breath, chest pain, or palpitations. An electrocardiogram shows normal sinus rhythm. A transthoracic echocardiogram reveals severe, anteriorly directed mitral regurgitation with isolated prolapse of the middle scallop of the posterior leaflet. Flow reversal is detected in the pulmonary veins. The calculated regurgitant volume is 75 ml, the regurgitant fraction 63%, and the effective regurgitant orifice 53 mm², features consistent with severe mitral regurgitation. The transthoracic echocardiogram also shows mildly depressed left ventricular function (ejection fraction, 58%), slightly elevated left ventricular dimensions (end-systolic dimension, 42 mm), and normal right ventricular systolic pressure. The patient is referred to a cardiac surgeon for consideration of mitral-valve repair.

THE CLINICAL PROBLEM

Mitral-valve prolapse is defined as the displacement of some portion of one or both leaflets of the mitral valve into the left atrium during systole. In developed countries, it is the most common cause of chronic mitral regurgitation; in a study of the Framingham Offspring Study cohort, the prevalence of mitral-valve prolapse was 2.5%.¹ More than 150 million people worldwide may be affected.²⁻⁴ The disorder has both genetic and acquired forms, and several chromosomal loci for autosomal dominant mitral-valve prolapse have been identified.⁵⁻⁹ Although mitral-valve prolapse is more common in women, more men are referred for surgery⁴; whether this reflects a difference between the sexes in the morphologic features or natural history of the disorder or referral bias is unclear.

The natural history of mitral-valve prolapse is heterogeneous and is largely determined by the severity of mitral regurgitation. Although a majority of patients remain asymptomatic and may have a near-normal life expectancy, approximately 5 to 10% have progression to severe mitral regurgitation.^{10,11} Left untreated, mitral-valve prolapse with severe mitral regurgitation results in limiting symptoms, left ventricular dysfunction, heart failure, pulmonary hypertension, and atrial fibrillation. Spontaneous rupture of mitral chordae may occur, and endocarditis and stroke are serious complications. The mortality rate of persons who have mitral-valve prolapse with severe mitral regurgitation is approximately 6 to 7% per year.^{12,13}

PATHOPHYSIOLOGY AND THE EFFECT OF THERAPY

The mitral valve and subvalvular apparatus include the annulus, valve leaflets, chordae tendineae, papillary muscles, and left ventricular wall. The valve has anterior and posterior leaflets, and each leaflet typically consists of three discrete segments or scallops. These are designated P1, P2, and P3 in the posterior mitral-valve leaflet,

From the Division of Cardiac Surgery, St. Michael's Hospital, University of Toronto, Toronto (S.V.); and the Division of Cardiac Surgery, Ottawa Heart Institute, University of Ottawa, Ottawa (T.G.M.). Address reprint requests to Dr. Verma at St. Michael's Hospital, University of Toronto, 30 Bond St., Toronto, ON M5B 1W8, Canada, or at subodh.verma@sympatico.ca.

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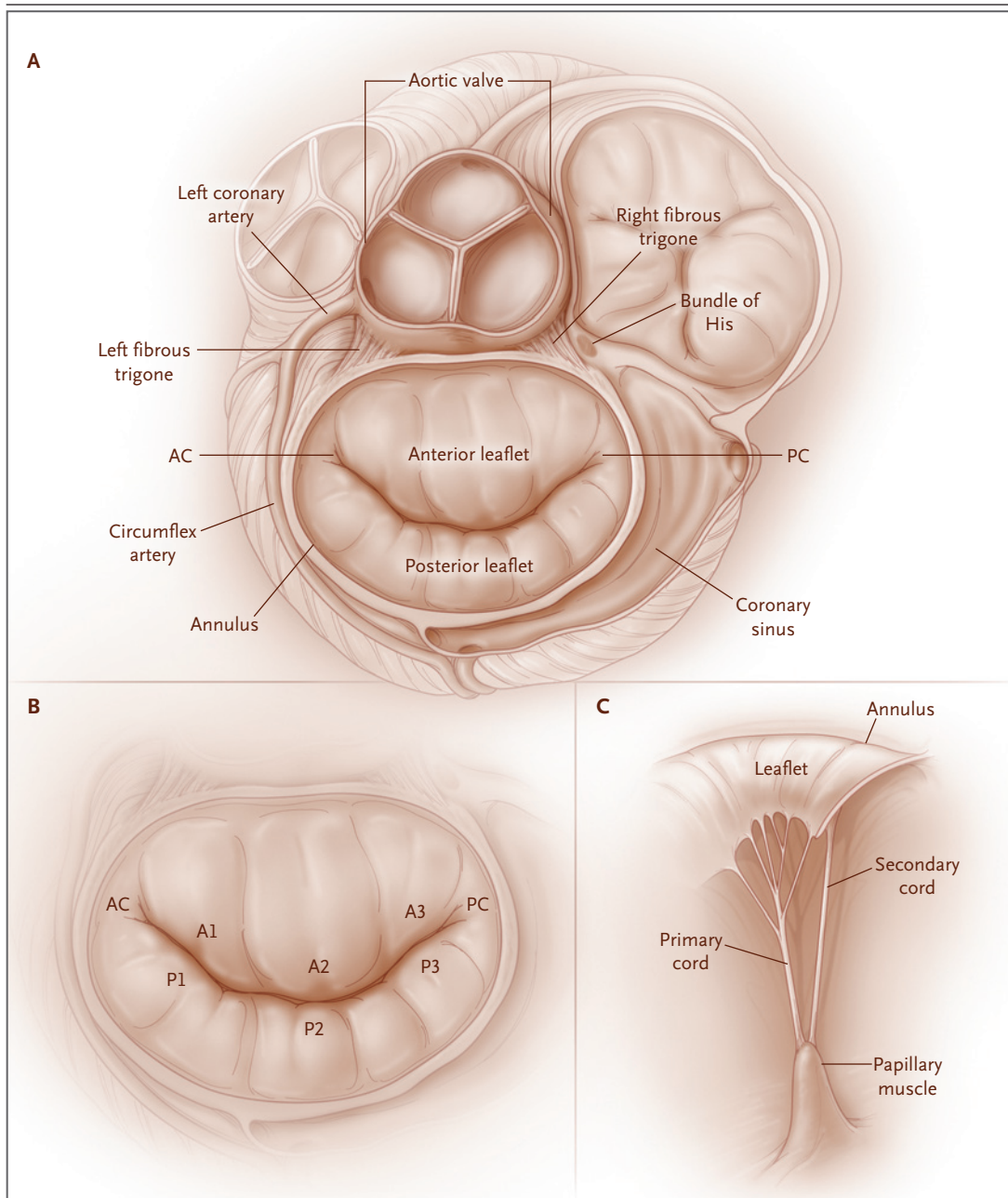


Figure 1. The Mitral Valve.

The mitral valve has anterior and posterior leaflets, which are separated by the anterior commissure (AC) and the posterior commissure (PC) (Panel A). The leaflets are inserted on the circumference of the mitral annulus, which is in continuity with the aortic annulus and the left and right fibrous trigones. The circumflex coronary artery, coronary sinus, aortic valve, and bundle of His are all close to the mitral valve. Panel B shows the mitral-valve leaflets, each of which usually consists of three discrete segments or scallops. These are designated A1, A2, and A3 for the anterior leaflet and P1, P2, and P3 for the posterior leaflet. The valve leaflets each receive chordae tendineae from the anterolateral and posteromedial papillary muscles (Panel C). Primary chordae are attached to the free edge of the valve leaflet, and secondary chordae are attached to the ventricular surface of the leaflet.

and A1, A2, and A3 in the anterior leaflet (Fig. 1). The valve leaflets receive chordae tendineae from the anterolateral and posteromedial papillary muscles. Competence of the mitral valve relies on coordinated interaction of the valve and subvalvular apparatus. During systole, the papillary mus-

cles contract, increasing tension on the chordae tendineae and preventing the valve leaflets from everting into the left atrium.

Mitral-valve prolapse is characterized predominantly by myxomatous degeneration. In younger patients, the disease is often manifested by excess leaflet tissue and is known as Barlow's syndrome, the most extreme form of myxomatous degeneration. On the other hand, in older patients, the prolapsing mitral valve tends not to have excess leaflet tissue, an entity known as fibroelastic deficiency. Both conditions can lead to leaflet prolapse and chordal elongation or rupture, representing the spectrum of degenerative mitral-valve disease.¹⁴ These anatomic abnormalities result in the mitral orifice not closing completely during systole, causing regurgitation. Annular dilatation may also develop over time, leading to further progression of mitral regurgitation.

Patients with mild-to-moderate mitral regurgitation from mitral-valve prolapse may remain asymptomatic and without clinical deterioration for many years. However, increasing severity of mitral regurgitation, even among asymptomatic patients, imposes a volume load on the left ventricle, which, if sustained over time, results in ventricular dilatation, hypertrophy, neurohumoral activation, and heart failure. In addition, elevation in the mean left atrial pressure leads to left atrial enlargement, atrial fibrillation, pulmonary congestion, and pulmonary hypertension.

The goal of surgical correction for mitral-valve prolapse is to restore a competent mitral valve. There are two options for surgical correction of severe mitral regurgitation due to mitral-valve prolapse: valve replacement or valve repair.

Mitral-valve replacement can be performed with the use of either a mechanical or a biologic prosthesis. However, there are several drawbacks to mitral-valve replacement. These include the need for lifelong anticoagulation therapy and the risk of thromboembolism with the use of mechanical valves; the risk of prosthetic-valve deterioration and failure with the use of bioprosthetic valves; and the risk of prosthetic-valve endocarditis. In addition, if the chordae tendineae are severed during surgery, the ventricular wall is no longer anchored to the valve apparatus, and the tethering effect of the chordae is lost. As a result, left ventricular wall stress increases and left ventricular function deteriorates.¹⁵⁻¹⁹ The goals of mitral-valve repair are to obtain a proper line of coaptation on both leaflets, to correct annular

dilatation, and to preserve (or repair, if necessary) the subvalvular apparatus.

CLINICAL EVIDENCE

We are unaware of any randomized trials that have compared medical management to surgery for severe mitral regurgitation due to mitral-valve prolapse. However, evidence from observational series strongly suggests that surgical intervention is beneficial.^{12,20-22} One study evaluated the effect of early surgery on long-term outcomes in 221 patients who had mitral regurgitation with flail leaflets.²⁰ The 63 patients undergoing surgery within 1 month after diagnosis had a significantly better 10-year survival rate than those whose mitral regurgitation was managed conservatively (79% vs. 65%; adjusted risk ratio, 0.30; 95% confidence interval [CI], 0.12 to 0.71; $P=0.008$). In another report, 394 patients with mitral regurgitation and flail leaflets were studied.²¹ During a median follow-up period of 3.9 years, the linearized mortality rate associated with nonsurgical management was 2.6% per year. Mitral-valve surgery was performed in 315 patients (repair in 250, replacement in 65). Surgical intervention was independently associated with a reduced risk of death (adjusted hazard ratio for death, 0.42; 95% CI, 0.21 to 0.84; $P=0.01$).

To our knowledge, there are also no randomized trials comparing mitral-valve repair with replacement. Again, however, data from observational studies suggest a benefit of mitral repair.²³⁻²⁶ A meta-analysis of 29 studies compared mitral-valve repair with replacement for various conditions, including myxomatous degeneration.²³ Mitral-valve replacement was associated with lower survival than was repair (hazard ratio for death, 1.58; 95% CI, 1.41 to 1.78).

In a study from Finland, mitral-valve repair was compared with replacement in 184 consecutive patients who were followed for a mean of 7.3 years.²⁴ There was a significant survival benefit for the patients who underwent mitral-valve repair as compared with those who underwent replacement (5-year survival, 81.2% vs. 73.5%), which persisted after adjustment for baseline propensity score ($P=0.02$). In contrast, in a report from the Cleveland Clinic, 3286 patients who underwent an isolated primary operation for degenerative mitral-valve disease (mitral repair, 93%; mitral replacement, 7%) between 1985 and 2005 were studied.²⁵ Propensity scoring was

used to select 195 matched pairs for analysis. Among the propensity-matched patients, there was no significant difference in survival at 5, 10, or 15 years.

CLINICAL USE

Patients with mitral-valve prolapse should have a careful assessment of symptoms and should undergo electrocardiography (primarily to evaluate cardiac rhythm) and transthoracic echocardiography to assess the mechanism and severity of mitral regurgitation, as well as left ventricular size and function. A semiquantitative scale is often used to grade mitral regurgitation: 1+ (trace), 2+ (mild), 3+ (moderate), and 4+ (severe). However, quantitative Doppler assessments are recommended to define severe mitral regurgitation more precisely; these variables include a regurgitant volume of at least 60 ml, a regurgitant fraction of at least 50%, and an effective regurgitant orifice of at least 40 mm².²⁷

Patients who have severe mitral regurgitation with symptoms or with left ventricular dysfunction (ejection fraction, <60%), dilatation (left ventricular end-systolic dimension, >40 mm), or both should be offered surgery.^{28,29} Likewise, asymptomatic patients without left ventricular dysfunction or dilatation but with atrial fibrillation or pulmonary hypertension should be considered for surgery. Asymptomatic persons with mild-to-moderate mitral regurgitation and no evidence of left ventricular dysfunction or dilatation should be observed until the development of either symptoms or severe mitral regurgitation.

Before the advent of mitral-valve repair, valve replacement was the preferred procedure for severe mitral regurgitation. Valve replacement may still be preferred in certain situations, such as in patients with advanced age, infective endocarditis, a requirement for a combined or complex surgical procedure, or extensive calcifications of the leaflets or annulus. In such cases, chordal-sparing valve replacement for mitral regurgitation may be a suitable alternative to repair.

Individual and institutional experience is crucial in determining the likelihood of success of a repair procedure. High-volume centers have the lowest mortality rates and the highest proportion of patients undergoing mitral-valve repair rather than replacement.³⁰ In counseling the patient, the surgeon should precisely evaluate the likelihood of successful repair in light of his or

her own experience and may recommend a second opinion. If there is a possibility that intraoperative conversion to mitral replacement may be necessary, the decision between a mechanical valve and a bioprosthesis should be discussed with the patient before the operation.

Mitral-valve surgery is not recommended in patients with clinically significant coexisting conditions, such as advanced respiratory, hepatic, or renal dysfunction, or those with marked extracardiac arteriopathy or recent cerebrovascular events. Depressed left ventricular function is an independent predictor of poor outcomes but is not a contraindication to mitral-valve repair.³¹ In patients with coexisting coronary artery disease, mitral-valve repair combined with coronary-artery bypass surgery should be the procedure of choice.³² Two validated scoring systems for determining risk during cardiac surgery are commonly used to determine perioperative risk.^{33,34}

We routinely perform intraoperative transesophageal echocardiography during all mitral-valve repair procedures.^{28,29} Transesophageal echocardiography provides precise anatomic and functional information that is helpful in planning the operation, including the extent of leaflet deformity, the mechanism and severity of mitral regurgitation, the condition of the subvalvular apparatus, the diameter of the mitral annulus, left atrial dimensions, and ventricular function.³⁵

Successful mitral-valve repair encompasses four general principles.³⁶ First, repair must restore an adequate surface of coaptation of both leaflets in systole.^{14,37} Second, full leaflet motion should be restored or preserved. Third, to prevent progressive dilatation, an annuloplasty ring or band should be used to reinforce the repair by stabilizing the annulus. Mitral-valve repair without annuloplasty reinforcement is not recommended. Last, the surgeon should ensure that no more than trace-to-mild mitral regurgitation is present at the completion of the repair.

In patients with isolated prolapse of the posterior middle scallop (P2), which is encountered in the majority of patients with degenerative mitral regurgitation, repair usually involves limited resection of this scallop, including the removal of the minimum number possible of adjacent chordae and supporting apparatus. The remaining segments of the posterior leaflet, namely P1 and P3, are then brought together (Fig. 2). If excessive posterior-leaflet tissue is present, the

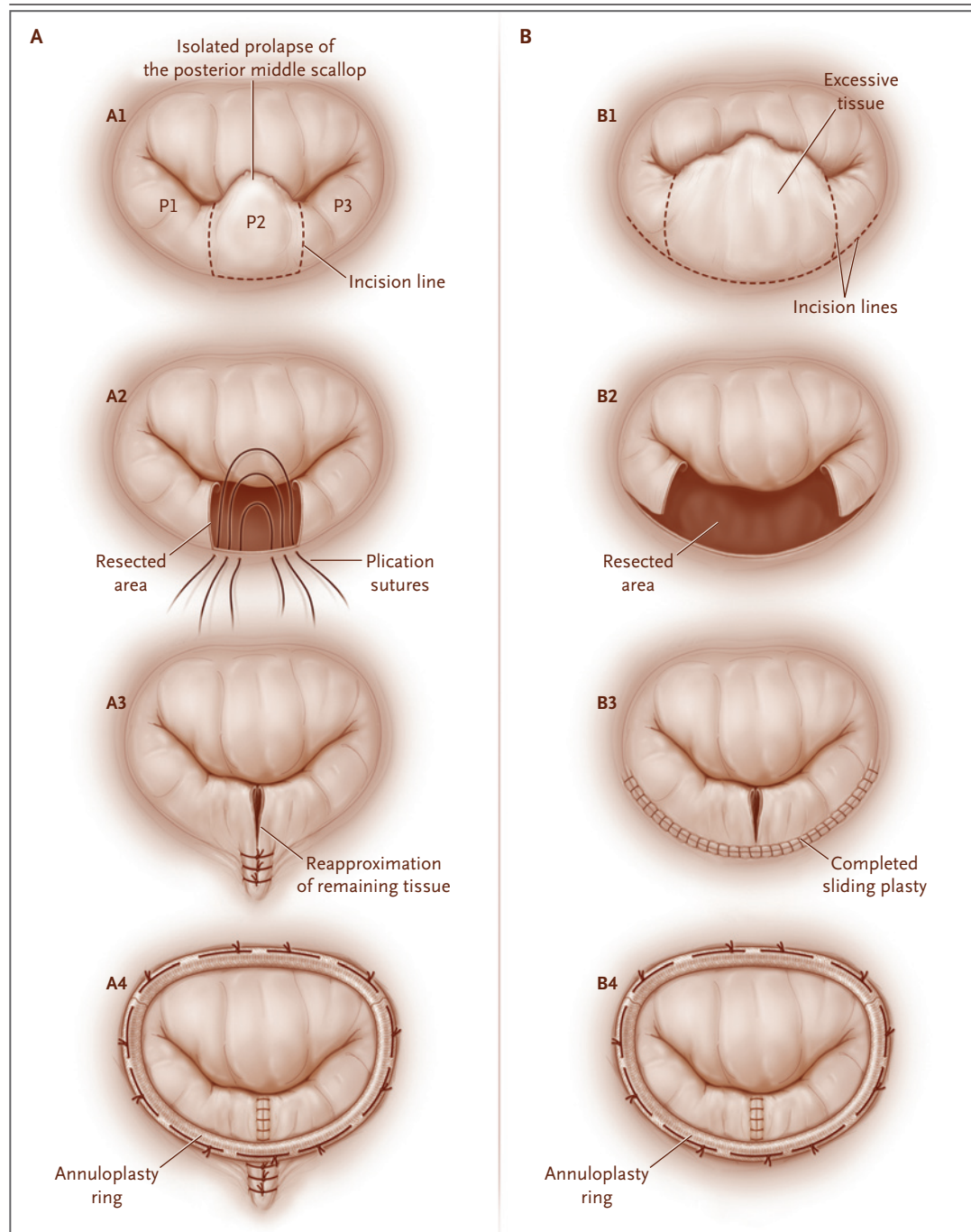


Figure 2. Mitral-Valve Prolapse.

The most common leaflet abnormality seen in mitral-valve prolapse is isolated prolapse of the posterior middle scallop (P2) (Panel A1). In patients with isolated prolapse of P2, repair usually involves limited resection of this scallop by means of a quadrangular or triangular incision (Panel A2). The remaining parts of the posterior leaflet, namely P1 and P3, are then brought together (Panel A3). After the leaflet repair is complete, an annuloplasty ring or band is used to reinforce and stabilize the annulus, thus preventing progressive dilatation (Panel A4). If excessive posterior leaflet tissue is present (Panel B1), the height of the posterior leaflet is reduced by incising P1 and P3 from the annulus (Panel B2), followed by reapproximation of the free edges (“sliding plasty”) (Panel B3). After the leaflet repair is complete, an annuloplasty ring or band is inserted (Panel B4).

height of the posterior leaflet is reduced by incisions in P1 and P3, followed by reapproximation of the free edges (“sliding plasty”) (Fig. 2). Finally, the annulus, which is distorted or dilated or both, is stabilized with an annuloplasty ring or band (Fig. 2). Limited resection, artificial chordal replacement (with Gore-Tex expanded polytetrafluoroethylene sutures), or both may be appropriate, followed by annuloplasty reinforcement, in cases of mitral-valve prolapse without redundant leaflet tissue.

Repairs of the anterior leaflet, either in isolation or with concomitant posterior leaflet repair, are more complex procedures that are best handled by surgeons who are experienced in mitral repair. Various techniques may be used, including limited triangular resection of the anterior leaflet, chordal transposition, chordal shortening, artificial (Gore-Tex) chordal replacement, and edge-to-edge repair^{10,21,28,38-41} (Fig. 3).

The repair is assessed initially by visual inspection and by injecting saline through the mitral valve to look for regurgitation (the “saline test”), and then by intraoperative transesophageal echocardiography after the patient is weaned from cardiopulmonary bypass. Patients should not leave the operating theater with more than 1+ mitral regurgitation on transesophageal echocardiography.^{36,42} Since anesthesia may result in substantial changes in preload and afterload, it is important to perform the intraoperative transesophageal echocardiography under conditions that approximate postoperative conditions in a patient who is awake. This can be achieved by adjusting inotropes and vasopressors to raise the afterload and blood pressure.

After mitral-valve repair, the left ventricle must be able to eject the entire stroke volume into the aorta. This constitutes a substantial increase in afterload as compared with ejection into the left atrium. Therefore, afterload reduction is important to maintain optimal cardiac output. In addition, because myocardial dysfunction may be present (even in patients with an apparently normal preoperative ejection fraction),⁴³ inotropic support may be necessary to improve contractility. Patients with a low preoperative ejection fraction and heart failure may require more intensive treatment to allow the left ventricle to recover, including temporary pacing, intraaortic balloon counterpulsation, or in rare cases, support with a ventricular assist device.

In the absence of preoperative atrial fibrillation, and if normal sinus rhythm is maintained throughout hospital admission, aspirin alone may be sufficient for patients who had mitral-valve repair with ring annuloplasty. Otherwise, patients typically undergo anticoagulation with warfarin for 3 months, with a target international normalized ratio of 2.0 to 2.5. Antibiotic prophylaxis for dental procedures is recommended in all patients receiving an annuloplasty ring or other prosthetic material.⁴⁴

There are currently no standard recommendations regarding postoperative echocardiographic follow-up after mitral-valve repair. It is customary at our center to perform transthoracic echocardiography once before discharge and again at 6 to 8 weeks after discharge. Usually patients are then transferred to the care of their cardiologist and family physician, and we recommend that echocardiography be performed annually thereafter.

We estimate that the overall costs for mitral-valve repair, including hospital admission, professional fees, operating time, and prosthetic material (annuloplasty ring or band), are currently approximately \$40,000 at our institution. Data from the Nationwide Inpatient Sample indicate that the mean estimated institutional cost for mitral repair in the United States increased from \$28,405 in 2001 to \$38,642 in 2005.⁴⁵

ADVERSE EFFECTS

Mitral-valve repair is associated with an operative mortality of 3% or less.^{22,38,46-50} This figure is nearer 1% in high-volume centers.³⁰ The most common cause of death is heart failure. Predictors of death include advanced age, poorer New York Heart Association class, atrial fibrillation, lower preoperative ejection fraction, greater preoperative left ventricular end-systolic dimension, and coexisting conditions including diabetes, renal disease, chronic lung disease, and obesity.^{22,38,51,52}

In an analysis from the Society of Thoracic Surgeons National Adult Cardiac Surgery Database,⁵² major postoperative complications before discharge included prolonged (>24 hours) ventilatory support (7.3% of patients), renal failure (2.6%), and stroke (1.4%). Reoperation during initial hospitalization was required in 6.3% of patients. Thromboembolism after mitral-valve repair occurs in approximately 5% of patients within the first 5 years after surgery.^{38,39}

Figure 3. Special Repair Techniques.

Ruptured chordae tendineae can be replaced with an artificial substitute (Gore-Tex expanded polytetrafluoroethylene sutures) (Panel A). Ruptured or surgically severed primary chordae can be replaced with secondary chordae, a process called chordal transfer (Panel B). Edge-to-edge repair (Panel C) is performed by sewing the anterior and posterior leaflets together at the central points of their middle scallops, which corrects the prolapse while leaving two functional valve orifices on each side.

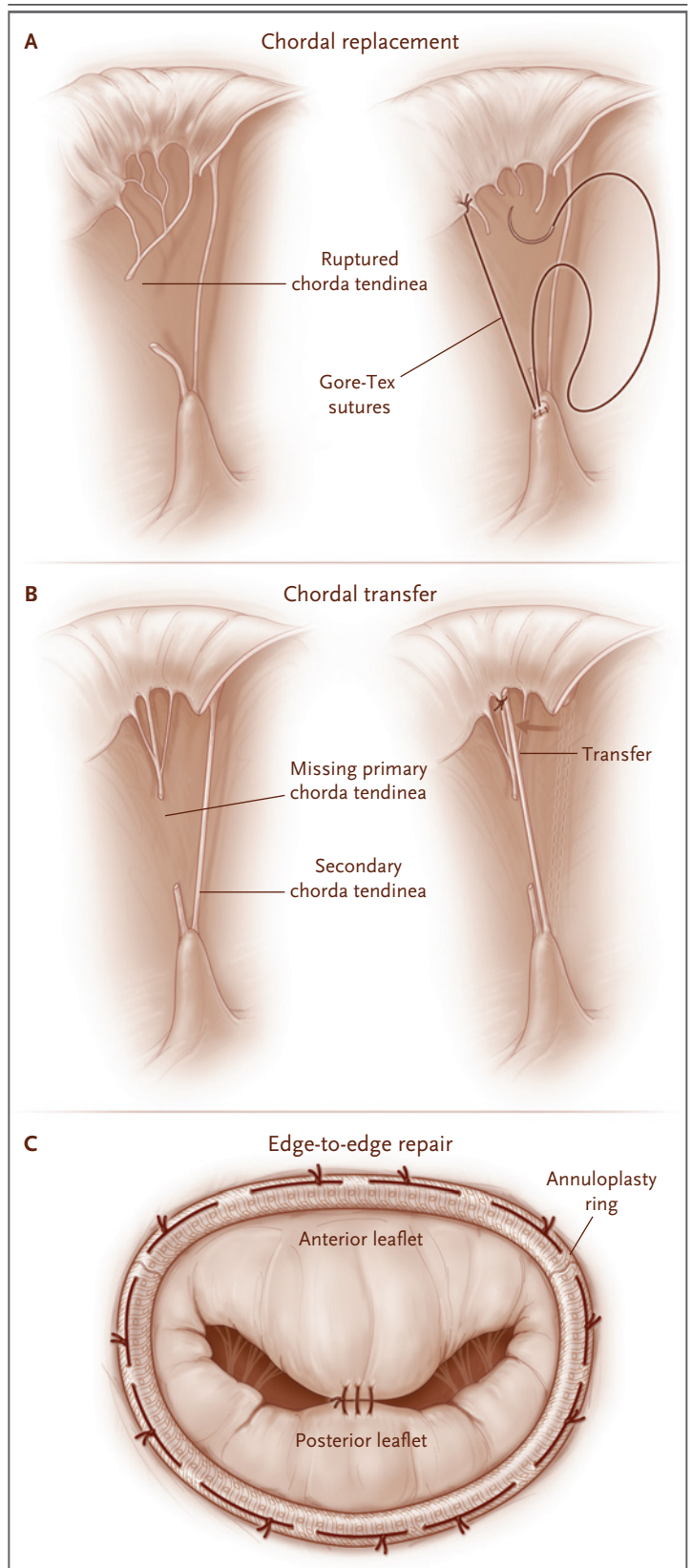
Intraoperative conversion to mitral-valve replacement occurs in 2 to 10% of cases. Systolic anterior motion of the mitral valve may occur postoperatively if leaflet coaptation is not optimal, and mitral stenosis can occur if the annuloplasty ring is too small. Other rare adverse effects of mitral-valve repair include damage to important structures around the mitral apparatus, such as the circumflex coronary artery, the aortic valve, and the bundle of His.

The most important late complication of mitral-valve repair is recurrent mitral regurgitation, which may occur in as many as 30% of patients.³⁶ Reoperation to treat recurrent mitral regurgitation after primary repair is required in approximately 0.5 to 1.5% of patients per year.^{49,51}

AREAS OF UNCERTAINTY

We are unaware of any randomized trials that have compared mitral-valve repair with mitral-valve replacement for mitral-valve prolapse, and it is unlikely that such a trial will be conducted. Therefore, the current recommendation for mitral-valve repair in the treatment of severe degenerative mitral regurgitation is based on observational data.

It is unclear whether asymptomatic patients who have severe mitral regurgitation without left ventricular dysfunction or dilatation, atrial fibrillation, or pulmonary hypertension should undergo early surgery. Some investigators have found evidence of reduced morbidity and mortality with surgery and recommend early intervention,^{22,50} whereas others have found that watchful waiting does not seem to result in worse outcomes.⁴⁶ The guidelines of the American Heart Association (AHA) and the American College of Cardiology (ACC) recommend mitral-valve repair for such patients if the operative success rate is expected to exceed 90%.^{28,29} Conversely, the European So-



ciety of Cardiology (ESC) recommends watchful waiting.⁵³

There is growing experience with minimally invasive mitral-valve repair performed through a right minithoracotomy. In a single-center series involving 1339 patients, the 30-day mortality rate was 2.4%, the 5-year survival rate was estimated to be 82.6%, and the reoperation rate was 3.7%.⁵⁴ These results are similar to those obtained with traditional mitral-valve repair. This approach requires further evaluation with respect to widespread generalizability and cost-effectiveness; it is currently performed at only a few specialized centers.

GUIDELINES

The ACC and the AHA established guidelines for the management of valvular disease in 2006, with an update in 2008.^{28,29} These guidelines gave a class I recommendation to mitral-valve surgery for chronic severe mitral regurgitation in the presence of symptoms, a left ventricular ejection fraction of less than 60%, or an end-systolic dimension of more than 40 mm. Mitral-valve repair was recommended over replacement for most patients (class I recommendation). The guidelines advise that such persons be referred to surgical centers at which the surgeons are experienced in mitral-valve repair. The ESC guidelines of 2007 made similar recommendations.⁵³ As noted above,

the societies differ somewhat in terms of their recommendations for patients who have asymptomatic mitral-valve prolapse with severe mitral regurgitation but normal left ventricular volumes and function; the ACC-AHA guidelines give a class IIA recommendation in this regard.

RECOMMENDATIONS

The patient in the vignette is asymptomatic but has signs of ventricular dysfunction and elevated left ventricular dimensions. He should therefore be offered mitral-valve surgery and should be referred to a center with demonstrated expertise in mitral-valve repair. His operative risk should be formally assessed with the use of one of the validated risk-scoring algorithms. Intraoperative transesophageal echocardiography should be performed to provide a detailed anatomical and functional assessment at the time of surgery that would permit a final decision to be made about the specifics of the operative procedure. Unless severe deformity of the valve leaflets or subvalvular apparatus is present, we would recommend mitral-valve repair rather than replacement. Since mitral-valve prolapse is often genetically transmitted, it may be worth considering echocardiographic screening of first-degree relatives.

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