CLINICAL PRACTICE

Aortic Regurgitation

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This Journal *feature begins with a case vignette highlighting a common clinical problem.*
Evidence supporting various strategies is then presented, followed by a review of formal guidelines,
when they exist. The article ends with the authors' clinical recommendations.

A 48-year-old woman who reports mild fatigue but no dyspnea, chest pain, or palpitation is found to have a diastolic cardiac murmur. The blood pressure is 140/50 mm Hg, and the pulses are bounding. Cardiac examination reveals decreased S1 and increased S2 intensity, with a grade 1/6 systolic murmur and a grade 3/6 diastolic murmur along the left sternal border. Doppler color-flow echocardiography shows a bicuspid aortic valve with an eccentric jet of aortic regurgitation. The left ventricle is moderately enlarged, with an end-diastolic diameter of 66 mm (or 39 mm per square meter of body-surface area) and an end-systolic diameter of 46 mm (or 27 mm per square meter); the ejection fraction is 51 percent, and the ascending aorta is enlarged, at 48 mm. How should this patient be treated?

THE CLINICAL PROBLEM

The most common cause of aortic regurgitation in developing countries is rheumatic disease, with clinical presentation in the second or third decade of life. In Western countries, rheumatic disease is now rare, and severe aortic regurgitation is most frequently due to diseases that are congenital (in the bicuspid valve) or degenerative (such as annuloaortic ectasia), which typically present in the fourth to sixth decades.[1] In rare cases, aortic regurgitation is acute, caused by endocarditis or aortic dissection.

The overall prevalence of aortic regurgitation was 4.9 percent in the Framingham Heart Study[2] and 10 percent in the Strong Heart Study[3]; the prevalence of aortic regurgitation of moderate or greater severity was 0.5 percent and 2.7 percent, respectively. These differences may reflect the difference in the distribution of racial and ethnic groups in the cohorts (predominantly whites in the Framingham Heart Study and predominantly Native Americans in the Strong Heart Study) or differences in the rates of rheumatic fever. The prevalence of aortic regurgitation increases with age,[2,3] and severe regurgitation is clinically more often observed in men than in women.[4,5]

Aortic regurgitation is usually detected by clinical examination, manifested as a characteristic decrescendo diastolic murmur, or incidentally by echocardiography. The valve lesions create an orifice that allows regurgitant flow throughout diastole (measured as the regurgitant volume), a physiologic mechanism that explains a poor tolerance to bradycardia, given the prolonged diastolic duration. The diastolic regurgitation and the increase in the systolic stroke volume cause increased systolic pressure, widened pulse pressure, and bounding pulses, which are suggestive of the diagnosis. Hence, aortic regurgitation is a unique valvular disease with both left ventricular volume overload (indicated by an enlarged left ventricle on echocardiography or angiography) and pressure overload (indicated by increased end-systolic pressure). However, because left atrial pressure increases late in the course of the disease, symptoms (including dyspnea and angina) usually develop slowly.

Patients with severe aortic regurgitation have higher mortality than the general pop-

ulation, and the disorder is also associated with substantial morbidity.[5] Ten years after the diagnosis of severe aortic regurgitation, heart failure occurs in approximately half the patients, and most surviving patients require aortic-valve replacement.

Subgroups of patients who are at increased risk for death from cardiovascular causes have been identified. Patients with severe symptoms (including dyspnea or angina with mild effort or at rest, categorized as New York Heart Association and Canadian Cardiovascular Society class III or IV) are at particularly high risk, with an annual mortality of nearly 25 percent, and even those patients with mild symptoms (class II) have an annual mortality rate (6.3 percent) that exceeds the rate in the general population.[5] Marked left ventricular enlargement is associated with an increased risk of sudden death.[6] However, absolute left ventricular diameters (i.e., those uncorrected for body size) underestimate the degree of left ventricular enlargement in women; as compared with men, women tend to have surgery at a later stage of the disease, have more severe symptoms at the time of surgery, and have a higher risk of death postoperatively.[7] Even in the absence of symptoms, men and women whose end-systolic diameter is 25 mm per square meter or more or whose ejection fraction is below 55 percent have an increased risk of death.[5] In addition, the risk of aortic dissection or rupture is clearly increased in patients with annuloaortic ectasia and an aortic diameter of 6 cm or more (close to 7 percent per year),[8] and even aortic diameters between 5.5 and 6 cm are associated with an increased risk.[8,9] Asymptomatic patients without left ventricular dysfunction do not have an excess risk of death, as compared with the general population,[5,6,10] but do have high cardiovascular-event rates (i.e., death from cardiac causes, heart failure, or new symptoms) at 5 to 6 percent per year.

STRATEGIES AND EVIDENCE

EVALUATION

Classifying the severity of regurgitation is the first step in evaluating patients with aortic regurgitation (Table 1). Clinically, bounding arterial pulses, a widened pulse pressure, a loud diastolic murmur,[12] and a third heart sound[13] are signs of severe regurgitation but are not always specific. Doppler echocardiography has become the mainstay of the assessment of the severity of aortic regurgitation.[11] Suggestive of severe regurgitation are signs of a broad jet width on color-flow imaging, steep jet velocity deceleration (reflecting equalization of aortic and ventricular pressure), and prolonged diastolic flow reversal in the aorta. The use of Doppler echocardiography makes it possible to quantify the effective regurgitant orifice (severe if ≥0.30 cm²) and regurgitant volume (severe if ≥60 ml per beat) (Fig. 1 and 2, and the video clip available with the full text of this article at www.nejm.org).[14-16] A simple, reliable measurement is the "vena contracta" — that is, the width of the regurgitant flow at the orifice, a surrogate measurement for the size of the orifice. Measurements that are 0.5 cm or more have a high sensitivity for the diagnosis of severe regurgitation, and measurements that are 0.7 cm or more have a high specificity for the diagnosis.[17] On rare occasions, this approach is inconclusive, and either transesophageal echocardiography or angiography of the aortic root is necessary to determine the severity of aortic regurgitation. Left ventricular size and function (particularly, the end-systolic diameter and ejection fraction) should be routinely assessed, as should dilatation of the ascending aorta. If transthoracic imaging is suboptimal for the latter, transesophageal echocardiography, computed tomography, or magnetic resonance imaging can be used. Exercise testing may be warranted in asymptomatic patients with limited physical activity to evaluate functional limitations and may also provide information about changes of left ventricular function with stress.[10]

SURGICAL MANAGEMENT

Surgery relieves the aortic regurgitation but is not appropriate for all patients because of the small but definite risks of the procedure and because aortic prostheses may cause complications.[18] There are no

Table 1. Classification of the Severity of Aortic Regurgitation.*

Variable	Aortic Regurgitation			
	Mild	Moderate‡		Severe
Width of vena contracta (mm)†	<3.0	3.0–5.9		≥6.0
Ratio of width of aortic regurgitant jet to left ventricular outflow (%)	<25	25–44	45–64	≥65
Regurgitant volume (ml per beat)	<30	30–44	45–59	≥60
Regurgitant fraction (%)	<30	30–39	40–49	≥50
Effective regurgitant orifice (mm²)	<10	10–19	20–29	≥30

* The classification is from the American Society of Echocardiography.[11]
† The vena contracta is the regurgitant flow at the orifice on color-flow imaging.
‡ The subdivisions of the moderate class correspond to the subcategories of "mild to moderate" and "moderately severe."

data from randomized trials comparing surgical management of aortic regurgitation with nonsurgical therapy, and data on the benefits and risks of surgery are derived only from observational studies. These studies have demonstrated lower morbidity and mortality among high-risk patients who undergo surgery than among those who do not.[4,5] A potentially confounding issue is that patients who are referred for surgery tend to be more fit than those who are not, but there is general consensus that surgery is appropriate in high-risk patients who have no surgical contraindications. The severity of regurgitation, the symptoms and degree of functional impairment, the degree of left ventricular dysfunction, and the degree of aortic enlargement are central to clinical decision making.

Symptomatic Patients

The presence of severe symptoms (dyspnea or angina with mild effort or at rest, categorized as class III or class IV in both the New York Heart Association and the Canadian Cardiovascular Society classifications) is a definite indication for aortic-valve surgery. Surgery in these patients results in symptomatic relief,[4] and long-term mortality appears to be considerably lower than that among patients with severe symptoms who are treated medically.[5] Although some practitioners have advocated using severe symptoms as the sole criterion for surgery (e.g., in young patients with rheumatic aortic regurgitation),[19] this strategy is associated with excess mortality, even after successful correction of aortic regurgitation.[4] Thus, surgery should be considered earlier in the course of the disease.[20] Patients with mild symptoms and those with symptoms that improved or resolved with medical therapy remain at notable risk without surgery. In those patients, surgery relieves the symptoms and has a low risk, and postoperative survival is similar to the expected survival in the general population.[4]

Asymptomatic Patients

Among asymptomatic patients with aortic insufficiency, surgery is warranted if frank left ventricular enlargement or moderate dysfunction is present.[20] In these patients, a delay of surgery until symptoms develop is associated with substantial postoperative risks of frank left ventricular dysfunction and death.[21,22] Extreme left ventricular dilatation (i.e., an end-diastolic diameter of 80 mm or more) is a recognized risk factor for sudden death.[6] However, this degree of ventricular dilatation is generally ac-
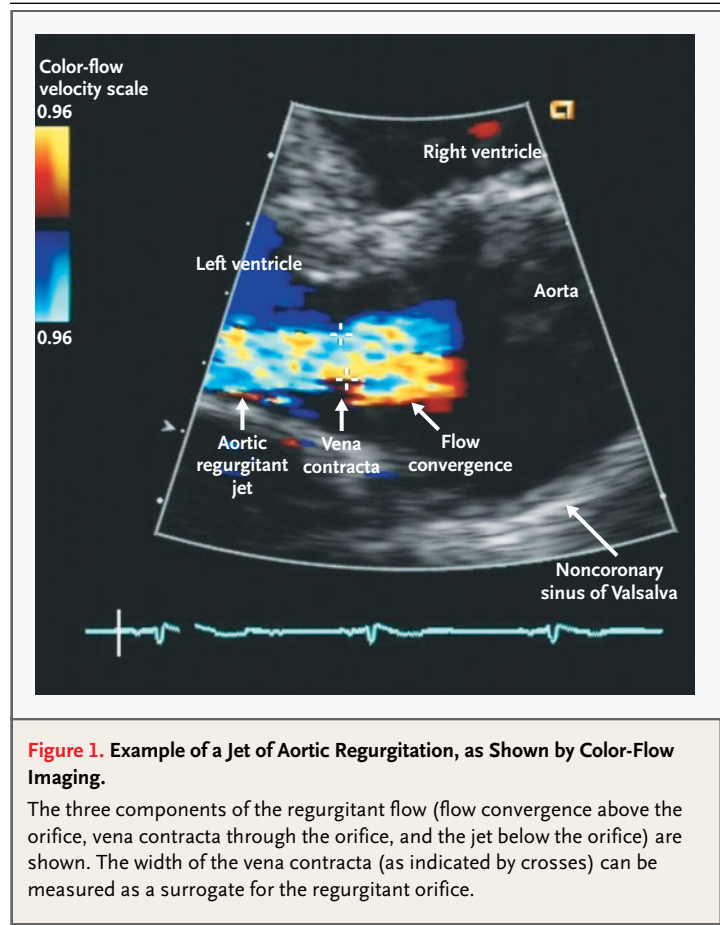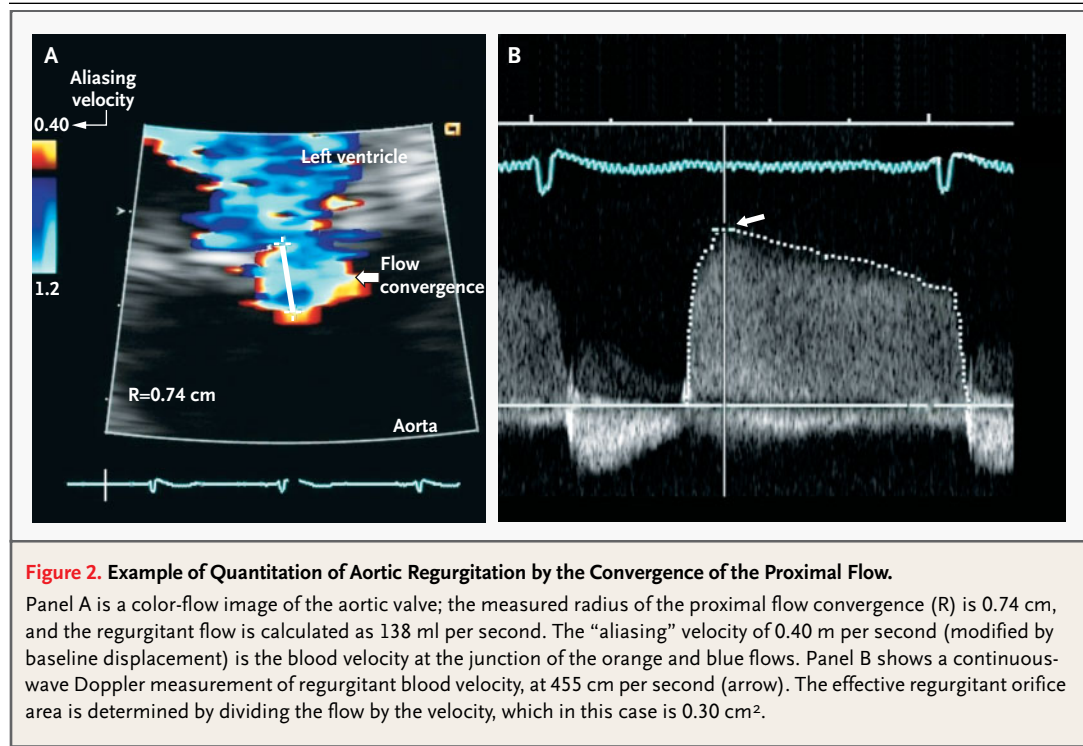

Figure 1. Example of a Jet of Aortic Regurgitation, as Shown by Color-Flow Imaging.

The three components of the regurgitant flow (flow convergence above the orifice, vena contracta through the orifice, and the jet below the orifice) are shown. The width of the vena contracta (as indicated by crosses) can be measured as a surrogate for the regurgitant orifice.

companied by overt left ventricular dysfunction[23]; a strategy of waiting to proceed with surgery until this degree of deterioration is seen has been associated with increased postoperative mortality and is not advisable.

On the basis of observational data, surgery is indicated in patients with an end-systolic diameter of 55 mm or more[20] (or 25 mm per square meter or more, a measurement that applies equally to men and women since it accounts for body-surface area[5,7]) or an ejection fraction below 55 percent.[20,24] The postoperative outcome for patients with a reduced ejection fraction depends on the magnitude of the reduction.[25] For patients with a preoperative ejection fraction below 35 percent, the 10-year postoperative survival rate is only 41 percent[25]; with an ejection fraction of 35 to 49 percent, it is 56 percent, and with an ejection fraction of 50 percent or more, it is 70 percent.[25] Hence, surgery should ideally be performed in asymptomatic patients when the ejection fraction is between 50 and 55 per-

Figure 2. Example of Quantitation of Aortic Regurgitation by the Convergence of the Proximal Flow.

Panel A is a color-flow image of the aortic valve; the measured radius of the proximal flow convergence (R) is 0.74 cm, and the regurgitant flow is calculated as 138 ml per second. The "aliasing" velocity of 0.40 m per second (modified by baseline displacement) is the blood velocity at the junction of the orange and blue flows. Panel B shows a continuous-wave Doppler measurement of regurgitant blood velocity, at 455 cm per second (arrow). The effective regurgitant orifice area is determined by dividing the flow by the velocity, which in this case is 0.30 cm².

cent.[22,25] However, patients with a markedly decreased ejection fraction should not be denied surgery. These patients generally have an improvement in the ejection fraction postoperatively[25] as a result of relief of the high afterload,[26] particularly if the ventricular dysfunction has lasted for less than one year,[27] and they may become asymptomatic after surgery.[25] Combined correction of aortic regurgitation and aortic aneurysm should be considered in asymptomatic patients with aneurysms of the ascending aorta that are more than 5.5 to 6 cm in diameter, given the increased risk of aortic rupture or dissection.[8,9]

Risks of Surgery
Aortic-valve replacement is the usual intervention for aortic regurgitation and in the United States is associated with a mortality of 4 percent when performed in isolation and 6.8 percent when performed with coronary bypass surgery.[28] The operative mortality is lower in high-volume centers[29] and among patients who have minimal or no symptoms (1 to 2 percent mortality[4]) or better preoperative left ventricular function (8 percent mortality when the ejection fraction is 35 percent or less vs. 2 percent when the ejection fraction is 50 percent or more).[25] In patients with no or minimal symptoms

before surgery and a normal ejection fraction (55 percent or more), long-term postoperative survival is equivalent to that of the general population.[4]

For patients with ascending aortic aneurysms, composite graft replacement (an ascending aortic graft with a prosthesis) is associated with a mortality of 1 to 10 percent, depending on the severity of aortic regurgitation, ventricular dysfunction, and clinical presentation, but the surgery appears to improve outcome, as compared with medical management.[9,25,30] In patients with mild aortic regurgitation, a valve-sparing ascending aortic replacement may minimize the long-term risks associated with valvular prostheses.[30]

NONSURGICAL MANAGEMENT
Mild or moderate aortic regurgitation is usually managed conservatively, unless dilatation of the ascending aorta justifies surgery. A strategy of conservative management of severe aortic regurgitation in asymptomatic patients is reasonable if the patients have neither marked left ventricular enlargement nor left ventricular dysfunction, since several studies have shown that asymptomatic young patients with normal left ventricular function have a survival rate identical to that in the general population.[5,6,10,31]

Vasodilator therapy may be considered for pa-

Table 2. Guidelines for Indications for Surgery in Patients with Severe Aortic Regurgitation.

Indication Class*	ACC–AHA Guidelines[20]	European Society of Cardiology Guidelines[24]†
I	NYHA class III or IV symptoms	Left ventricular diastolic diameter >70 mm
	NYHA class II symptoms with progressive left ventricular dilatation, reduced ejection fraction, or reduced exercise tolerance	Left ventricular systolic diameter >55 mm or >25 mm/m² of body-surface area
	CCS class II angina	Ascending aortic dilatation >55 mm
	Ejection fraction 25–49%	
	Surgery indicated for another valve or coronary bypass	
II	NYHA class II symptoms isolated (IIa)	Rapid increase in left ventricular diameters
	Asymptomatic left ventricular dilatation >75 mm in diastole and >55 mm in systole (IIa)	Bicuspid aortic valve or Marfan syndrome with aortic diameter >50 mm
	Ejection fraction <25% (IIb)	
	Asymptomatic left ventricular dilatation 70–75 mm in diastole and 50–55 mm in systole (IIb)	
	Asymptomatic, decreased ejection fraction with exercise (IIb)	

* Class I indicates that there is evidence or general agreement that the procedure is useful; class II indicates that there is conflicting evidence or opinion. The guidelines of the American College of Cardiology and the American Heart Association (ACC–AHA) divide class II into IIa, which indicates that the weight of evidence favors surgery, and IIb, which indicates that the efficacy of surgery is less well established. NYHA denotes New York Heart Association, and CCS Canadian Cardiovascular Society.

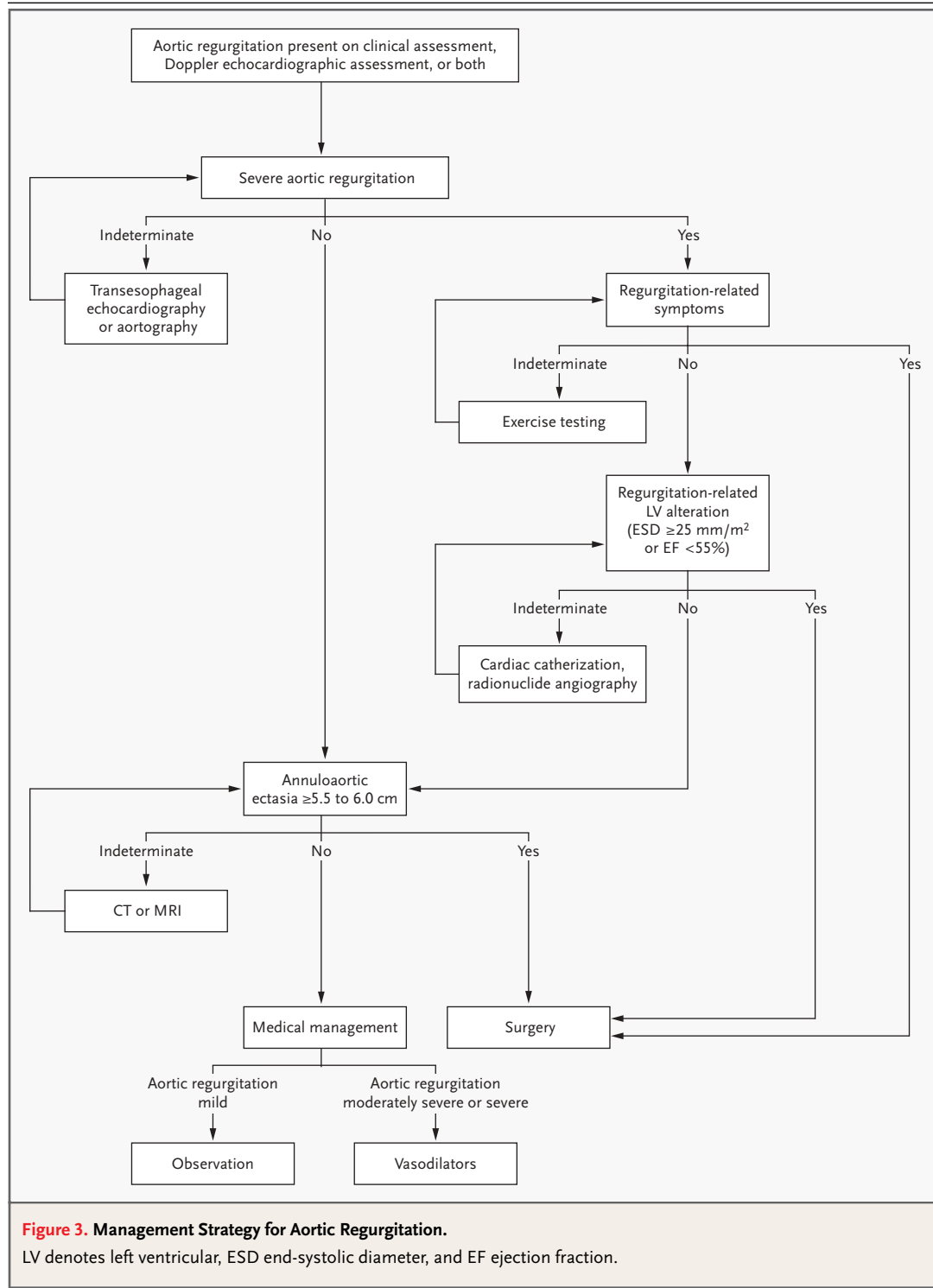† Guidelines are only for asymptomatic patients.

tients who are not candidates for surgery but have regurgitation of a severe degree[32] or possibly of a moderate degree, since studies have included patients who would now be classified as having moderate aortic regurgitation.[33-35] Controlled trials indicate that both nifedipine[35] and angiotensin-converting–enzyme inhibitors[33] reduce left ventricular wall stress and volumes. In a trial comparing nifedipine with digoxin, patients treated with nifedipine were less likely to need surgery (as determined by left ventricular abnormalities or symptoms) than those who were treated with digoxin[34]; however, the lack of a placebo group, the small size of the study, and the end point of surgery make the long-term benefits of nifedipine uncertain. In a small, open-label trial, beta-blocker therapy decreased the rate of aortic enlargement among patients with the Marfan syndrome.[36] However, bradycardia prolongs diastole and may increase aortic regurgitant volume, which raises a concern regarding beta-blockade in patients with severe regurgitation. Patients who are treated medically may subsequently require surgery because of progression of aortic regurgitation (which occurs at a rate of 5 to 6 percent per year among patients with initially severe but asymptomatic aortic regurgitation[6,10]). Therefore, with medical treatment, close follow-up and repeated evaluations (yearly or every six months in patients with severe aortic regurgitation) are nec-

essary. Although the risk of endocarditis is low,[5] all patients should receive prophylaxis for dental work and surgical procedures, as recommended by the American Heart Association.[37]

AREAS OF UNCERTAINTY

Although prospective studies of the natural history of aortic regurgitation have been conducted,[6,10,31] the effect of the absolute severity of regurgitation, as measured by regurgitant volume or orifice,[14,15] on the clinical outcome is unknown. Different regurgitant volumes (e.g., 60 ml per beat vs. 100 ml per beat) may be similarly classified as severe but may have different outcomes. Furthermore, little is known about the rate and determinants of the progression of aortic regurgitation.[38] It is not possible to identify in advance those cases that will progress quickly, for which aggressive management may be warranted. In addition, symptoms are an imperfect measure of functional limitations.[39] The value of cardiopulmonary exercise testing in clinical decision making is unclear.

Also uncertain is the optimal approach to surgical correction of aortic regurgitation. The durability of aortic-valve repair,[40] pulmonary autografts,[41] and homografts is imperfect, so standard valve replacement is used most frequently. Progress in aortic-valve repair may expand future surgical indications.

Figure 3. Management Strategy for Aortic Regurgitation.

LV denotes left ventricular, ESD end-systolic diameter, and EF ejection fraction.

Despite wide agreement that left ventricular dysfunction or marked enlargement or both predict a worse outcome and are indications for surgery, specific indexes are disputed. Natural-history studies have alternatively suggested that the best predictors of outcome are an end-diastolic diameter of 80 mm or more,[6] an end-systolic diameter of 50 mm or more[6] (or of 25 mm or more per square meter[5]), an

ejection fraction of less than 55 percent,[5] or exertional changes in the ejection fraction and wall stress.[10] However, more research is needed to determine which criteria are most useful, and more data are needed to guide the decision about surgery on the basis of the left ventricular function.[20,25] Finally, the effects of vasodilators in patients with moderate aortic regurgitation remain unclear.

GUIDELINES

Guidelines from the American Society of Echocardiography[11] underscore the importance of quantitative measurement of aortic regurgitation (Table 1). Recommendations issued by the American Heart Association and the American College of Cardiology (Table 2) in 1998 suggested that severe symptoms or left ventricular alteration (an end-diastolic diameter ≥75 mm, an end-systolic diameter ≥50 mm, or an ejection fraction below 50 percent) were widely accepted indications for surgery (class I indications), whereas mild dyspnea was considered an indication with limited or conflicting evidence (class II).[20] The 2002 guidelines of the European Society of Cardiology (Table 2), incorporating more recent data, underscore the importance of considering surgery for asymptomatic patients with a left ventricular end-systolic diameter that is more than 25 mm per square meter.[24]

CONCLUSIONS AND RECOMMENDATIONS

Evaluation of patients with aortic regurgitation combines clinical and Doppler assessment (Fig. 3) with quantitation of the regurgitant volume and orifice (Fig. 1 and 2). If the regurgitation is severe, surgery is indicated in symptomatic patients (even those with mild symptoms), and it should be performed promptly if aortic regurgitation is acute. In asymptomatic patients, particularly those who are sedentary, cardiopulmonary exercise testing with measurement of oxygen consumption provides information about functional capacity.

In asymptomatic patients with severe aortic regurgitation, such as the woman described in the vignette, an ejection fraction below 55 percent or an end-systolic diameter of 25 mm per square meter or more is an indication for surgery. Correction for body size with the use of body-surface area[5] is particularly important in women, in whom the severity of aortic regurgitation and of left ventricular enlargement may otherwise be underestimated.[7] Coronary angiography is warranted before surgery in patients who are considered at risk for coronary disease (e.g., men over the age of 35 years, postmenopausal women, and women with coronary risk factors). The usual operation is aortic-valve replacement with a mechanical prosthesis in young patients and with a bioprosthesis in older patients. Patients who have mechanical prostheses require long-term anticoagulation (with a target international normalized ratio of 2.5 to 3.5).[42]

Regardless of the degree of regurgitation and the severity of symptoms, surgery is often indicated for patients who have annuloaortic ectasia, a large ascending aortic aneurysm, and good life expectancy. For symptomatic patients in whom the causal link between symptoms and regurgitation is uncertain, and for those who have advanced left ventricular dysfunction (with an ejection fraction below 35 percent), the decision whether to operate is challenging. Our approach is to consider other potential causes of symptoms or ventricular dysfunction and to quantify the regurgitation. We tend to offer surgery to patients with severe regurgitation, since marked improvement may occur postoperatively.[25]

For patients who do not require surgery, we prescribe prophylaxis against endocarditis. Despite limited evidence from clinical trials, for most patients with moderately severe or severe regurgitation, we prescribe vasodilators. We recommend follow-up echocardiography every two to five years in patients with mild regurgitation, every year in those with moderate-to-severe regurgitation and minimal ventricular dilatation, and every six months in patients whose ventricular alteration is close to that constituting an indication for surgery.

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