Valvular Heart Disease: Aortic Regurgitation

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Valvular Heart Disease
Aortic Regurgitation

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Abstract—Aortic regurgitation (AR) is characterized by diastolic reflux of blood from the aorta into the left ventricle (LV). Acute AR typically causes severe pulmonary edema and hypotension and is a surgical emergency. Chronic severe AR causes combined LV volume and pressure overload. It is accompanied by systolic hypertension and wide pulse pressure, which account for peripheral physical findings, such as bounding pulses. The afterload excess caused by systolic hypertension leads to progressive LV dilation and systolic dysfunction. The most important diagnostic test for AR is echocardiography. It provides the ability to determine the cause of AR and to assess the severity of AR and its effect on LV size, function, and hemodynamics. Many patients with chronic severe AR may remain clinically compensated for years with normal LV function and no symptoms. These patients do not require surgery but can be followed carefully for the onset of symptoms or LV dilation/dysfunction. Surgery should be considered before the LV ejection fraction falls below 55% or the LV end-diastolic dimension reaches 55 mm. Symptomatic patients should undergo surgery unless there are excessive comorbidities or other contraindications. The primary role of medical therapy with vasodilators is to delay the need for surgery in asymptomatic patients with normal LV function or to treat patients in whom surgery is not an option. The goal of vasodilator therapy is to achieve a significant decrease in systolic arterial pressure. Future therapies may focus on molecular mechanisms to prevent adverse LV remodeling and fibrosis. **(*Circulation*. 2005;112: 125-134.)**

Key Words: aorta ■ echocardiography ■ valves ■ ventricles

Aortic regurgitation (AR) is characterized by diastolic reflux of blood from the aorta into the left ventricle (LV) due to malcoaptation of the aortic cusps. Its clinical presentation is variable and depends on a complex interplay of a number of factors, including acuity of onset, aortic and LV compliance, hemodynamic conditions, and severity of the lesion. Although chronic AR is generally well tolerated for many years, acute AR may lead to rapid cardiac decompensation and, if untreated, to early death.[1] This review focuses on the clinical manifestations of AR, evaluation of its severity and hemodynamic consequences, and its treatment.

Prevalence

The prevalence of chronic AR and incidence of acute AR are not precisely known. Singh et al[2] reported the prevalence of chronic AR detected by color Doppler echocardiography in a large unselected adult population (the Framingham Offspring Study). The overall prevalence AR in men was 13% and in women 8.5%. However, most of the AR in this population was trace or mild in severity; moderate or severe AR was rare (Table 1). Multiple logistic regression analysis revealed age and male gender to be predictors of AR. Interestingly, hypertension did not predict AR on multivariate analysis, confirming results of earlier studies that hypertension is associated with modest increases in aortic root size but not AR when age is included in the model.[3,4] The Strong Heart Study[5] showed an overall prevalence of AR of 10% in a Native American population. Most cases were of mild severity; age and aortic root diameter, but not gender, were independent predictors of AR in this study.

Etiology

AR results from malcoaptation of the aortic leaflets due to abnormalities of the aortic leaflets, their supporting structures (aortic root and annulus), or both. Diseases that primarily affect the leaflets include bicuspid aortic valve and other congenital abnormalities, atherosclerotic degeneration, infective endocarditis, rheumatic heart disease, connective tissue or inflammatory diseases, antiphospholipid syndrome, and use of anorectic drugs.[6–12] The leaflets can also be affected by trauma, due either to chest wall or deceleration injury, or a jet lesion, due to dynamic or fixed subaortic stenosis. Diseases that primarily affect the annulus or aortic root include idiopathic aortic root dilation, aortoannular ectasia, Marfan syndrome, Ehlers-Danlos syndrome, osteogenesis imperfecta, aortic dissection, syphilitic aortitis, or various connective tissue diseases.[13] A bicuspid aortic valve is commonly associated with dilation of the aortic root in addition to the

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TABLE 1. Prevalence of AR in the Framingham Offspring Study

	Age, y				
	26–39	40–49	50–59	60–69	70–83
Men	(n=91)	(n-352)	(n=433)	(n=359)	(n=91)
None	96.7%	95.4%	91.1%	74.3%	75.6%
Trace	3.3%	2.9%	4.7%	13.0%	10.0%
Mild	0%	1.4%	3.7%	12.1%	12.2%
≥Moderate	0%	0.3%	0.5%	0.6%	2.2%
Women	(n=93)	(n=451)	(n=515)	(n=390)	(n=90)
None	98.9%	96.6%	92.4%	86.9%	73.0%
Trace	1.1%	2.7%	5.5%	6.3%	10.1%
Mild	0%	0.7%	1.9%	6.0%	14.6%
≥Moderate	0%	0%	0.2%	0.8%	2.3%

By multivariate analysis, only age and gender predicted AR prevalence. Adapted from Singh et al.[2]

congenital leaflet abnormality.[14,15] Ankylosing spondylitis can cause disease of both the leaflets and the aortic root. Finally, chronic severe AR of any cause can lead to progressive enlargement of the aortic root and further worsening of AR over time.

Acute AR is most commonly caused by bacterial endocarditis, aortic dissection, or blunt chest trauma.[16–18] Other less common causes of acute AR include nonbacterial endocarditis,[19] laceration of the aorta,[20] and complications of invasive procedures such as aortic valvuloplasty and percutaneous balloon dilatation of aortic coarctation.[21] Fortunately, acute AR, which has a poor prognosis, is rare.

The prevalence of chronic AR is much higher, and its causes are different. In a prospective study of 104 patients with chronic AR, 35% had unknown causes, 26% idiopathic root dilation, 13% congenital abnormalities, 12% rheumatic heart disease, 10% infective endocarditis, and 7% degenerative valve disease.[22] A different study of 246 patients demonstrated 40% degenerative causes, 28% congenital causes, 19% aortic root enlargement, 6% rheumatic causes, 3% aortitis, and 3% endocarditis.[23] These numbers only represent a rough estimate because demographic changes in population age, geographic location, and socioeconomic status may affect prevalence of different diseases, such as rheumatic heart disease.

Pathophysiology

Chronic severe AR imposes a combined volume and pressure overload on the LV. The volume overload is a consequence of the regurgitant volume itself and is therefore directly related to the severity of the leak. Thus, whereas mild AR produces only minimal volume overload, severe AR can produce massive LV volume overload and progressive chamber dilation. The pressure overload results from systolic hypertension, which occurs as a result of increased total aortic stroke volume, because both the regurgitant volume and the forward stroke volume are ejected into the aorta during systole.[24] Systolic hypertension can contribute to a cycle of progressive dilation of the aortic root and subsequent worsening of AR.

In early, compensated severe AR, the LV adapts to the volume overload by eccentric hypertrophy, in which sarcomeres are laid down in series and myofibers are elongated.[25,26] Eccentric hypertrophy preserves LV diastolic compliance, such that LV filling pressures remain normal or mildly increased despite a large regurgitant volume. In addition, eccentric hypertrophy increases LV mass, such that the LV volume/mass ratio is normal, and LV ejection fraction (LVEF) is maintained by increased preload. The slope of the LV pressure volume relationship (elastance or E_{max}), a load-independent measure of myocardial function, is normal.[27] Over time, progressive LV dilation and systolic hypertension increase wall stress and the volume/mass ratio. As this occurs, there is a phase during which LVEF is still normal, but E_{max} decreases, indicating early myocardial dysfunction that is largely masked by increased preload. At this stage, LVEF still increases after successful valve replacement.[27] Eventually, the increase in wall stress leads to overt LV systolic dysfunction, manifested by a decline in LVEF and severely reduced E_{max}. In chronic severe AR, end-systolic wall stress can be as high as in aortic stenosis.[28] Marked LV hypertrophy (cor bovinum) develops with increased LV volume and mass and spherical geometry.[29]

In decompensated severe AR, LV systolic dysfunction is accompanied by decreased LV diastolic compliance as a result of hypertrophy and fibrosis, leading to high filling pressures and heart failure symptoms. Exertional dyspnea is the most common manifestation, but angina can also occur because of a reduction in coronary flow reserve with predominantly systolic coronary flow.[30,31] In experimental animals, the transition from a compliant (chronic compensated AR) to a stiff (decompensated AR) LV chamber appears to involve upregulation of several cardiac fibroblast genes.[32,33] Acute AR leads to rapid decompensation due to low forward cardiac output and pulmonary congestion. There is not time for compensatory LV dilation to occur, and severe hypotension occurs rather than the systolic hypertension that is characteristic of chronic severe AR. The different stages of AR are shown in Figure 1.

Physical Findings

A variety of physical signs have been described for AR. On auscultation, a high-frequency, decrescendo diastolic murmur is typically heard over the third or fourth intercostal space at the left sternal border. In some patients, a mid and late diastolic apical rumble (Austin-Flint murmur) is heard, possibly because of vibration of the anterior mitral leaflet as it is struck by a posteriorly directed AR jet.[34] A systolic ejection murmur due to high ejection volumes should be present in significant AR. Further findings on auscultation are soft or absent second heart sound and presence of a third heart sound. In acute AR, the diastolic murmur may be absent because of rapid equilibration of aortic and LV diastolic pressures. The only clue may be an absent second heart sound in the setting of severe hypotension and pulmonary edema.

In chronic severe AR, the elevated stroke volume and systolic hypertension produce a variety of interesting physical findings. Among these are the bounding carotid pulse (Corrigan's pulse), head bobbing (de Musset's sign), pulsation of

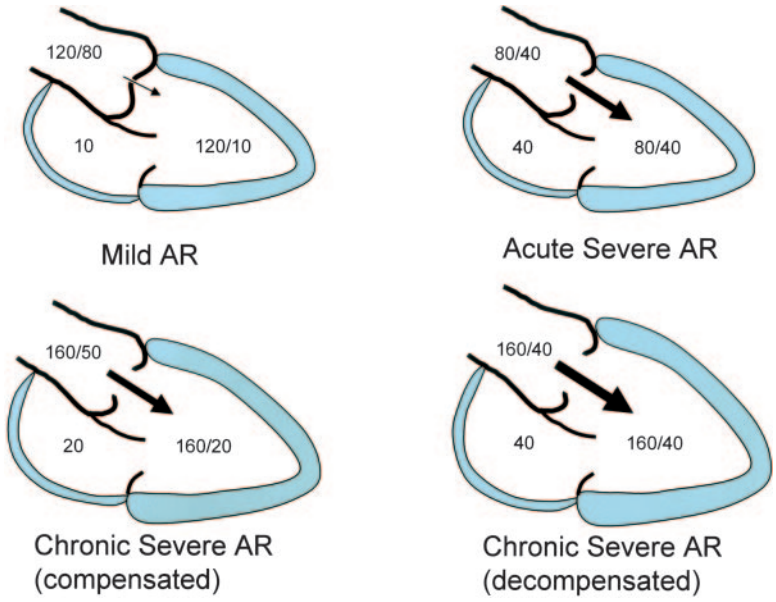

Figure 1. Different stages of AR. Top left, In mild AR, LV size, function, and hemodynamics are normal. Top right, In acute severe AR, there is equilibration of aortic and LV pressures (80/40 mm Hg in this example). Left atrial pressure is elevated, leading to pulmonary edema. Bottom left, In chronic severe, compensated AR, the LV may begin to dilate, but LVEF is often maintained in the normal range by increased preload. There is systolic arterial hypertension and a wide pulse pressure. However, LV filling pressures are normal or only slightly elevated, such that dyspnea is absent. Bottom right, In decompensated chronic severe AR, the LV is dilated and hypertrophied, and LV function is often depressed as a result of afterload excess. Forward output is decreased, leading to fatigue and other low-output symptoms. Fibrosis and hypertrophy decrease LV compliance, leading to increased filling pressures and dyspnea.

the uvula (Muller's sign), and pistol shot sounds over the femoral artery with compression (Traube's sign). During compression with a glass slide, capillary pulsations can be seen on the fingernail (Quincke's sign).

Progression and Natural History

Progression of AR involves a complicated interaction of several variables, including AR severity, aortic root pathology, and the adaptive response of the LV. AR severity may worsen as a result of progressive leaflet pathology and/or further dilation of the aortic root. In addition, LV dilation occurs gradually and progressively, depending on the severity of AR, hemodynamic factors, and the degree of eccentric hypertrophy and remodeling, which may vary from patient to patient and may be related to genetic factors. Reimold et al[35] have shown that quantitative measures of AR severity by echocardiography worsen over time. Padial et al[36] showed that patients with more rapidly progressive increases in aortic root size also tend to have significant worsening of AR severity and LV dilation.

A few studies have investigated the mortality and morbidity of chronic AR if left without surgical treatment. Bonow et al[37] studied 104 asymptomatic patients with severe AR and normal LVEF. The rate of attrition (defined as death, symptoms, or asymptomatic LV dysfunction) was <5%/y over 11-year follow-up. The rate of sudden death was only 0.4%/y. At 11 years, 58% of patients remained asymptomatic with normal LV systolic function. Borer et al[22] found similar results in 104 different patients monitored for a mean of 7.3 years. The rate of attrition was 6.2%/y and was predicted by the change in LVEF or LVEF adjusted for wall stress from rest to exercise. At 5 years, 75% of patients remained free of death, symptoms, or LV dysfunction. Dujardin et al[23] investigated the fate of 246 patients with moderately severe or severe AR with a mean follow-up time of 7 years. Unlike the 2 prior studies, these patients were not all asymptomatic with normal LV systolic function. The 10-year mortality rate was 34%, with independent predictors of survival being age, functional class, comorbidity index, atrial fibrillation, LV end-systolic diameter, and ejection fraction (EF). As shown in Figure 2, patients with greater NYHA functional class or LV end-diastolic diameters >25 mm/m^2 had an adverse prognosis. Taken together, these studies indicate that asymptomatic patients with normal LV function generally have a favorable prognosis and indicate that decline in LVEF with exercise or serial follow-up may identify patients who will

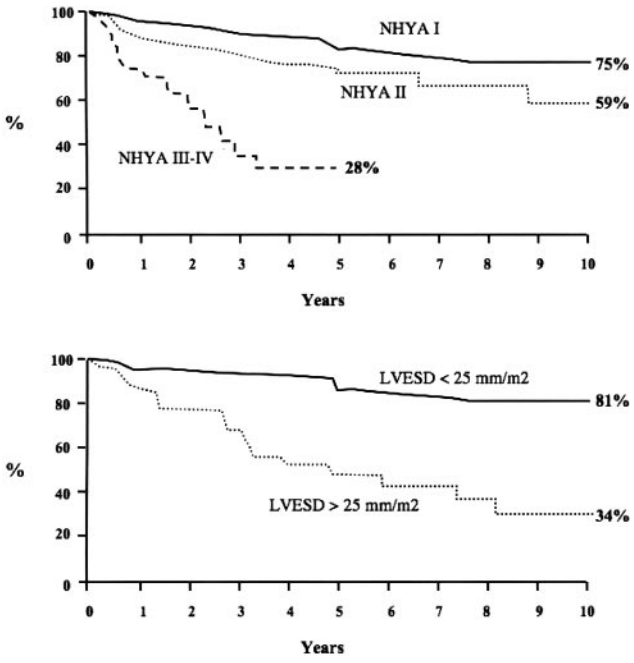

Figure 2. Top, Survival of patients with chronic severe AR by symptoms (NYHA class). Survival in asymptomatic patients (class I) is no different than expected (P=0.38). However, patients with class II symptoms have a significantly worse survival (P=0.02), and patients with class II to IV symptoms have a markedly worse survival (P<0.001). Bottom, Survival for patients stratified by LV end-systolic dimension (LVESD). Patients with LV end-systolic dimension <25 mm/m^2 have a markedly worse survival (P<0.001). Adapted from Dujardin et al.[23]

TABLE 2. Natural History of AR

Asymptomatic patients with normal LV systolic function
Progression to symptoms and/or LV dysfunction <6%/y
Progression to asymptomatic LV dysfunction <3.5%/y
Sudden death <0.2%/y
Asymptomatic patients with LV systolic dysfunction
Progression to symptoms >25%/y
Symptomatic patients
Mortality rate >10%/y

Adapted with permission from ACC/AHA guidelines.[38]

require surgical intervention. Patients with even moderate symptoms or evidence of LV dilation are at higher risk and should be considered for early intervention. The American College of Cardiology/American Heart Association Guidelines for Management of Patients with Valvular Heart Disease have nicely summarized the natural history of chronic AR (Table 2).[38]

Echocardiography

The most important diagnostic test for evaluation of AR is echocardiography. It allows (1) assessment of the anatomy of the aortic leaflets and the aortic root, (2) detection of the presence and severity of AR, and (3) characterization of LV size and function. The American Society of Echocardiography guidelines for quantification of valvular regurgitation emphasize the need to integrate all of this information to properly evaluate patients with AR.[39]

Anatomy of the Aortic Root and Leaflets

Echocardiographic evaluation of the anatomy of the aortic root, annulus, and leaflets is important in defining the etiology and severity of AR. As noted earlier, disorders such as aortic root dilation, bicuspid aortic valve, endocarditis, degenerative aortic valve disease, and dissection of the ascending aorta have different implications with regard to treatment. Although it is common to see mild AR with a structurally normal aortic valve and supporting apparatus, it is rare for severe AR to occur without major lesions of the leaflets or the aortic root. Figure 3 shows echocardiographic examples of different causes of AR.

Color Flow Mapping

Doppler color flow mapping is widely used to identify the presence of AR and estimate its severity. In general, color flow jets are composed of 3 distinct segments. The proximal flow convergence zone is the area of flow acceleration into the orifice, the vena contracta is the narrowest and highest-velocity region of the jet at or just downstream from the orifice, and the jet itself occurs distal to the orifice in the LV cavity in the case of AR. Measurement of jet area or penetration into the LV cavity is not accurate in assessing AR severity. Perry et al[40] compared the ratio of AR jet width to LV outflow tract (LVOT) width in a parasternal long-axis view to angiography. A jet width/LVOT width <25% is specific for mild AR, whereas a jet width/LVOT width ratio >65% is specific for severe AR (Figure 4). This works best when the regurgitant orifice is relatively round in shape.

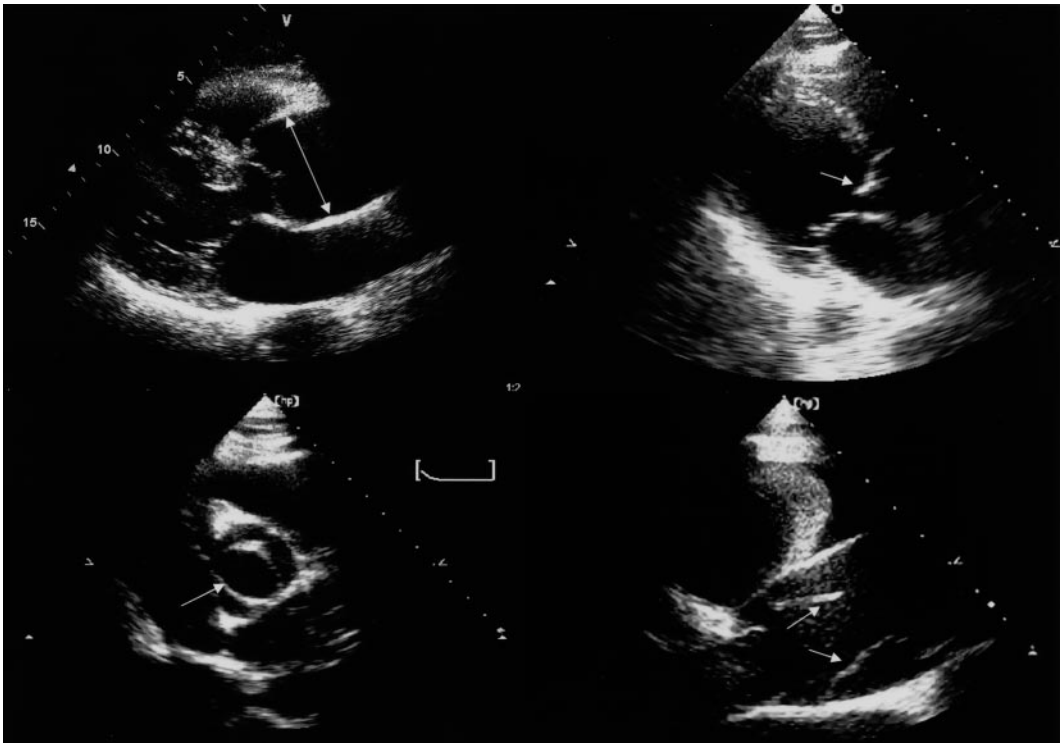

Figure 3. Echocardiographic images from different patients with AR due to different pathologies. Top left, Parasternal long-axis view showing a dilated aortic root (arrows) due to aortoannular ectasia. Top right, Parasternal long-axis view showing large, mobile vegetation (arrow) on the aortic valve in a patient with infective endocarditis. Bottom left, Parasternal short-axis view showing a bicuspid aortic valve with characteristic elliptical opening (arrow). Bottom right, Parasternal long-axis view of a patient with acute AR due to aortic dissection. Intimal flap is shown by arrows.

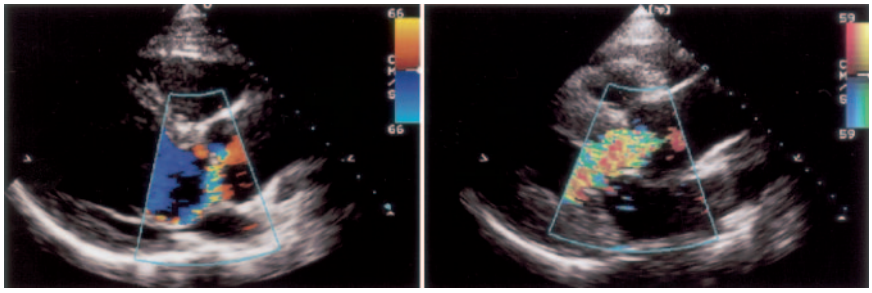

Figure 4. Color flow images from parasternal long-axis views in patients with mild (left) and severe (right) AR. Jet width is <25% of LVOT width in mild AR. This jet is eccentric; width is measured at the origin of the jet adjacent to the leaflets. In severe AR, jet width is usually >50% of LVOT width. A jet width/LVOT width >65% (as in this patient) is specific for severe AR.[39]

When it is elliptical, as in bicuspid aortic valves, this ratio can lead to underestimation of AR severity.[41] The short-axis view is helpful in identifying such cases.

Vena Contracta Imaging

Vena contracta is defined as the narrowest central flow region of a jet. In AR, it can be measured in a parasternal long-axis or short-axis view in a color Doppler mode. Animal studies have shown good correlation of vena contracta width and severity of AR.[42] Clinical studies have confirmed the usefulness of this measurement for judging AR severity.[43,44] Tribouilloy et al[43] demonstrated in a study with 79 patients that a vena contracta width of ≥6 mm correlates well with severe AR, having a sensitivity of 95% and a specificity of 90%. Conversely, a vena contracta width <0.3 cm is specific for mild AR. Willett et al[44] compared vena contracta width by transesophageal echocardiography to simultaneous aortic flow probe measurements of regurgitant volume and fraction in an intraoperative setting. Figure 5 shows an example of the vena contracta in a patient with moderate AR.

Jet Eccentricity

Eccentricity of the regurgitant jet may contribute to the understanding of mechanisms of aortic valve dysfunction.[45] A centrally directed jet entrains fluid on all sides and generally appears larger and wider than eccentric jets directed anteriorly toward the ventricular septum or posteriorly toward the anterior mitral leaflet. This should be taken into account when AR severity is graded.

Proximal Isovelocity Surface Area Method

It is less common to identify a clear proximal flow convergence in AR compared with MR. However, when it is present, the Nyquist velocity should be shifted toward the direction of the jet to produce a clearly visible, round proximal isovelocity surface area (PISA) region that is as large as possible. The surface area of the PISA region is $2\pi r^2$, where r is the radius from the alias line to the orifice. Peak regurgitant flow is obtained by multiplying this value by the aliasing velocity, and effective regurgitant orifice area is the peak regurgitant flow divided by the peak velocity obtained by continuous wave Doppler. The PISA method has been shown to work in AR but is less accurate in eccentric jets or aortic root dilation.[46]

Quantitative Doppler Flow Measurements

AR volume and fraction can be calculated by comparing flow at the aortic level (total stroke volume) with that at the mitral valve level (forward stroke volume).[39] The total stroke volume is generally measured in the LVOT by multiplying the LVOT area times the velocity time integral of pulsed Doppler LVOT flow. The mitral stroke volume is measured in similar fashion but is more prone to error because of difficulty in accurately measuring the mitral annulus and placing the pulsed Doppler sample volume at the level of the annulus. Effective regurgitant orifice area can be calculated by dividing the regurgitant volume by the velocity time integral of the AR jet obtained from continuous wave Doppler. This method, although tedious, provides quantitative measures of AR severity. The cut points for AR severity measured by regurgitant volume, regurgitant fraction, and effective regurgitant orifice area are shown in Table 3.[39]

Supportive Findings

A number of echocardiographic findings provide supporting evidence for AR severity. By M-mode echocardiography, early mitral valve closure indicates increased LV filling pressures and is often present in severe AR, unless masked by tachycardia.[47] The continuous wave Doppler spectral signal

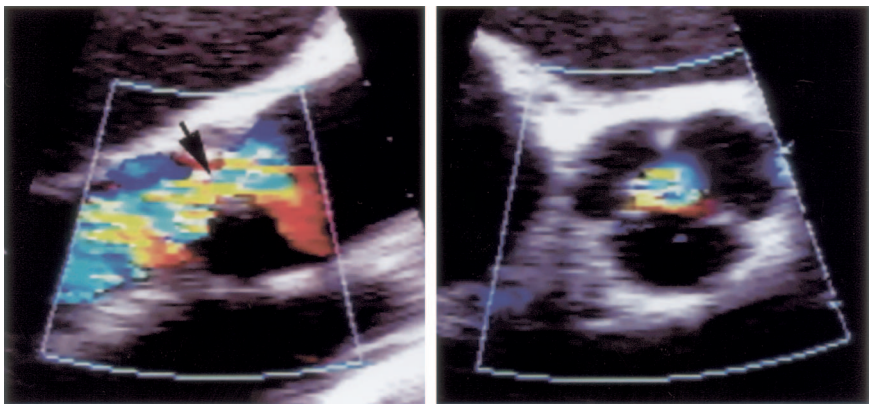

Figure 5. Vena contracta images of AR jet by transesophageal echocardiography in long-axis (left) and short-axis (right) views. The vena contracta is seen as the narrowest part of the jet as it emerges from the regurgitant orifice. The short-axis view is difficult to orient precisely in the plane of the vena contracta but is useful in determining whether the jet is central and round (in which case the long-axis vena contracta accurately describes AR severity) or markedly elliptical, as in bicuspid aortic valves (in which the long-axis vena contracta may underestimate AR severity). Reprinted from Willett et al,[44] copyright 2001, with permission from the American College of Cardiology Foundation.

TABLE 3. Application of Specific and Supportive Signs, and Quantitative Parameters in the Grading of Aortic Regurgitation Severity

	Mild	Moderate		Severe
Specific signs for AR severity	Central jet, width <25% of LVOT† Vena contracta <0.3 cm† No or brief early diastolic flow reversal in descending aorta	Signs of AR >mild present but no criteria for severe AR		Central jet, width ≥65% of LVOT† Vena contracta >0.6 cm†
Supportive signs	Pressure half-time >500 ms Normal LV size*	Intermediate values		Pressure half-time <200 ms Holodiastolic aortic flow reversal in descending aorta Moderate or greater LV enlargement‡
Quantitative parameters§				
RVol, mL/beat	<30	30–44	45–59	≥60
RF, %	<30	30–39	40–49	≥50
EROA, cm^2	<0.10	0.10–0.19	0.20–0.29	≥0.30

*LV size applied only to chronic lesions.

†At a Nyquist of 50–60 cm/s.

‡In the absence of other etiologies of LV dilatation.

§Quantitative parameters can help sub-classify the moderate regurgitation group into mild-to-moderate and moderate-to-severe regurgitation as shown.

AR indicates aortic regurgitation; EROA, effective regurgitant orifice area; LV, left ventricle; LVOT, left ventricular outflow tract; RVol, regurgitant volume; and RF, regurgitant fraction.

Table reprinted with permission of the American Society of Echocardiography from Zoghbi et al,[39] Table 6.

of the AR jet provides clues to the severity of the leak. With severe AR, diastolic pressure will decrease rapidly in the aorta, thus leading to a shorter pressure half-time or more rapid deceleration slope (Figure 6).[48,49] As a general rule, an AR pressure half-time <200 ms indicates severe AR, whereas a pressure half-time >500 ms suggests mild AR.[39] LV end-diastolic pressure can be calculated as the diastolic blood pressure minus the end-diastolic pressure gradient calculated from the modified Bernoulli equation (Figure 6).[48] Importantly, the rate of deceleration of AR velocities simply reflects the rate of equilibration of the diastolic pressure gradient between the aorta and LV. In chronic compensated AR, a large regurgitant volume may not significantly shorten the pressure half-time. Conversely, moderate AR into a stiff LV, especially in the acute or subacute setting, may significantly shorten pressure half-time. Thus, pressure half-time and early mitral closure should be considered markers of the hemodynamic consequences of AR rather than the regurgitant volume itself. A complete echocardiographic study provides measurements of the severity of the leak (regurgitant volume, fraction, and orifice area) and the hemodynamic effects of AR (LV volumes, pressure half-time, LV end-diastolic pressure).

Another important supportive sign of severe AR is diastolic flow reversal in the descending aorta. Although brief early diastolic flow reversal is often seen in normal subjects, holodiastolic flow reversal usually indicates at least moderate

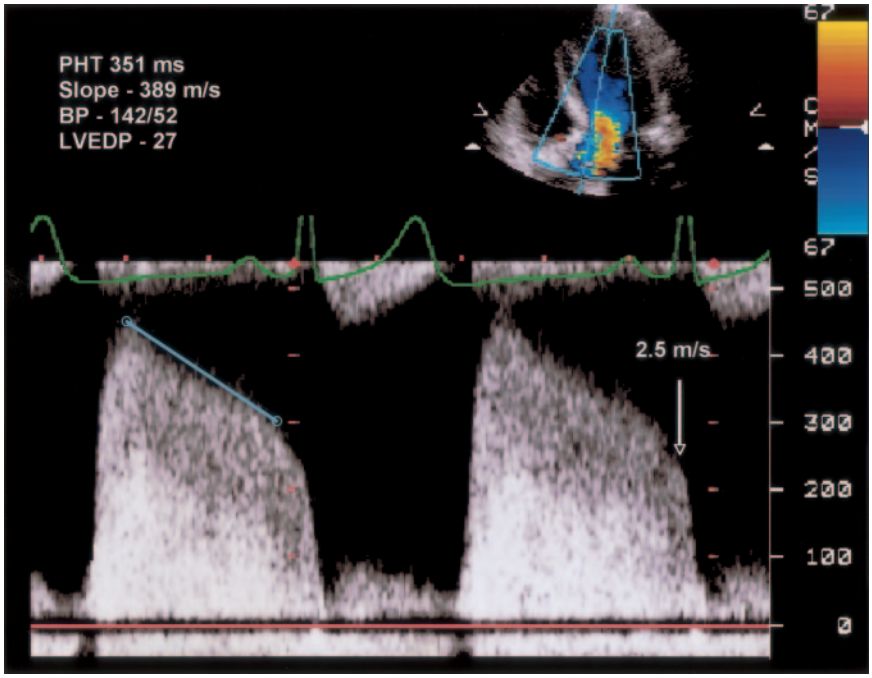

Figure 6. Continuous wave Doppler of AR jet in a patient with moderate AR and a long-standing history of hypertension. The slope of velocity deceleration is fairly steep, with a pressure half-time (PHT) of 315 ms. LV end-diastolic pressure (LVEDP) can be calculated by converting end-diastolic velocity (measured at the R wave peak) to pressure gradient by $4V^2$ and subtracting this value from the diastolic blood pressure (BP). Patients with chronic compensated AR may have a relatively flat slope, reflecting a compliant LV with a normal or only slightly elevated LVEDP.

AR.[50] Diastolic flow reversal in the descending aorta is best measured with pulsed-wave Doppler from a suprasternal probe position.

LV Size and Geometry

Echocardiography is useful in measuring LV dimensions, volumes, and LVEF, all of which are important determinants of the need for surgery in chronic severe AR. Serial progression of LV dilation predicts the need for surgery.[37] Because LV chamber dilation and systolic dysfunction can occur from other causes (ie, cardiomyopathy), it is important to establish a link between severity of AR and LV dysfunction. This can be difficult at times and underscores the need for accurate, careful quantification of AR severity. Repeated echocardiography to assess progression of LV dilation and severity of AR is recommended every 2 to 3 years in stable asymptomatic patients with normal LV size and function.[38] In asymptomatic patients with LV dilation, more frequent echocardiography (every 6 to 12 months) is indicated.[38]

Cardiac Catheterization

Even if echocardiography accurately identifies severity of AR and degree of LV function, catheterization may be needed to evaluate coronary anatomy in patients requiring surgical intervention. As a general rule, men aged >35 years, premenopausal women aged >35 years with risk factors for coronary artery disease, or postmenopausal women should undergo preoperative coronary arteriography.[38] Supravalvular aortography provides a semiquantitative approach to grade AR during heart catheterization. Visual grading of AR severity is based on the amount of contrast that appears in the LV after aortography. Mild or 1+ AR is contrast appearing in the LV but clearing with each beat. Moderate or 2+ AR is faint opacification of the entire LV over several cardiac cycles. Moderately severe or 3+ AR is opacification of the entire LV with the same intensity as in the aorta. Severe or 4+ AR is opacification of the entire LV on the first heart beat with an intensity higher than in the aorta. Unfortunately, this method is subjective, depends on the amount of contrast injected and the size of the LV, and correlates poorly with regurgitant volume, particularly in patients with dilated LVs.[51]

Cine MRI can also be used to detect and quantify AR.[52–54] Phase velocity encoding is used to calculate forward stroke volume through the aortic valve. Total LV stroke volume is determined from LV end-diastolic and end-systolic volumes, which are measured by summing the volumes of a stack of slices of known thickness (typically 8 to 10 mm) through the LV from base to apex. The difference between aortic and LV stroke volumes is the regurgitant volume. Although cine magnetic resonance is not as well validated as echocardiography for quantification of AR severity, it provides highly accurate measurements of LV volumes, mass, and EF and therefore could be useful for detecting progressive LV dilation and timing of operation for asymptomatic severe AR.

Role of Exercise Testing

Many asymptomatic patients with valvular heart disease have gradually and imperceptibly reduced their activities or lead a sedentary lifestyle. In such patients, exercise testing may be very useful in eliciting symptoms or determining functional capacity. Some studies have suggested that an exercise-induced decrease in LVEF is a predictor of poor outcome that warrants surgery.[22,55–57] However, most of these studies included patients who already had symptoms, LV dilation, or decreased resting LVEF. Thus, it is not clear that exercise LVEF is helpful in determining the need for surgery in asymptomatic patients with normal LV size and function.[38]

Surgical Treatment

In acute AR, immediate surgical intervention is necessary because the acute volume overload results in life-threatening hypotension and pulmonary edema.[1] Vasodilator therapy with sodium nitroprusside may stabilize the patient during transport to the operating department. Aortic balloon counterpulsation is contraindicated because it worsens AR. β-Blockers should be avoided in acute AR because they prolong diastole and may worsen AR. Atrial pacing to increase heart rate might be of theoretical benefit[58,59]; however, this does not have an established role in clinical practice. Several studies have demonstrated that emergency aortic valve replacement can be performed with low operative mortality and good long-term results in acute AR.[60–62]

In contrast to acute AR, patients with chronic AR may be asymptomatic for many years or even their entire life. Therefore, the critical issue is to determine if and when surgical intervention is required. There are no randomized controlled trials to guide surgical decision making. However, reasonable guidelines have been proposed on the basis of the aforementioned natural history of AR, retrospective studies, and expert opinion.[38] The operative mortality for isolated aortic valve replacement is ≈4%.[63–65] It is higher with concomitant aortic root replacement or coronary bypass surgery or if there are substantial comorbidities, including advanced age. As shown in Table 2, the death rate for asymptomatic patients with normal LV size and function is <0.2%/y. Therefore, asymptomatic patients with normal LV size and systolic function do not require surgery but should be monitored carefully for development of symptoms, LV dysfunction, or progressive LV dilation. In contrast, symptomatic patients with chronic severe AR have a mortality >10%/y and therefore should undergo surgery unless there are excessive comorbidities or a condition with a known short life expectancy. The more difficult issue is when to operate on asymptomatic patients to prevent irreversible LV dysfunction from occurring. Outcomes are better in patients with an LVEF >55% or an end-systolic LV diameter <55 mm (or <25 mm/m^2).[23,38,66,67] This has been termed the "55 rule."[67] Careful, serial echocardiographic follow-up is necessary to identify patients for surgery before their LV values reach these thresholds.

Surgery for symptomatic patients with severe AR has been shown to reduce LV volumes, LV mass, and wall stress and to increase LVEF.[68–71] Even patients with dilated LV or low LVEF can benefit from surgery. Chaliki et al[72] reported the results of surgery in 450 patients with severe AR. Operative mortality was 14%, 6.7%, and 3.7% for those with LVEF <35%, 36% to 49%, and ≥50%, respectively (Figure 7).

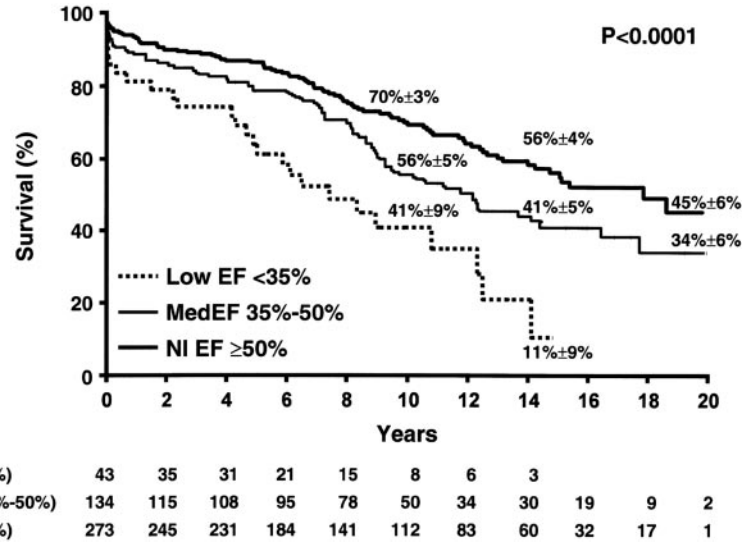

Figure 7. Data from Chaliki et al[72] show survival in patients after aortic valve replacement as a function of preoperative LVEF. LoEF indicates markedly reduced LV function; MedEF, moderately reduced LV function; and NI EF, normal LV function. Reprinted with permission.

Moreover, surgical survivors with low preoperative LVEF had improved symptoms and LV function. Thus, it is almost never "too late" to operate in chronic severe AR, although patients with severe LV dysfunction and a systolic blood pressure <120 mm Hg may be at particularly high risk.[73]

Medical Therapy

The regurgitant volume in AR is determined by the regurgitant orifice area, the square root of the diastolic pressure gradient across the valve, and the duration of diastolic flow (which may not be holodiastolic if the LV is stiff and pressure equilibrates early).[74] Medical therapy is not able to significantly reduce regurgitant volume in chronic severe AR because the regurgitant orifice area is relatively fixed and the diastolic blood pressure is already low.[74] Further reducing diastolic blood pressure might adversely affect coronary perfusion and should be avoided. Moreover, the square root function dictates that a 25% reduction in diastolic pressure gradient would only achieve a 13% reduction in regurgitant volume.[74] Therefore, the main goal of medical therapy is to reduce the systolic hypertension associated with chronic severe AR and thereby reduce wall stress and improve LV function.[74,75] A number of small studies have investigated the effects of various vasodilators on hemodynamics and LV function in chronic AR.[76–82] Only 2 randomized, placebo-controlled studies have demonstrated significant reductions in LV end-diastolic diameter and an increase in LVEF with vasodilator therapy using hydralazine in 45 patients[77] and nifedipine in 72 patients.[82] Medical therapy with nifedipine has been shown to delay the need for surgery compared with digoxin in a randomized trial.[83] Thus, medical therapy may be beneficial in delaying the need for surgery in asymptomatic patients with normal LV function. It may also be useful in patients with severe AR who are not considered candidates for surgery. Importantly, the goal of medical therapy is to significantly reduce systolic blood pressure to relieve the afterload mismatch that burdens the LV in chronic severe AR. It is conceivable that further insights into molecular mechanisms of myocardial adaptation to volume overload may yield new therapeutic targets to reduce myocardial fibrosis and hypertrophy and preserve LV systolic function. Endocarditis prophylaxis is important for all patients with AR.

Future developments in interventional cardiology may offer new alternatives for patients with severe AR who are not considered surgical candidates. Percutaneous transcatheter implantation of a heart valve prosthesis may be possible in such patients, although this is still investigational at this time.[84]

Conclusions

On the basis of available evidence and consensus opinion, surgery is indicated for patients with severe AR who either (1) are symptomatic or (2) have evidence of increasing LV size or decreasing LVEF. It appears that it is best to operate before LV end-diastolic diameter increases to >55 mm or 25 mm/m^2 or before LVEF falls to <55%. This underscores the importance of careful quantification of AR severity and LV function. The role of medical therapy, particularly vasodilators, is primarily to decrease systolic hypertension and delay the onset of LV dysfunction in asymptomatic patients.

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Correction

In the Contemporary Review in Cardiovascular Medicine, "Valvular Heart Disease: Aortic Regurgitation," by Bekeredjian and Grayburn, which appeared in the July 5, 2005, issue of the journal (*Circulation*. 2005;112:125–134), the authors inadvertently used the term, "end-diastolic," when they meant to say "end-systolic."

In the abstract, it should read, "Surgery should be considered before the LV ejection fraction falls below 55% or the LV end-systolic dimension reaches 55 mm," and in the conclusion, it should read, "It appears that it is best to operate before LV end-systolic diameter increases to $>$55 mm or 25 mm/m^2 or before LVEF falls to $<$55%."

The authors regret this error.

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