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STRUCTURAL HEART DISEASE (RJ SIEGEL AND NC WUNDERLICH, SECTION EDITORS)

Aortic Regurgitation

Nir Flint[1,2] · Nina C. Wunderlich[3] · Hezzy Shmueli[1,2] · Sagit Ben-Zekry[4] · Robert J. Siegel[1] · Roy Beigel[4]

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Abstract

Purpose of Review Aortic regurgitation (AR) is a common form of valvular disease which is characterized by reflux of blood from the aorta into the left ventricle (LV) during diastole. AR results from various etiologies, affecting the aortic valve cusps or the aortic root. The clinical presentation of patients with AR depends on the severity of the regurgitation and differs whether AR develops acutely or if it progresses over a prolonged period, allowing the cardiac chambers to adapt. Echocardiography is the primary method to determine the etiology of AR and to define its severity. We review the current data regarding the diagnosis and treatment of AR.

Recent Findings No single parameter is sufficient to determine AR severity; thus, an integrative, multi-parametric approach is required. Echocardiography is key for imaging the aortic valve morphology and flow as well as aortic root and ascending aorta. Determining LV ejection fraction and dimensions is essential for patient management and optimizing timing for intervention. Three-dimensional (3D) echocardiography is useful in the evaluation of AR etiology and severity. The use of Trasncatheter aortic valve replacement (TAVR) has emerged as an alternative to surgery in patients at high operative risk.

Summary The diagnosis and management of AR requires a comprehensive approach and routine clinical and echocardiographic follow-up. Surgical or percutaneous therapy is indicated when symptoms develop and in those who have LV dysfunction or LV dilation.

Keywords Aortic regurgitation · Etiology · Diagnosis · Echocardiography · Treatment · Surgical therapy · TAVR

Introduction

Aortic regurgitation (AR) is a common form of valvular disease [1] which results from several etiologies that can be divided into primary abnormalities of the valve cusps or secondary to abnormalities of the aortic valve supporting structures (i.e., the aortic root and annulus). Table 1 lists the various common, and less common, causes and etiologies for AR. The

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✉ Roy Beigel
beigelr@yahoo.com

Nir Flint
nir.flint@cshs.org

Nina C. Wunderlich
wunderlich@kardio-darmstadt.de

Hezzy Shmueli
yehezkelgidon.shmueli@cshs.org

Sagit Ben-Zekry
sagit.benzekry@sheba.health.gov.il

Robert J. Siegel
robert.siegel@cshs.org

[1] Smidt Heart Institute, Cedars-Sinai Medical Center, Los Angeles, CA, USA

[2] Department of Cardiology, Tel-Aviv Sourasky Medical Center affiliated to the Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

[3] Cardiovascular Center Darmstadt, Darmstadt, Germany

[4] The Leviev Heart Center, Sheba Medical Center, Tel-Hashomer, affiliated to the Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel

Table 1 Etiologies of aortic regurgitation

Abnormalities within the aortic valve	Abnormalities of the aortic root and ascending aorta
Idiopathic	Idiopathic
Age related: calcific degenerative aortic valve	Age related: degenerative aortic dilatation/aneurism
Congenital:	Congenital/genetic:
Bicuspid aortic valve ± aortic root dilatation	Aortic dilatation due to bicuspid aortic valve
Unicuspid/quadricuspid aortic valve*	Cystic medial necrosis (either isolated or associated with Marfan syndrome)
Rupture of a fenestrated valve*	Turner syndrome
	Familial thoracic aortic aneurysm syndrome
Infectious: endocarditis	Infectious: syphilitic aortitis
Rheumatic:	Rheumatic:
Rheumatic fever	Ankylosing spondylitis
Systemic lupus erythematosus*	Ulcerative colitis
Rheumatoid arthritis*	Giant cell arteritis
Ankylosing spondylitis*	Psoriatic arthritis
Takayasu arteritis*	Reactive arthritis
	Behçet syndrome
Drug-Induced (anorectic agents: fen-phen) *	Drug-induced*
Trauma causing prolapse of an aortic cusp	Trauma causing aortic dissection
Iatrogenic	Hypertension
Post-balloon dilatation	
Degenerative bioprosthetic aortic valve	

*Not common

most common etiology of AR is atherosclerotic degeneration of the valve, especially in the presence of a bicuspid aortic valve. The latter is a common congenital abnormality seen in 0.5–2% of the general population and predisposes to both aortic valve stenosis and regurgitation. A bicuspid aortic valve is also associated with an aortopathy manifested by dilatation of the aortic root or the proximal ascending aorta, which can further contribute to secondary AR [2].

The pathophysiology and hemodynamic/clinical presentation of the patient with AR depend on the severity of the regurgitation and differs whether AR develops abruptly (acute AR) or over a prolonged period (chronic AR) allowing the left ventricle to accommodate to the volume overload. The major differences between acute and chronic AR are shown in Table 2.

Acute AR

Acute severe AR may develop from valvular abnormalities (most commonly infective endocarditis) and aortic abnormalities (mostly aortic dissection) or due to iatrogenic causes such as traumatic injury (i.e., motor vehicle accident) or during transcutaneous aortic valve procedures. Acute AR is characterized by an abrupt increase in left ventricular (LV) end-diastolic volume. The relatively non-compliant, normal size LV is suddenly exposed to a very high preload as well as an excessive afterload (due to increased LV wall stress). The increased afterload further contributes to depression of LV systolic function and a decrease in stroke volume despite there being a relatively preserved myocardial contractility [3]. As the LV volume has not had time to accommodate the rapid increase in the regurgitant flow into the LV during diastole, there is an acute rise in the LV end-diastolic pressure (LVEDP). The result is a rapid and marked increase in LVEDP as well as an increase in left atrial (LA) pressure and pulmonary capillary wedge pressure. As shown in Fig. 1, an acute volume overload causes the ventricle to operate at the extreme of the pressure–volume curve. Reflex tachycardia helps to maintain cardiac output. In severe cases where the LVEDP exceeds the LA pressure, premature, presystolic, closure of the mitral valve with or without diastolic mitral regurgitation can occur, and patients often present with pulmonary edema and even cardiogenic shock. An "exaggerated" hemodynamic response can be seen in patients with preexisting LV hypertrophy (due to chronic pressure overload such as in hypertension and aortic stenosis), as these patients often have a small LV cavity, concentric hypertrophy, and a non-compliant LV with a reduced preload reserve. Further deterioration accompanied by a depression in LV function

Table 2 Major differences between acute and chronic severe aortic regurgitation (AR)

	Acute severe AR	Chronic severe AR
Clinical findings/presentation	Pulmonary edema	Can often be asymptomatic
	Refractory heart failure	Might present with gradually increasing symptoms
Heart rate	Elevated	Normal or slightly elevated
Left ventricular size	Normal to slightly enlarged	Markedly enlarged
Systolic aortic pressure	Normal or slightly decreased	Elevated
Diastolic aortic pressure	Normal or slightly decreased	Decreased
Pulse pressure	Normal or slightly increased	Increased
Left ventricular ejection fraction	Normal	Normal or increased
		In later stages can be decreased
Left ventricular end-diastolic pressure	Markedly elevated	Normal to slightly elevated
Stroke volume	Normal to slightly elevated	Markedly elevated
		In later stages can be decreased
Cardiac output	Decreased	Normal
		In later stages can be decreased

Adapted from: Beigel R, Siegel RJ: Aortic regurgitation: pathophysiology. In ASE's comprehensive echocardiography, second edition [2016], with permission from Elsevier [55]

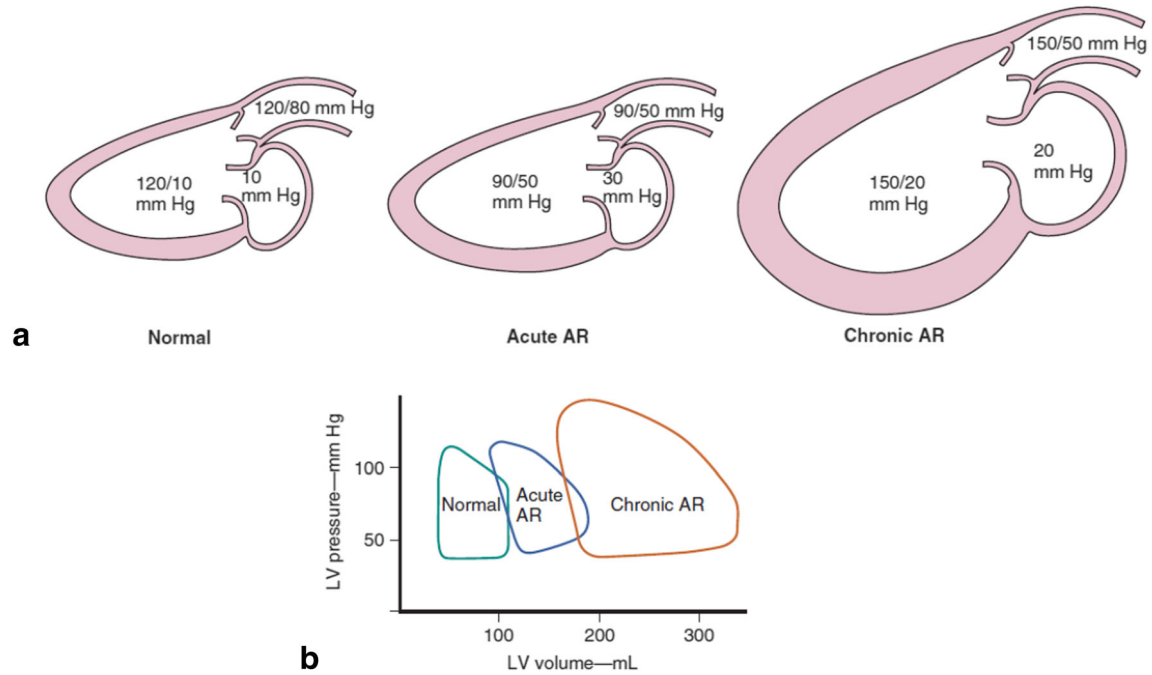


Fig. 1 **a** Schematic presentation of patients with acute severe (middle) and chronic severe (right) aortic regurgitation (AR) as compared with a normal heart (left). In acute severe AR, there is a normal effective forward flow along with an elevated end-diastolic pressure and volume. In chronic AR, the ventricle dilates and hypertrophies eccentrically in order to maintain near-normal wall stress levels. **b** Pressure-volume loops of acute AR (middle) and chronic AR (right) compared to a normal heart (left). In acute AR, both volume and pressure overload are acting on an unconditioned ventricle and causing a large change in pressure per volume. In chronic AR, the adapted ventricle is more compliant and able to accommodate markedly higher volumes with a rather modest change in pressure per volume. (Reprinted from: Beigel R, Siegel RJ: Aortic regurgitation: pathophysiology. In ASE's comprehensive echocardiography, second edition [2016], with permission from Elsevier) [55]

and stroke volume can occur when the LVEDP approaches the aortic diastolic pressure causing a drop in LV myocardial perfusion pressure (defined as aortic diastolic pressure minus LVEDP). This may cause subendocardial hypoperfusion and signs and symptoms of myocardial ischemia. Distention and dilation of the left ventricle can cause secondary mitral regurgitation due to distention/dilatation of the mitral annulus as well as the elevated left ventricular filling pressures. This can further elevate the LA and pulmonary capillary wedge pressures causing pulmonary edema.

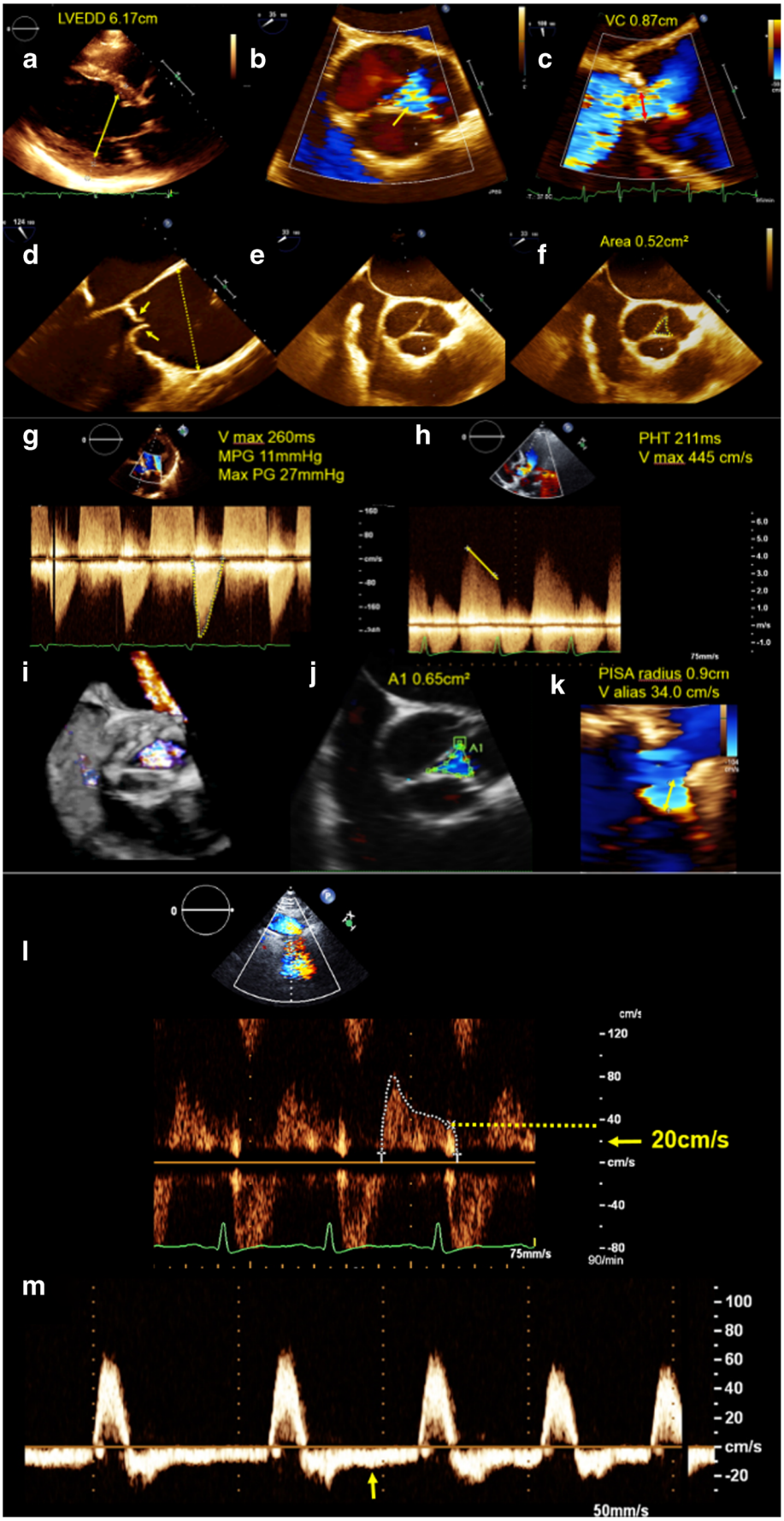
Chronic AR

The most common causes of AR are (a) atherosclerotic degeneration of the valve, which is an acquired condition, associated with aging, hypertension, and hyperlipidemia, and (b) congenital bicuspid aortic valve, both can result in an inadequate closure of the aortic valve. The regurgitant volume (RegV) is mainly affected by the effective regurgitant orifice (ERO), and to a lesser extent, the diastolic pressure gradient between the aorta and the LV. Prolongation of diastole as occurs during bradycardia also increases the regurgitant load [4]. As AR progresses over time, the LV end-diastolic volume rises and can reach a point where the LV preload reserve is reached, and all sarcomeres within the LV are maximally distended such that any further increase in the LV afterload can result in a decreased LV stroke volume [3]. The sum of the RegV and the blood filling the LV through the mitral valve is ejected forward into the high-pressure aorta during systole. The augmentation in the ejected forward stroke volume causes systolic hypertension along with wide pulse pressure, caused by the decrease in aortic diastolic pressure. LV wall stress in severe AR may reach a level similar to that found in patients with aortic stenosis [5]. The Laplace law expresses systolic wall stress: $p \times r/2h$ (p = LV pressure; r = LV radius; h = wall thickness). In patients with AR, both LV pressure (p) and LV radius (r) are increased, and while wall thickness (h) is increased as well, it does not compensate for the combined increase in both p and r [6]. Consequently, the significant increase in systolic wall stress and LV afterload in AR results in increased LV myocardial oxygen requirements [7].

As shown in Figs. 1 and 2, the chronic volume overload accompanying long-standing AR leads to an increased LV end-diastolic volume and pressure and a subsequent increase in LV compliance allowing the LV to accommodate the increased volume while maintaining more optimal filling pressures. This process of chronic LV volume overload results in chamber enlargement along with eccentric ventricular hypertrophy, and increased LV mass which facilitates large LV stroke volume [8].

Fig. 2 Case example of an 81-year-old male patient with severe aortic regurgitation (AR). **a** Parasternal long-axis view shows end-diastolic LV dilation as a hemodynamic consequence of severe AR. **b** Short-axis TEE view with color Doppler in diastole. The regurgitant orifice area can be appreciated. **c** Long-axis TEE view at 100° allows for the measurement of the vena contracta width of 0.87 cm, consistent with severe AR. The AR jet fills the LVOT nearly completely. **d** Long-axis 2D TEE view in diastole shows thickened and retracted aortic leaflets (yellow arrows) with limited coaptation and a relevant aneurysm of the ascending aorta (77 mm, measurement not shown). **e**, **f** A lack of coaptation in diastole in short-axis views and the planimetric evaluation of the coaptation gap (0.52 cm^2). **g** Continuous wave Doppler measurement reveals mildly elevated aortic gradients likely due to increased forward stroke volume. **h** Pressure half time of 211 ms also indicates severe AR. **i** A 3D full volume shows the AR in diastole in a short-axis view. The measurement of the 3D vena contracta area by applying cropping tools (Q-lab, Philips) is seen in **j**. A measurement of the PISA radius is demonstrated in **k**. The calculated ERO in this case of 0.38 cm^2 is consistent with severe AR and was calculated as follows: $(2\pi(6.28) \times r^2(0.81\ cm) \times V_{alias}(34\ cm/s)/V\ max(445\ cm/s) = 0.38\ cm^2)$. **l** Descending aorta end-diastolic flow velocity (dotted yellow line) measured by pulsed-wave Doppler is 35 cm/s (> 20 cm/s is associated with severe AR). **m** Diastolic flow reversal in the distal aorta (yellow arrow)

In the early phases of chronic AR, compensatory mechanisms keep the left ventricular ejection fraction (LVEF) in the normal range. However, over time, the LV dilates and hypertrophies to normalize wall stress by maintaining the ratio of ventricular wall thickness to cavity radius. These adaptive mechanisms permit the LV to accommodate larger stroke volumes, with only little increase in the LV filling pressure. In patients with chronic AR, LV end-diastolic volumes can be increased three or four times more than normal, which allows patients to sustain high cardiac outputs. The term cor bovinum has been used to describe patients with chronic severe AR with significant LV dilatation, and LV end-diastolic volumes. LV compliance is usually also increased, allowing only slightly increased LV end-diastolic pressure. All the abovementioned compensatory mechanisms allow patients to remain stable and asymptomatic for many years, even in the presence of severe AR. However, this is a progressive condition and the chronic volume overload and increased afterload result in an increase in end-systolic dimensions and eventually a reduction in LVEF. As opposed to patients with severe mitral regurgitation where the LVEF is generally normal or even supra-normal, the LVEF in patients with severe AR is at the low normal range with higher end-systolic dimensions. If wall thickening fails to keep up with the volume overload, there is an increase in wall stress which then results in a reduction in LV systolic function and LVEF due to myocyte damage [9]. As LV filling pressures rise, symptoms of fatigue and dyspnea may appear. Angina can develop even in the presence of normal coronary arteries and can be due to the combination of a reduced coronary blood flow reserve in the hypertrophied myocardium [10], lower than normal diastolic pressures, shorter diastolic time (due to increasing heart rate), and the elevated LVEDP causing a decrease in the


a
LVEDD 6.17cm
b
c
VC 0.87cm
d
e
f
Area 0.52cm²
g
V max 260ms
MPG 11mmHg
Max PG 27mmHg
h
PHT 211ms
V max 445 cm/s
i
j
A1 0.65cm²
A1
k
PISA radius 0.9cm
V alias 34.0 cm/s
l
cm/s
120
80
40
20cm/s
cm/s
-40
-80
90/min
75mm/s
m
100
80
60
40
20
cm/s
-20
50mm/s

gradient for coronary blood flow and myocardial perfusion (aortic diastolic pressure—LVEDP) [11]. Distention and dilation of the LV can also lead to secondary (functional) MR due to mitral annular dilation. Subsequently, cardiac output is reduced, and the LV end-diastolic pressure and volume rise, leading to elevation of the LA and pulmonary artery wedge pressures which can cause a pulmonary edema and an increase in the pulmonary artery, right ventricular, and right atrial pressures. Chronically elevated left-sided filling pressures can eventually lead to right heart failure as well.

Evaluation of Patients with AR

Clinical Evaluation

Acute AR

Patients with acute severe AR commonly present with overt pulmonary edema as well as signs of low forward cardiac output. Tachycardia is present usually with normal or low blood pressure and without widened pulse pressure. Auscultation reveals a soft S1 due to premature closure of the mitral valve. The diastolic murmur of AR may be absent because of the rapid equilibration of aortic and LV diastolic pressures [12]. The only clue may be an absent or a soft aortic component of the second heart sound in the setting of severe hypotension and pulmonary edema. In some patients, a mid and late diastolic apical rumble (Austin Flint murmur) is heard. The high LVEDP in the presence of an acute "wide-open" severe AR essentially equilibrates with aortic diastolic pressure. Consequently, LVEDP is higher than LA pressure which results in premature mitral valve closure while there is still antegrade flow from LA to LV. This then generates a diastolic murmur across the mitral valve which is due to a functional form of mitral stenosis [13], as confirmed by Fortuin et al. in a phonocardiographic–hemodynamic correlation study [13]. Acute AR, unless treated urgently with aortic valve replacement (AVR), carries a poor prognosis.

Chronic AR

The physical findings associated with chronic AR include a high-frequency decrescendo diastolic murmur, generally best heard over the third or fourth intercostal space at the left sternal border. When present, the murmur usually signifies at least moderate AR, and its intensity usually correlates with the severity of the lesion. Pulse pressure can be wide, especially when AR is significant with low diastolic blood pressure. The elevated stroke volume and systolic hypertension produce a variety of unique physical findings. Among these are the bounding arterial pulses (Corrigan's pulse), head bobbing (de Musset's sign), pulsation of the uvula (Muller's sign), and pistol shot sounds over the femoral artery with

Table 3 Echocardiographic parameters used for the evaluation of chronic aortic regurgitation

	Mild AR	Moderate AR	Severe AR
Structural and qualitative parameters			
Valve morphology	Normal or abnormal	Normal or abnormal	Usually abnormal/flail/large coaptation defect
LV size	Normal	Normal or dilated	Usually dilated
Flow convergence, color flow	None or very small	Intermediate	Large
Jet density, CW	Incomplete or faint	Mostly dense	Dense (variable in eccentric jets)
Pressure half time (ms), CW	Slow, > 500	Medium, 200–500	Steep, < 200
Diastolic flow reversal in descending aorta	Brief, early diastolic reversal	Intermediate	Prominent holodiastolic reversal. Diastolic VTI = systolic VTI
Semiquantitative parameters			
Vena contracta width (cm)	< 0.3	0.3–0.6	> 0.6
Jet width/LVOT width, central jets (%), color flow	< 25	25–64	≥ 65
Jet CSA/LVOT CSA, central jets (%)	< 5	5–59	≥ 60
Quantitative parameters			
EROA (cm^2)	< 0.1	0.1–0.29	≥ 0.3
Regurgitant volume (ml/beat)	<30	30–59	≥ 60
Regurgitant fraction (%)	< 30	30–49	≥ 50

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AR aortic regurgitation, *CW* continuous wave spectral Doppler; *CSA* cross sectional area, *EROA* effective regurgitant orifice area, *LV* left ventricular, *LVOT* LV outflow tract, *VTI* velocity time integral

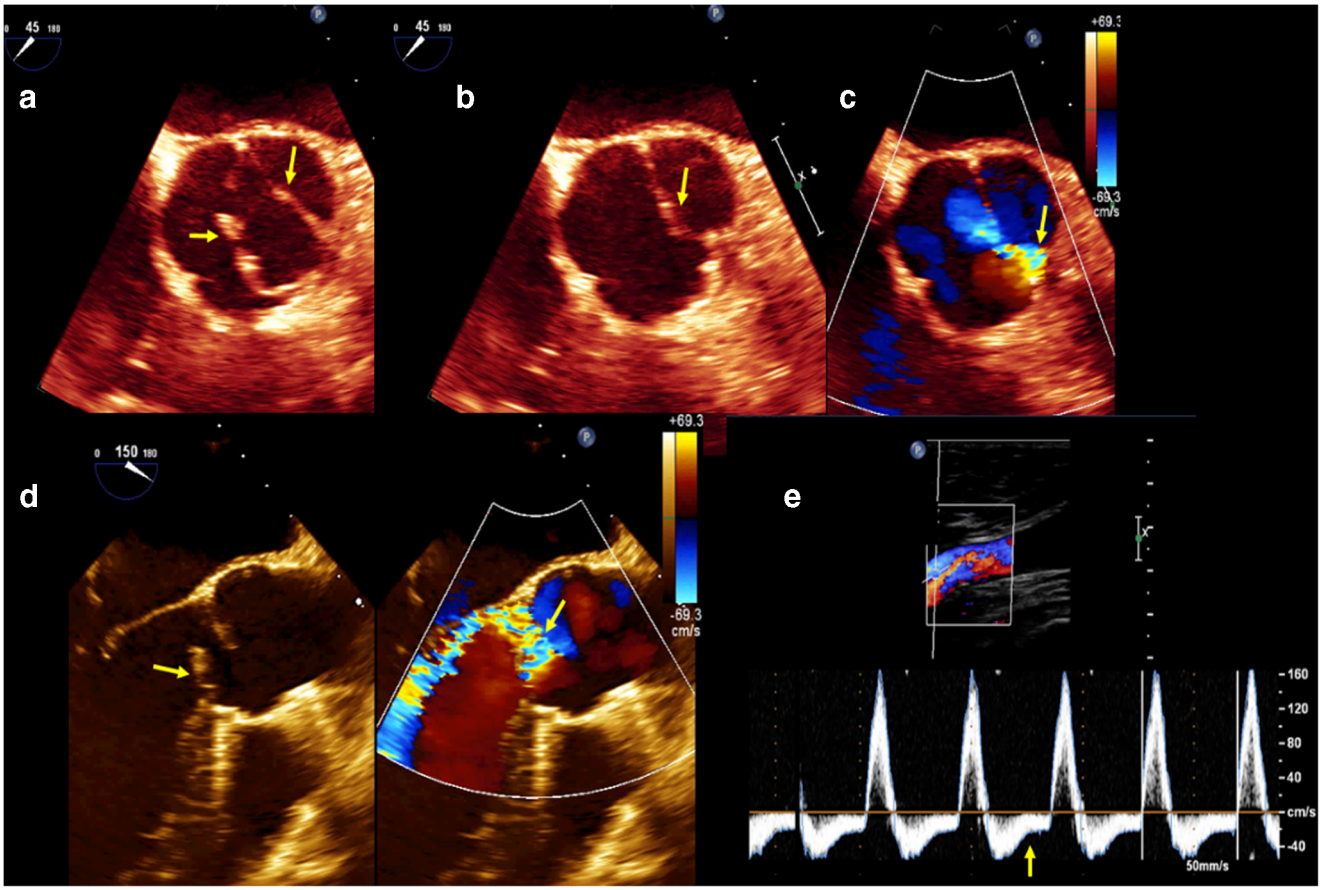

Fig. 3 A patient with a bicuspid aortic valve. **a** Short-axis TEE demonstrating fusion of the right and non-coronary cusps—the aortic valve has a "fish mouth" appearance during systole. **b** Short-axis view during diastole, while the valve is closed. **c** Color flow during diastole demonstrates eccentric aortic regurgitation (AR) (yellow arrow) which is also visible in **d** at the long-axis view (yellow arrow) where a partial prolapse of the cusp can be appreciated. **e** Pulsed Doppler of the descending aorta demonstrates holodiastolic flow reversal (yellow arrow), consistent with severe AR

compression (Traube's sign). During compression with a glass slide, capillary pulsations can be seen on the fingernail (Quincke's sign) [14]. In more progressive phases of untreated AR, in the setting of left heart failure, signs of right heart failure such as distended jugular veins and peripheral edema may appear.

Echocardiographic Evaluation

Echocardiography is the primary method used to determine both the etiology and severity of AR. Echocardiographic evaluation of aortic valve morphology, as well as careful measurement of the different segments of the aorta (annulus, root, sinotubular junction, and ascending aorta), can reveal in many cases the underlying mechanism of AR. LVEF and LV dimensions are essential in the evaluation of AR as they help guide therapy. Changes in LV size and function should be monitored serially to optimize the timing for surgical intervention. As no single parameter is adequate for determining AR severity, grading of AR is done using a multi-parameter approach as summarized in Table 3 and further detailed and demonstrated in Fig. 2. The hemodynamics of acute and chronic AR are different. "Classic" AR findings are frequently not present with acute AR. In addition, eccentric regurgitant jets (Fig. 3 and Video 1) can lead to underestimation of the severity of AR, unless an integrative, multi-parameter approach is used.

Two-Dimensional Echocardiography and Color Doppler

Two-dimensional (2D) transthoracic echocardiography (TTE) is useful for the initial echocardiographic evaluation of AR. TTE should focus on abnormalities in valve morphology such as a flail cusp or a wide coaptation defect, as well as evaluation of LV size, geometry, and extent of hypertrophy. Ultrasound enhancing agents (contrast) can be used in technically difficult studies to improve overall accuracy [15]. The surrounding structures, mainly the aortic root and ascending aorta, should be evaluated for the presence of significant aneurysms or dilatation which can cause secondary AR [16]. Transesophageal echocardiography (TEE) is useful in patients with poor acoustic TTE windows. TEE is especially helpful in evaluating aortic

valve vegetations, valve and root abscesses, and prosthetic aortic valves as well as for the detailed assessment of the aortic root and ascending aorta, especially in cases where aortic dissection is suspected. TEE is also warranted if aortic valve repair or replacement is planned (Fig. 2d–f and Video 2). Despite inherent limitations [17] color flow Doppler (CFD) is helpful for determining AR severity. AR can be visualized in the parasternal long-axis, short-axis, and apical views (Fig. 2b, c and Videos 1 and 3). The parasternal views are preferred over the apical views due to better axial resolution [18••]. A color jet area or jet width greater than 65% of left ventricular outflow tract (LVOT) diameter or area is indicative of severe AR [18••]. It is important to use the proper gain settings and Nyquist limits (50–60 cm/s) in order to avoid overestimation or underestimation of AR severity by CFD. A major limitation of color Doppler for AR assessment include the presence of eccentric jets, diffuse jets, and jets originating along the entire coaptation line [18••]. In many cases, the assessment of AR is mainly based on jet size in the LVOT which is mostly often done using visual estimation rather than direct quantitative measurement. Visual estimation provides a qualitative assessment of the degree of AR. In cases of severe or trivial AR, this approach is adequate for clinical decision-making. Vena contracta (VC) width is a semi-quantitative parameter derived from color Doppler for evaluation of AR severity. VC is measured at the narrowest portion of the AR jet, just before it expands into the ventricle during diastole. The VC provides a way to estimate the ERO area (EROA), assuming a circular regurgitant orifice. VC wider than 6 mm is indicative of severe AR [19] (Fig. 2c). Three-dimensional (3D) measurements of the VC area (Fig. 2j) have been shown to be more accurate [20, 21] than 2D VC; however, this method has not been implemented yet into current guidelines.

The proximal isovelocity surface area (PISA) method, which is based on the conservation of mass principle, allows quantification of AR by evaluating the zone of flow convergence. Validated initially for patients with mitral regurgitation [22], the use of PISA is reported to be feasible in patients with AR [23], but less data is available to support its routine use to grade AR severity. Unlike the continuity method (further discussed), the presence of significant mitral regurgitation does not affect the validity of the measurements obtained using PISA. PISA is obtained in the parasternal or the apical views, assumes a hemispherical shape of the proximal flow convergence, and by using the conversion of mass principle, the effective RegV and EOA can be calculated [23] (Fig. 2k).

Spectral Doppler

Spectral Doppler, both continuous wave (CW) and pulse wave (PW), is useful for AR grading. A dense CW signal reflects more regurgitant red blood cells and thus a larger regurgitant volume. Conversely, less dense signals suggest only mild regurgitation. Using the pressure half time (PHT) method is also helpful for evaluating the severity of AR [24, 25]. After interrogating the AR jet by CW Doppler, the PHT identifies the rate of velocity deceleration which is related to the rate of diastolic pressure equalization between the aorta and LV. The more severe the AR, the faster the equilibration of aortic diastolic pressures and LV diastolic pressures. A PHT of < 200 ms signifying a relatively rapid increase in the left ventricular diastolic pressure (mainly due to a large regurgitant volume) and supports a diagnosis of severe AR (Fig. 2h).This method should be used cautiously, as it is dependent on numerous technical and physiologic factors such as whether AR is acute or chronic, AR jet characteristics (central vs. eccentric), the site and positioning of sampling of the AR jet by spectral Doppler and its angle of alignment to the flow, the diastolic blood pressure, and the compliance of the LV.

Pulse wave Doppler allows evaluation of flow in the descending and abdominal aorta. A brief diastolic flow reversal in the aorta is normal; however, the presence of holodiastolic flow reversal in the descending aorta is associated with severe AR. An aortic diastolic velocity time integral (VTI) which is similar to the systolic VTI (Fig. 2l), and a relatively high end-diastolic velocity (> 20 cm/s), is also consistent with at least moderate AR [26, 27]. In older individuals who have a less compliant aorta, these measurements can be problematic and less definitive [18••].

Quantification of the retrograde regurgitant volume through the aortic valve can be assessed with spectral Doppler using the continuity equation. The continuity method assumes that the forward flow through the aortic valve equals the forward flow through other valves (most commonly used is the flow through the mitral valve) + the regurgitant flow through the aortic valve. Thus, the regurgitant volume = LVOT flow − mitral flow [28]. This is based on the assumption that both the mitral annulus and the aortic annulus are circular, as well as that there is no significant (> minimal) mitral regurgitation. A regurgitant volume of > 60 ml is consistent with severe AR. This evaluation requires precision and attention to detail when making measurements as even small errors in measurements can significantly affect the obtained calculations [18••, 29].

Additional Imaging Modalities

Cardiac Magnetic Resonance Imaging

Cardiac magnetic resonance imaging (CMR) provides important data regarding valve morphology and left ventricular function, dimensions, and volumes as well as quantification of regurgitant volume and fraction [30, 31]. CMR is indicated in the case of suboptimal echocardiographic images, and

whenever there is discordance between measurements or between AR grading and the patient clinical status [18••]. Measurements obtained by CMR tend to be more reproducible than those obtained by echocardiography [32].

Management of Patients with Aortic Regurgitation

Follow-up

The clinical course of chronic AR is generally slowly progressive with adaptive mechanisms that include an increase in LV size, volume, and mass with eccentric hypertrophy. When patients with severe AR develop symptoms such as exertional dyspnea and/or angina, this can signify worsening of AR or worsening of LV function (systolic or diastolic). In the setting of severe AR, the development of symptoms is associated with a worsening prognosis, and it is a class I indication for a surgical AVR [33]. For asymptomatic AR, American Heart Association/American College of Cardiology (AHA/ACC) guidelines [33] as well as European Society of Cardiology (ESC) guidelines [34••] recommend routine serial follow-up that should include periodic evaluation of LV function as well as assessment of LV dimensions, in intervals according to AR severity (every 3–5 years for mild AR, 1–2 years for moderate AR, and 6–12 months for severe AR). Exercise testing is useful to determine if patients are truly asymptomatic or only asymptomatic due to inactivity, and when patients have equivocal symptoms and borderline LV function and dimensions. Exercise testing can also provide important prognostic information such as functional capacity and contractile reserve [33].

Medical Therapy

The goals of medical therapy for patients with AR are to control systolic hypertension, to achieve a near-normal systolic BP, to delay the onset of LV dysfunction in asymptomatic patients, and to reduce patients' symptoms once they occur. There is no evidence that medical therapy in patients with severe symptomatic AR improves prognosis, and as such, medical therapy is complimentary, rather than an alternative to surgery. Medical therapy is unlikely to significantly reduce regurgitant volume in chronic severe AR as the regurgitant orifice area is relatively fixed, and the diastolic blood pressure is already low [35]. Medical therapy can help alleviate symptoms in patients with severe AR which are at high risk for surgery [33]. The first-line medications recommended for patients with hypertension include either an angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) or a dihydropyridine calcium channel blocker [36, 37]. Beta blockers are usually not recommended as a first-line therapy in patients with AR and hypertension, as slowing of the heart rate prolongs diastole and thus increases regurgitant volume, which leads to higher stroke volume and elevation in the systolic blood pressure [33]. However, in a retrospective analysis, beta blockers were found to be associated with a survival benefit in patients with severe AR, provided the heart rate was > 70 beats per minute [38]. In patients with Marfan syndrome, the use of beta blockers or ARBs may slow the progression of aortic root dilatation and reduce surgical complications [34••]. In patients with bicuspid aortic valve and aortic dilation, beta blockers presumably reduce shear stress and thus slow ascending aorta dilation; however, there is insufficient evidence to support their routine use [39].

Surgical Therapy

For patients with symptomatic severe acute AR, emergent or early surgical therapy is warranted. This is especially true in the setting of acute infective endocarditis leading to acute AR or a type A aortic dissection with associated AR. Earlier surgery, compared to delayed surgery, has been shown to improve survival and reduce morbidity [40]. Results from a series of patients undergoing emergent aortic valve surgery for acute AR due to various indications demonstrated low operative mortality and good long-term results [41–43]. For patients with chronic AR, many patients remain asymptomatic over a long period of time. However, patients require regular follow-up and serial TTE [33]. While some patients develop symptoms, others may remain asymptomatic in spite of deterioration in LV systolic and diastolic function and excessive LV dilation; both are the echocardiographic harbingers of developing overt heart failure. The development of heart failure is associated with poor prognosis for patients with AR [44–46]. Most AR patients undergo surgical AVR. In cases with significantly dilated aortic root or ascending aorta, this portion of the aorta is also replaced. In high-volume centers, especially in patients with bicuspid aortic valve, aortic valve repair has been reported with good results [47]. Despite recent advances, the durability of aortic valve repair remains a major concern, and thus, repair should be reserved for patients with favorable anatomy and be performed by an experienced surgeon [33, 47]. The reported operative mortality for isolated surgical AVR in the current era is below 2% and is decreasing [43, 48, 49]. Operative mortality is higher with concomitant aortic root replacement or coronary bypass surgery or in case of substantial comorbidities or advanced age. While mortality in asymptomatic patients with severe AR and a normal LV size and function is < 0.2%/year, it can reach > 10%/year in symptomatic individuals. Therefore, while asymptomatic patients with severe AR and a normal LV size and systolic function can be managed conservatively, they should be monitored closely for the development of symptoms, LV dysfunction, or progressive LV dilation. Current AHA/ACC and ESC guidelines provide a strong (class I) recommendation for AVR in

symptomatic patients with severe AR. For asymptomatic severe AR, the same level of recommendation is given if patients show signs of LV dysfunction (defined as LVEF < 50%) or if other cardiac surgery is planned. Excessive LV dilation, defined as LV end-systolic diameter > 50 mm, is a class IIa indication for surgery in an asymptomatic patient. LV end-diastolic diameter > 65 mm (> 70 mm in recent ESC guidelines) is a class IIb indication in asymptomatic patients at low surgical risk (class IIa in ESC guidelines) [33, 34••].

Percutaneous Therapy

In contrast to aortic stenosis, the absence of valvular calcification in many patients with native pure AR, as well as aortic annular dilation, complicates the use of transcatheter aortic valve replacement (TAVR) for the treatment of AR. However, the Euro Heart Survey showed that only 20% of patients with severe AR and an LVEF between 30 and 50% were referred to surgery. Moreover, only 3% of patients with an LVEF < 30% were referred to surgery. Advanced age and multiple comorbidities were the frequent reasons for conservative rather than surgical management, resulting in an annual mortality rate of 10 to 20% [50]. While still not recommended by standard guidelines, performing TAVR in patients with severe native AR deemed high risk for surgery seems reasonable. A recent meta-analysis evaluating TAVR use in patients with AR demonstrated that TAVR was technically feasible in selected high-risk patients with native pure AR [51]. There are several limitations to consider when considering TAVR for the subgroup of patients with severe AR. First, the etiology of AR of which around half of all cases is due to an aortopathy, rather than native valve dysfunction. This frequent coexistence of severe AR and pathological dilation of the aortic root and ascending aorta limit the use with current devices that are not suitable for annulus dimensions exceeding 30 mm in diameter. Additionally, dilation of the left ventricle and absence of calcification among patients with native pure AR pose an additional challenge on adequate anchoring of TAVR devices, risking migration of the valve. However, new-generation devices featuring repositionability and specific fixation and sealing techniques have already shown to provide superior outcomes compared to first generation TAVR valves [52•]. Other percutaneous valves specifically designed to treat AR are in different stages of clinical trials and will potentially improve outcomes of TAVR in patients with AR [53, 54].

Conclusion

AR should be categorized as either acute or chronic. Acute severe AR is associated with symptoms and hemodynamic instability and should be treated promptly with aortic valve repair or replacement. Conversely, chronic AR is generally a slowly progressive condition with adaptive mechanisms of an increase in LV size, volume, and myocyte hypertrophy, which allows significant AR to be well tolerated for many years. Patients with chronic AR should be regularly seen in clinical follow-up and have serial echocardiograms as well as other modalities when a threshold for intervention is impending. With the onset of symptoms, excessive LV dilation or signs of LV systolic dysfunction, aortic valve replacement, or repair is indicated. Appropriate timing of aortic valve intervention improves outcome and prevents long-term complications. While TAVR has been most frequently used for aortic stenosis, it is increasingly used for patients with AR. New-generation valves are being developed for the percutaneous treatment of AR. While percutaneous AVR is becoming more frequent, it is still not routinely recommended as an alternative for surgery and is currently reserved for those patients deemed at high operative risk.

Compliance with Ethical Standards

Conflict of Interest Nir Flint, Nina C. Wunderlich, Hezzy Shmueli, Sagit Ben-Zekry, Robert J. Siegel, and Roy Beigel declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- •• Of major importance

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