Aortic Regurgitation

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Piera Capranzano and Corrado Tamburino

29.1 Epidemiology

Aortic regurgitation (AR) is characterized by blood regurgitation from the aorta into the left ventricle (LV) due to the failure of the valve leaflets to adequately close during the diastolic phase of the cardiac cycle. AR is usually an acquired valve disease, while the congenital etiologies, mainly bicuspid morphology, are rarer. Acquired AR can be caused by primary disease of the aortic valve leaflets and/or abnormalities of the aortic root. The alterations of the aortic valve leaflets are more often of a calcific-degenerative nature, or a result of acute or chronic endocarditic valve processes, or due to myxomatous degeneration. There has been a progressive reduction in primary valve disease of rheumatic origin, which is now a rare event. Systemic arterial hypertension, aortic dissection, and connectivopathies such as Marfan's syndrome, Reiter's syndrome, Ehlers-Danlos syndrome, or rheumatoid arthritis alter the aortic root, leading to dilation and subsequent valve closure dysfunction [1]. Pure AR is far less common than aortic stenosis, affecting about 13% of patients with isolated, native left-sided valvular heart disease [2].

29.2 Pathophysiology

Valve failure can develop progressively (chronic AR), leaving the ventricle time to compensate for this defect, or acutely (acute AR) with no adaptation of the LV and often representing an emergency. The pathophysiological alterations resulting

P. Capranzano, M.D. (✉) • C. Tamburino, M.D., Ph.D.
Cardiovascular department, Ferrarotto Hospital, University of Catania, Catania, Italy
e-mail: pcapranzano@gmail.com

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from AR are correlated to the degree of regurgitation and are different in chronic and acute AR. Chronic AR is a progressive condition involving several compensatory mechanisms [3]. In AR the overall systolic output volume comprises the antegrade output and the regurgitant volume, and the LV pumps the total volume into the aorta against high systemic impedance. The main compensatory mechanism is the rise in end-diastolic volume (increase in preload) caused by regurgitation. The LV manages to compensate volume overload by progressively dilating. In an initial phase, the rise in preload involves an increase in ventricular contractile efficiency, according to Starling's law. On the other hand, according to Laplace's law, LV dilation leads to an increase in systolic wall tension, which is addressed by the ventricle, with eccentric hypertrophy of the walls to normalize systolic stress. As a consequence, in AR, hypertrophy and dilation are combined. A valve defect can be well tolerated for a long time due to the compensatory mechanisms implemented.

As the pathology progressively evolves, due to the effects of chronic volume overload, hypertrophy can prove to be inadequate to dilation, thus leading to structural alterations of the ventricular myocardium. This brings about an increase in end-diastolic pressure and a reduction in systolic output, thus increasing left atrial and pulmonary vein and capillary pressure and eliciting the clinical manifestations of heart failure. The worsening in ventricular function is favored by the development of ischemic damage secondary to inadequate coronary artery perfusion due to reduced aortic diastolic pressure.

In acute AR, most frequently caused by acute infective endocarditis and aortic dissection, the inability of the LV to adapt to sudden volume overload leads to a rapid increase in ventricular diastolic pressure. This involves a sharp increase in atrial and pulmonary vein and capillary pressure, which elicits the clinical manifestations of acute heart failure, such as orthopnea and pulmonary edema [1, 3, 4].

29.3 Diagnosis

29.3.1 Noninvasive Diagnosis

In chronic AR patients, the symptoms due to reduced cardiac or coronary reserve, such as effort dyspnea and angina pectoris, have a late onset. Sudden onset of dyspnea at rest and low-flow symptoms characterize the clinical course of acute AR patients. Some of the objective signs typical of chronic AR are a wide and fast arterial pulse, increased differential pressure, decreasing aortic diastolic murmur, best audible in the third to fourth intercostal space on the left of the sternum in expiratory apnea, click and systolic ejection murmur, and end-diastolic murmur of mitral origin (the so-called Austin Flint murmur). In acute AR, the peripheral signs are missing, diastolic murmur is usually short, and there is a prevalence of the signs typical of low cardiac output and pulmonary venous congestion.

With regard to instrumental examinations, standard ECG can show the signs of left ventricular hypertrophy, left ventricular overload, or left bundle branch block

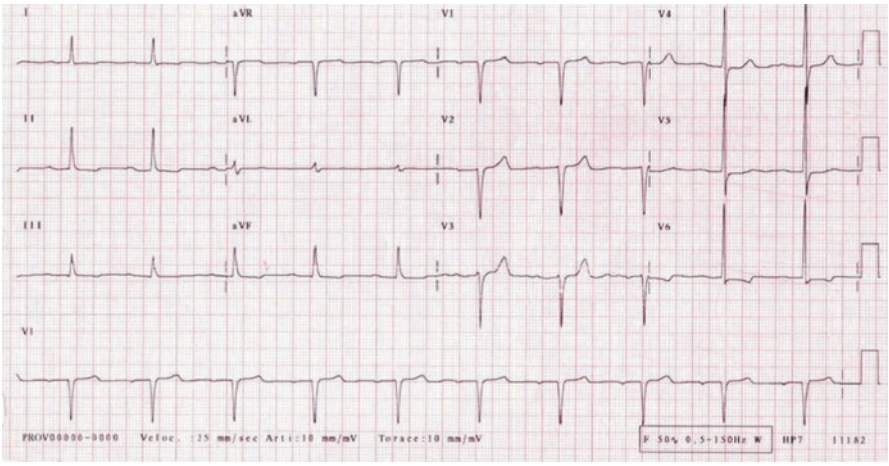

Fig. 29.1 ECG picture of hypertrophy and left ventricular overload in patient with aortic regurgitation

(Fig. 29.1); these signs are not present in acute AR, in which sinus tachycardia and specific disorders in ventricular repolarization can occur.

Chest x-ray can show an increase in the volume of the LV and, at times, of the thoracic aorta, especially in the ascending tract. However, the key examination for noninvasive diagnosis of AR is transthoracic echocardiogram (TTE) with color Doppler ultrasound.

This method allows the following:

- Assessment of the anatomy and structural alterations of the aortic valve apparatus and the presence and severity of aortic root dilation
- Estimation of the presence and severity of AR
- Assessment of the structural adaptations and degree of LV impairment

TTE provides very accurate morphological and functional information on the aortic valve and root, identifying, for example, the presence of bicuspid aortic valve disease, the thickening and reduced mobility of the cusps in the degenerative or postrheumatic forms, thickened and redundant leaflets in myxomatosis, erosion and perforation of the cusps in forms secondary to endocarditis, and aortic ectasia in Marfan's syndrome. In addition, AR can also be secondary to degenerative processes affecting biological valve devices; in this case, TTE diagnosis uses the techniques applied for native valve disorders with small expedients [5].

M-mode examination can show high-frequency diastolic fluttering of the anterior mitral leaflet, inverse diastolic doming of the anterior mitral leaflet, and, in acute AR, early diastolic closing of the mitral valve.

The color Doppler technique shows blood regurgitation through the aortic valve during diastole and allows estimation of the severity, assessing the following parameters [6] (Fig. 29.2):

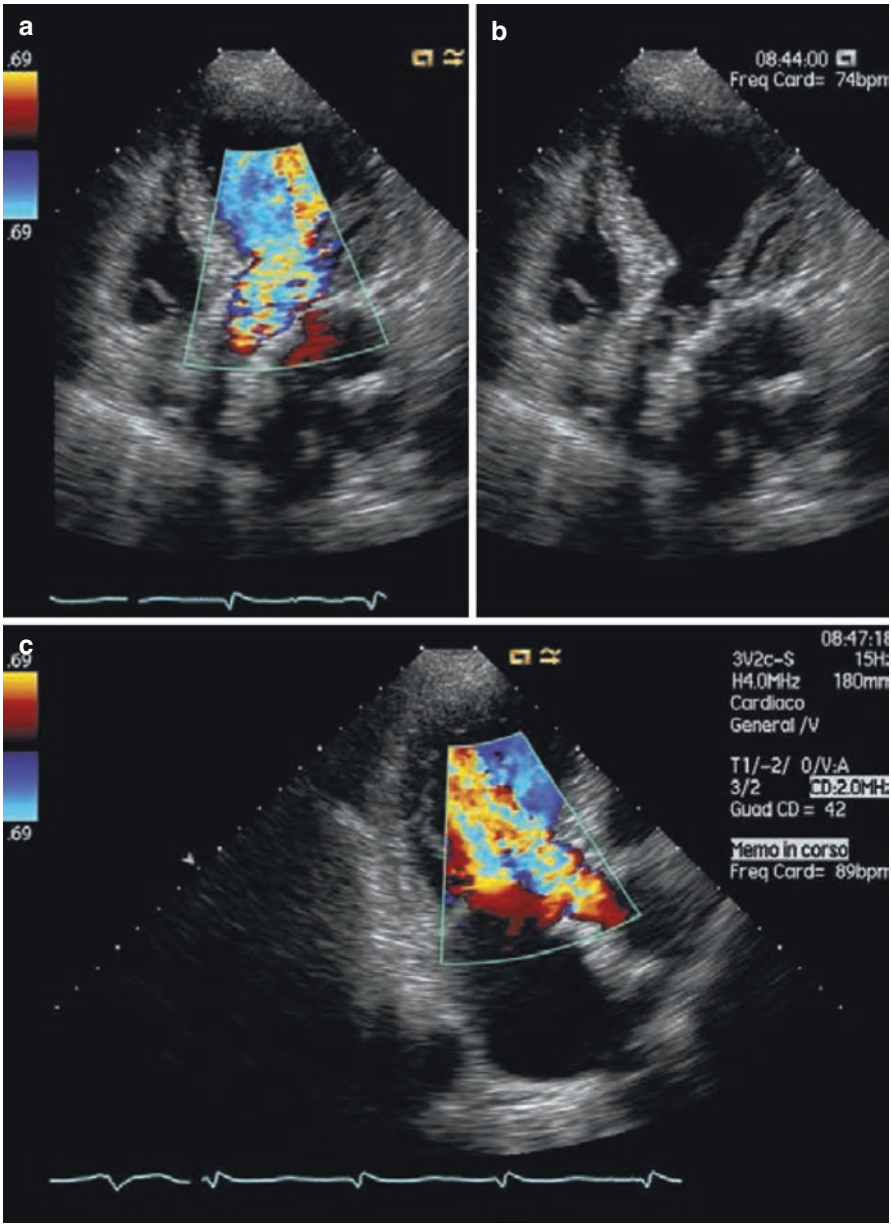

Fig. 29.2 Color Doppler ECG in apical four-chamber view (**a** and **b**) and three-chamber view (**c**) showing severe aortic regurgitation

- Width and area of the regurgitant jet cross section
- Vena contracta
- Effective regurgitant orifice area (EROA) by the proximal isovelocity surface area (PISA) method

The width and cross-sectional area of the regurgitant jet must be measured in parasternal view, right below the aortic valve (within 1 cm of the valve). The relationship between the maximum width of the proximal jet and left ventricular outflow diameter, measured in parasternal long-axis view, or the relationship between the jet cross-sectional area and the LVOT, measured in parasternal short-axis view, makes it possible to estimate the severity of regurgitation [7]; AR is defined as severe if the relationship between the jet widths is ≥65% or the relationship between the jet areas is ≥60% [8] (Table 29.1).

Accurate measurement of the width and area of the regurgitant jet depends on the shape of the regurgitant orifice and jet direction; by occupying a small portion of the outflow tract, eccentric jets can lead to underestimation of the severity of the valvulopathy, while central jets, by contrast, can overestimate it. Measurement of the vena contracta, at the aortic valve, in parasternal long-axis view, makes it possible to distinguish between severe forms if it is >0.6 cm and mild forms if <0.3 cm [6, 9] (Table 29.1). In order to obtain accurate measurement of the vena contracta, the convergence flow, vena contracta, and jet should be clearly visible. The use of this parameter, though, is not indicated in the presence of multiple jets.

The PISA method is based on the principle of conservation of mass: according to this principle, the quantity of regurgitant flow through the aortic valve is obtained from the flow quantity of a proximal surface area with a known flow velocity. This method allows the quantitative estimation of the EROA and volume [10].

Imaging of the proximal flow convergence region by TTE is performed from the apical and parasternal views or the upper right sternal border. This method cannot be used in the case of multiple jets and is less accurate for eccentric jets. In addition, the presence of an aneurysm of the ascending aorta, which deforms the valve plane, can lead to an underestimation of the degree of AR. AR is defined as severe when the EROA is ≥0.30 cm^2 [6, 9, 11] (Table 29.1).

Table 29.1 Criteria for the definition of aortic regurgitation severity

	Mild	Moderate	Severe
Doppler parameters			
Jet width in LVOT-color flow Doppler	Small in central jets	Intermediate	Large in central jets
Jet deceleration rate (CW) (PHT, ms)	>500	500–200	<200
Diastolic flow reversal in descending aorta (PW)	Brief, early diastolic reversal	Intermediate	Holodiastolic reversal
Quantitative parameters			
Jet width/LVOT width, %	<25	25–64	≥65
Jet CSA/LVOT CSA, %	<5	5–59	≥60
Vena contracta width, cm	<0.3	0.3–0.6	≥0.6
RV, ml/beat	<30	30–59	≥60
RF %	<30	30–49	≥50
EROA, cm^2	<0.10	0.10–0.29	≥0.30
Structural parameters			
LV size	Normal	Normal or dilatated	Usually dilatated

LVOT left ventricular outflow tract, *CW* continuous wave Doppler, *PHT* pressure half-time, *PW* pulsed wave Doppler, *CSA* cross-sectional area, *RV* regurgitant volume, *RF* regurgitation fraction, *EROA* effective regurgitant orifice area, *LV* left ventricle

PW Doppler allows quantification of AR by calculating the regurgitant volume (RV) and regurgitant fraction (RF). Aortic RV is obtained by subtracting the systolic volume crossing the LVOT from the mitral inflow or pulmonary outflow volume. RF is obtained from the equation: RF = (aortic RV/LVOT systolic volume) × 100%.

The EROA can be calculated this way as well, since the flow volume is given by the product of the area by the time-velocity integral of the regurgitant jet at CW Doppler [12]. This method applies to multiple and eccentric jets, but cannot be used in the presence of MR that is worse than mild, except for those cases in which pulmonary output is used as reference. An RV ≥ 60 ml and EROA ≥0.30 cm^2 are consistent with severe AR [6, 9] (Table 29.1).

PW Doppler also allows the observation of a diastolic Doppler signal due to aortic diastolic flow reversal in either the ascending or descending aorta. With increasing AR, the duration and velocity of the reversal increase (Figs. 29.3 and 29.4).

CW color Doppler recording of the flow time-velocity curve of AR with an apical approach is marked by a rapid increase in velocity during isovolumetric relaxation, followed by a gradual slowdown during diastole and a sudden drop during

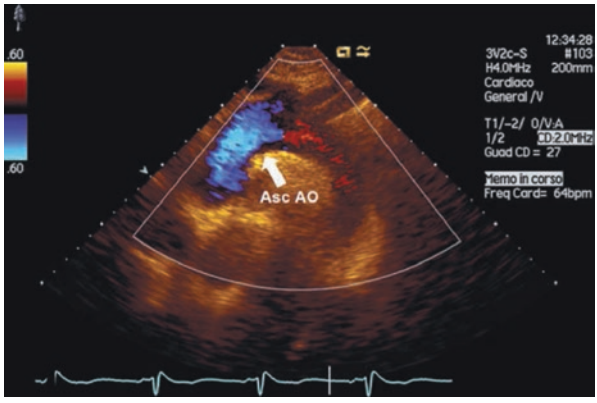

Fig. 29.3 Transthoracic echocardiogram: color Doppler image of an aortic regurgitation jet recorded in the ascending aorta (Asc Ao)

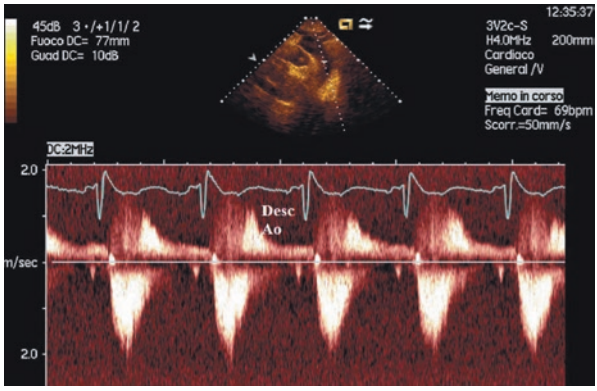

Fig. 29.4 Transthoracic echocardiogram: PW Doppler of the flow in the descending aorta in patient with aortic regurgitation. The reverse diastolic flow can be seen during diastole. Descending aorta (Desc Ao)

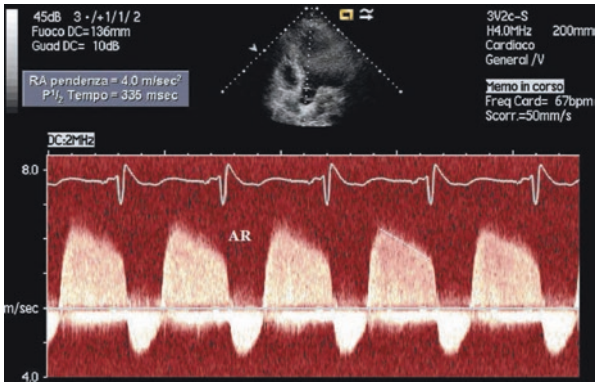

Fig. 29.5 Transthoracic echocardiogram: CW Doppler recording in a patient with aortic regurgitation showing how to measure the diastolic gradient of the regurgitant signal (AR) and the pressure half-time (PHT)

isovolumetric contraction. As the degree of severity of AR worsens, left ventricular diastolic pressure rises, and the pressure half-time (PHT) of the regurgitant flow and deceleration time of the mitral protodiastolic flow velocity become shorter [13]. A PHT > 500 ms is usually compatible with mild AR, whereas a value <200 ms is considered consistent with severe AR [6, 9] (Table 29.1) (Fig. 29.5). This technique has some limitations, though, as it is affected, for instance, by LV compliance, which, if reduced, leads to a shortening of PHT, due to the faster rise in LV pressure.

TEE is seldom used in the assessment of AR, but it may be needed if there is a poor acoustic window or if accurate assessment of aortic valve anatomy or Doppler scan is not possible.

Finally, in the overall assessment of a patient, an assessment of the LV is also needed for therapeutic and prognostic purposes; in particular, the increase in its end-systolic diameter to over 55 mm, without any other causes for volume overload, is an indication of severe ventricular function impairment.

The stress test in severe AR patients has not been validated. Cardiac MRI is recommended when the quality of the echocardiography images is not good or, together with multislice CT, for an assessment of the aorta when the echocardiography shows that it is dilated.

29.3.2 Invasive Diagnosis

The role of invasive diagnosis in AR is rather limited, since TTE and TEE provide an extensive and accurate analysis of the degree of regurgitation [9].

Cardiac catheterization may be useful in assessing differential pressure in the ascending aorta, but aortography with rapid injection of contrast in the aortic root (25–35 ml/s) is particularly successful in quantifying the degree of regurgitation (Fig. 29.6). In percutaneous treatment of pure aortic regurgitation, aortography is complementary to angio-CT and echocardiography to study the interaction of the device with the aortic apparatus and to achieve optimal implantation of the percutaneous device.

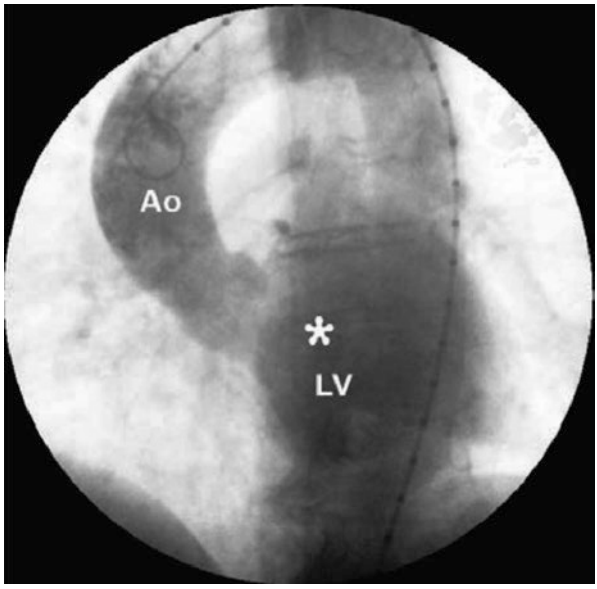

Fig. 29.6 Aortogram in LAO view showing major regurgitation with contrast medium in the left ventricle (*asterisk*). *Ao* aorta, *LV* left ventricle

29.4 Timing of Interventions

Moderate or severe AR is generally associated with a favorable prognosis for many years. Among asymptomatic subjects with severe AR and normal left ventricle ejection fraction (LVEF), more than 45% of patients maintain this condition and normal ventricular function at 10 years [14–16], with a percentage of <6% a year developing left ventricular dysfunction [9]. The risk of sudden death in these patients is less than 0.5% a year. However, as for AS, once the patient becomes symptomatic, there is rapid and progressive worsening. Heart failure can occur along with episodes of pulmonary edema, or cases of sudden death, usually among previously symptomatic patients with major LV dilation. Presurgery data show that death in nonoperated patients usually occurs within 4 years of the onset of angina pectoris and within 2 years of the onset of heart failure [17]. Over the past 20 years, many surgical case histories have shown that a low LVEF is one of the most important determinants of mortality after valve replacement, especially when ventricular dysfunction is irreversible and does not improve after surgery [9].

It is more likely that left ventricular dysfunction is reversible if diagnosed early on, before the LVEF becomes so low that the ventricle dilates greatly and develops significant symptoms; therefore, surgical intervention is important before these alterations become irreversible [6].

When AR has an acute development, urgent surgery is clearly indicated due to hemodynamic instability. In the case of chronic AR, considering the excellent prognosis in the short and medium term, surgical repair must be delayed in patients with

severe AR who are asymptomatic, have a good tolerance to effort, and have an LVEF >50% without marked LV dilation (i.e., end-diastolic diameter < 70 mm and end-systolic diameter < 50 mm). Similarly, without clear contraindications or associated pathologies, surgery is indicated in symptomatic patients with severe AR and asymptomatic patients with LVEF <50% and marked left ventricular dilation (end-diastolic diameter > 70 mm and end-systolic diameter > 50 mm). Since serious symptoms (NYHA class III or IV) and left ventricular dysfunction with LVEF <50% are independent risk factors for a worse postoperative survival, surgery must be performed in NYHA class II patients before they develop severe left ventricular dysfunction [18] (Table 29.2).

Finally, valve replacement must be performed regardless of the symptoms in cases of severe AR in patients who must undergo surgery for other contingent conditions (Table 29.2).

Indications for surgery in patients with severe AR secondary to aortic root dilation are similar to those for patients with primary valve disease. However, progressive expansion of the aortic root and/or a diameter > 50 mm in the case of Marfan's syndrome, greater than 50 mm (in the case of bicuspid valve with additional risk factors), and greater than 55 mm (in all other cases) with any other degree of regurgitation represent indications for surgery [18] (Table 29.2).

Table 29.2 Indications for valve replacement in aortic regurgitation, adapted from the 2012 European Guidelines for the treatment of valve diseases

	Class of recommendation-level of evidence
Severe AR	
Symptomatic patients (dyspnea; NYHA classes II, III, and IV; or angina)	I-B
Asymptomatic patients with resting LVEF ≤50%	I-B
Patients undergoing CABG and surgery of the ascending aorta or on another valve	I-C
Asymptomatic patients with resting LVEF >50% with severe LV dilatation:	
End-diastolic dimension >70 mm	IIa-C
End-systolic dimension >50 (or 25 mm/m^2 BSA)	IIa-C
Whatever the severity of AR	
Patients who have aortic root disease with maximal aortic diameter	I-C
≥50 mm for patients with Marfan's syndrome	IIa-C
≥45 mm for patients with Marfan's syndrome with risk factors[a]	IIa-C
≥50 mm for patients with bicuspid valves with risk factors[b]	
≥55 mm for other patients	IIa-C

AR aortic regurgitation, *NYHA* New York Heart Association, *CABG* coronary artery bypass grafting, *LV* left ventricle, *LVEF* left ventricular ejection fraction, *BSA* body surface area

[a]Family history of aortic dissection and/or aortic size increase >2 mm/year, severe AR or mitral regurgitation, desire for pregnancy

[b]Coarctation of the aorta, systemic hypertension, family history of dissection, or increase in aortic diameter > 2 mm/year

29.5 Percutaneous Therapy

Surgical valve replacement remains the treatment of choice in operable patients with native AR [18]. Transcatheter aortic valve replacement (TAVR) has become the standard of care for patients with aortic valve stenosis who have a prohibitive risk for surgical aortic valve replacement and an alternative to surgical aortic valve replacement in patients with aortic valve stenosis deemed at high surgical risk [18]. The role of TAVR for native severe AR treatment is rather marginal and currently consists of an "off-label" application in patients for whom cardiac surgery is an absolute contraindication; indeed the devices used are specifically designed for the treatment of aortic stenosis, to be implanted in heavily calcified and degenerated valves.

29.5.1 Patient Selection

As stated above, percutaneous treatment of native predominant AR has to be restricted only to patients with a prohibitive surgical risk based on the heart team assessment. Examples of comorbidities that heart teams considered significant enough to make the risk of surgery unacceptable include previous radiotherapy, hostile mediastinum, severe LV dysfunction, previous stroke, severe pulmonary hypertension, and severe pulmonary disease. Percutaneous devices specifically designed for native AR are in the development phase. On this background, from a clinical and anatomical perspective, patient selection is similar to that of aortic stenosis patients undergoing percutaneous replacement. Specifically, TAVR for AR can be attempted if the annulus is not at the upper limit for a specific device, and some technical issues have to be taken into account. However, it should be pointed out that TAVR in pure native AR represents an off-label indication for the majority of TAVR systems.

29.5.2 Procedure and Technical Aspects

The percutaneous technique is almost identical to the one used to treat AS, but some clarifications need to be made:

- Valvuloplasty before implantation is not performed.
- In AR of a native valve, there are generally no annulus calcifications (Fig. 29.6), while on the one hand, this reduces the incidence of complications due to the embolization of the calcium fragments during device expansion, and on the other, an important fluoroscopic landmarker to outline the annulus position and root anatomy is lost during valve release, which can be made more difficult, leading to major periprosthetic leaks. For an accurate positioning, some groups have advocated the use of two pigtail catheters for improved annular delineation (one catheter placed in the noncoronary sinus and the other in the left coronary sinus). Alternatively, transesophageal echocardiographic visualization can provide additional guidance but requires general anesthesia.

- Valve calcifications are an effective structure on which percutaneous biological devices can be anchored with a high radial force, reducing the risk of its migration and periprosthetic leaks to a minimum. For this reason, the use of rapid pacing is advisable for the deployment of the CoreValve/Evolut R for severe AR in order to decrease the regurgitant volume and systolic blood pressure, as well as the risk of prosthesis movement. It has been recommended that this be used at least from one-third frame deployment to two-thirds frame deployment. Indeed, this improves valve stability and reduces sudden movements and risk of valve dislocation during the one-third to two-thirds phases.
- Oversizing (significant more than 30% by area) of the device is advisable in AR without calcification to prevent dislocation and paravalvular regurgitation.

Due to all these technical challenges, valve deployment in an annulus without calcification and with a frequent concomitant dilation of the aortic root and/or the ascending aorta is more challenging and less predictable and can be complicated by supra-annular or ventricular dislocation of the prosthesis, the latter possibly occurring up to several hours after implantation.

The self-expanding Medtronic CoreValve (Medtronic, Minneapolis, Minnesota) has been used in the majority of cases due to its self-expanding frame with additional anchoring by means of support also against the ascending aorta [19]. Several newer-generation non-dedicated self-expanding transcatheter prostheses, such as the self-expandable and self-positioning ACURATE TA device (Symetis SA, Ecublens, Switzerland) and the self-expanding and repositionable Lotus Valve System (Boston Scientific, Marlborough, Massachusetts), have been investigated for the treatment of pure native AR [20, 21]. The risk of valve dislocation due to insufficient anchoring and annular rupture as a consequence of excessive oversizing have limited the use of these devices for native AR and prompted the development of dedicated devices enabling capture of aortic valve leaflets with specific clips to minimize the risk of valve embolization and paravalvular leaks. These more specific devices include the transapical, self-expanding JenaValve (JenaValve Technology, Munich, Germany) and J-Valve (JC Medical, Inc., Redwood City, California) [22, 23]. The JenaValve has three nitinol feelers, which facilitate "self-positioning" valve implantation. The three nitinol feelers and the frame of the prosthesis are integrated by an unmovable connection: each arm of the feelers is brought into the aortic sinuses, and the position of the prosthesis can be adjusted. The J-Valve has a self-expanding support frame connected movably with a three-prong clasper by three sutures; this movable connection allows adjusting the position of the prosthetic valve, while the clasper has already been placed in the aortic sinus. Thus, the claspers help in good positioning and also reinforce the anchoring of the prosthesis by clamping the native valve leaflets between it and the support frame.

In cases with a minimally calcified aortic annulus, the Helio transcatheter aortic anchoring device (Edwards Lifesciences) is another transfemoral system designed to enable annular fixation of a standard balloon-expandable SAPIEN XT transcatheter valve [24]. However, the Helio program has been interrupted.

29.5.3 Results

In 2013, the first and largest multicenter (14 centers) registry was published, including a total of 43 inoperable patients undergoing TAVR with the CoreValve prosthesis for the treatment of pure native AR [19]. The device success rate was 74.4%: eight patients required two transcatheter valves (18.6%), and nine patients (21%) had residual aortic regurgitation that was more than mild; one patient required conversion to open surgery [19]. The 30-day rate of major stroke was 4.7%. The all-cause mortality was 9.3% at 30 days and 21.4% at 12 months [19]. There was a strong correlation with absent valvular calcification [19]. Indeed, as stated above, absent aortic valve calcification may lead to reduced fixation of the lower part of the valve frame at the annulus during deployment, resulting in malpositioning. This may be exacerbated by enhanced movement of the prosthesis in the regurgitant jet. Dilation of the aortic root and ascending aorta, which is common in native AR, may also be a contributing factor. These limitations can be overcome by valve designs that are fully retrievable and repositionable, and valvular fixation can be improved even in the absence of calcifications.

The transapical TAVR with the use of the self-expandable and self-positioning ACURATE TA Symetis prosthesis in eight high-risk patients with pure severe AR was associated with no intraprocedural complications, with no stroke or deaths at 30 days, and with post-procedure AR grade I+ or lower in all eight patients [20].

The transapical, self-expanding JenaValve was associated with favorable clinical and hemodynamic results after 6 months in 31 patients [25]. Indeed, the implantation of the JenaValve was successful in 30 of 31 cases (97%); transcatheter heart valve dislodgement necessitated valve-in-valve implantation in one patient (3%) [25]. Post-procedural aortic regurgitation was none/trace in 28 of 31 (90.3%) and mild in 3 of 31 patients (9.7%) [25]. During follow-up, two patients underwent valvular reinterventions (surgical aortic valve replacement for endocarditis, valve-in-valve implantation for increasing paravalvular regurgitation) [25]. All-cause mortality was 13% at 30 days and 19% at 6 months [25]. A significant and persistent improvement in New York Heart Association class was observed [25].

In a recent report, six inoperable patients with native AR without significant valve calcification underwent successful transapical implantation of the J-Valve prosthesis [26]. During the follow-up period (from 31 days to 186 days), only one patient had trivial prosthetic valve regurgitation, and none of the patients had paravalvular leak of more than mild grade. There was no major postoperative complications or mortality [26].

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