Circulation: Cardiovascular Imaging

ADVANCES IN CARDIOVASCULAR IMAGING

Usefulness of Cardiac Magnetic Resonance Imaging in Aortic Stenosis

ABSTRACT: The objective of this review is to provide an overview of the role of cardiac magnetic resonance (CMR) in aortic stenosis (AS). Although CMR is undeniably the gold standard for assessing left ventricular volume, mass, and function, the assessment of the left ventricular repercussions of AS by CMR is not routinely performed in clinical practice, and its role in evaluating and quantifying AS is not yet well established. CMR is an imaging modality integrating myocardial function and disease, which could be particularly useful in a pathology like AS that should be considered as a global myocardial disease rather than an isolated valve disease. In this review, we discuss the emerging potential of CMR for the diagnosis and prognosis of AS. We detail its utility for studying all aspects of AS, including valve anatomy, flow quantification, left ventricular volumes, mass, remodeling, and function, tissue mapping, and 4-dimensional flow magnetic resonance imaging. We also discuss different clinical situations where CMR could be useful in AS, for example, in low-flow low-gradient AS to confirm the low-flow state and to understand the reason for the left ventricular dysfunction or when there is a suspicion of associated cardiac amyloidosis.

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Aortic stenosis (AS) is the most common valvular heart disease in developed countries with a prevalence increasing with age: only about 0.2% in adults between 50 and 59 years of age and mostly in bicuspid patients, but rises to 9.8% in octogenarians where the main cause is degenerative.[1] Although mortality is not increased in the absence of adverse prognostic factors when AS is asymptomatic, the mortality rate is very high when symptoms are present.[1,2] Consequently, current guidelines[3,4] recommend aortic valve replacement (AVR) for severe AS in symptomatic or selected asymptomatic patients. The two main challenges are, therefore, to accurately differentiate nonsevere from severe AS and to identify the asymptomatic patients with a high risk of adverse events. Transthoracic echocardiography (TTE) is the first-line imaging modality for the evaluation of AS, as it is noninvasive, widely available, and relatively inexpensive.[3–5] Indeed, TTE is the principal diagnostic tool for AS; it confirms the presence of AS and assesses the degree of valve calcification, as well as several parameters to grade AS severity, including peak jet velocity and mean transaortic pressure gradients, and provides an estimate of the aortic valve area (AVA) using the continuity equation.[3–5] TTE is also used as the first-choice imaging modality to assess left ventricular (LV) function and wall thickness, detect the presence of other associated valve diseases or

Key Words: aortic valve stenosis ■ magnetic resonance imaging ■ magnetic resonance spectroscopy ■ myocardium ■ prognosis

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aortic pathology, and provide prognostic information. Indeed, most of the parameters leading to surgery in asymptomatic patients (decreased LV ejection fraction [LVEF], highly increased peak aortic jet velocity, elevated pulmonary pressures, rapid progression…) are obtained by TTE. Although multislice computed tomography (CT) scan is mentioned in guidelines[3,4] as a complementary technique (particularly for the quantification of valve calcification) for evaluating AS in difficult cases, this is not yet true for cardiac magnetic resonance (CMR). However, several studies suggested the utility of CMR in evaluating and quantifying AS.[6–13] It is also increasingly recognized that CMR is the imaging modality of choice for the evaluation of AS repercussions on the LV. In this article, we discuss the emerging potential of CMR for the diagnosis and prognosis of AS. We detail its utility for studying all aspects of AS, including valve anatomy, flow quantification, LV volumes, mass, remodeling, and function, tissue mapping, and 4-dimensional (4D) flow magnetic resonance imaging (MRI). A summary of the advantages and limitations of the different CMR modalities in AS is provided in Table 1.

CMR FOR EVALUATING THE CONSEQUENCE OF AORTIC STENOSIS FOR THE LV

Characterization of LV Remodeling

The patterns of anatomic adaption for the chronic pressure overload observed in AS are heterogeneous. Indeed, on the basis of echocardiographic measurements of the LV mass and relative wall thickness,[14–16] 4 patterns have been described: normal ventricular geometry, LV concentric remodeling, concentric hypertrophy, and eccentric hypertrophy.[16] LV concentric remodeling (and hypertrophy) is a compensatory mechanism to normalize wall stress and maintain systolic function in AS. However, it is increasingly being associated with adverse clinical outcomes,[17,18] and it is thus crucial to be able to accurately identify these 4 patterns. Echocardiography is the most commonly used imaging technique to calculate the LV mass index, but it has several limitations relative to CMR (poor acoustic windows, misaligned LVs, difficulties in delineating the posterior wall, inaccurate estimation of the LV mass in the presence of asymmetrical hypertrophy, etc). Indeed, although CMR is less widely used in this setting, it is still the gold standard for assessing LV mass and wall thickness. Dweck et al[18] used CMR imaging to assess LV remodeling patterns in 91 patients with AS and found asymmetrical patterns of wall thickening to be common, as it was observed in 27% of patients. They proposed a new classification consisting of 6 distinct patterns of LV adaption, including normal geometry, concentric remodeling, asymmetrical remodeling, concentric hypertrophy, asymmetrical hypertrophy, and LV decompensation (eccentric hypertrophy).[19] They also demonstrated that the degree and pattern of hypertrophy are independent of the severity of AS. Recently, the same group[20] assessed the prognostic implication of such asymmetrical wall thickening in a prospective observational cohort study of 166 patients with AS. They found TTE to be less sensitive than CMR, missing a third of the cases of asymmetrical wall thickening, which was associated with increased myocardial injury, LV decompensation, and adverse events, acting as an independent predictor of AVR or death in this population.

According to most echocardiographic studies, sex appears to significantly influence LV remodeling, as men are more likely to have a higher LV mass, whereas women show more concentric remodeling.[21] Several CMR studies have also investigated sexual dimorphism in the myocardial response to AS.[22,23] Dobson et al[22] found that, despite similar baseline comorbidity and severity of AS, women had a lower indexed LV mass than men. In a study by Treibel et al,[23] CMR captured sexual dimorphism in LV remodeling, whereas TTE did not: CMR showed normal geometry and concentric remodeling to dominate in women versus concentric hypertrophy and eccentric hypertrophy in men, whereas TTE showed no significant sex-dependent differences in LV remodeling patterns.

The LV response and adaptation to AS is heterogeneous and appears to be independent of the severity of the valvular stenosis. Certain remodeling patterns are associated with worse outcome, and there may be sexual dimorphism in the myocardial response to AS. Echocardiography is less well suited for measuring wall thickness and limited by the availability of an acoustic window, whereas CMR has emerged as the gold standard for the noninvasive assessment of LV mass and wall thickness, allowing more precise classification of the various adaptive LV patterns. Whether early replacement of the aortic valve may be beneficial for asymptomatic patients with maladaptive LV remodeling is a major question and requires further studies using complementary TTE and CMR.

Assessment of LV Fibrosis

LV fibrosis in AS was first described in histopathologic studies[24] as part of the hypertrophic response: increasing myocyte size eventually leads to myocyte apoptosis and subsequent replacement fibrosis, possibly explaining the transition from hypertrophy to heart failure.[25] In AS, myocardial fibrosis (MF), defined by a significant increase in the collagen volume fraction of myocardial tissue, is a complex process involving at least 3 main alterations: endocardial thickening, subendocardial microscars, and diffuse interstitial fibrosis.[26] Although

Table 1. Advantages and Limitations of the Different CMR Modalities in AS

Technique	Advantages	Limitations
Aortic valve planimetry	Direct visualization of the stenotic orifice	Nonplanar orifice
	Reproducible	Highly calcified valve
	Useful in case of discordant echo findings or poor acoustic windows	Arrhythmia
		Different from the effective orifice area
Phase-contrast imaging	Good concordance with TTE	Specific sequences
	Reproducible	Time-consuming
	Useful in case of discordant echo findings or poor acoustic windows	Eccentric blood flow jets
		Risk of underestimation of velocity in case of incorrect placement of the section (not orthogonal to the flow)
		Risk of underestimation of AS severity in case of high flow velocities
LV remodeling characterization	Useful in cases of poor acoustic windows, misaligned LVs, asymmetrical hypertrophy	Classic CMR limitations: claustrophobia, respiratory artifacts, low availability, relatively high cost, time-consuming
	Gold standard for LV mass and wall thickness assessment	
	Reproducible	
LGE	Sole noninvasive technique allowing visualization and quantification of LV fibrosis	Only evaluates focal fibrosis
	Provides prognosis information	Requires intravenous access for gadolinium injection
		Risk of nephrogenic systemic fibrosis in case of severe renal failure
T1 mapping	Allows calculation of the ECV and interstitial fibrosis	Specific sequences
	Could be helpful for the assessment of the disease progression and of the response to AVR	Various protocols for T1 mapping
	Reproducible	Need to establish local reference range for T1 mapping values with healthy subjects
		Need a recent hematocrit value for the ECV calculation
4D flow	Dynamic quantification of blood with a full access to the 3-directional blood flow velocities	Specific sequences
	Assessment of eccentric blood flow jets such as in bicuspid aortic valves	Time consumption
	Understanding the flow dynamics and their repercussion on the aortic wall	Operator dependency
		Variety of sequence and analysis software
		Low availability

4D indicates 4 dimensional; AS, aortic stenosis; AVR, aortic valve replacement; CMR, cardiac magnetic resonance; ECV, extracellular volume; LGE, late gadolinium enhancement; LV, left ventricular; and TTE, transthoracic echocardiography.

myocardial biopsy is the gold standard to diagnose MF, it is invasive and suffers from certain limitations (mainly sampling errors and the inability to globally evaluate MF). CMR is the only noninvasive alternative that allows direct global assessment of MF,[27] using 2 approaches: late gadolinium enhancement (LGE) and myocardial T1 mapping. LGE permits the quantification of focal interstitial expansion, with direct visualization of focal replacement fibrosis, whereas myocardial T1 mapping assesses the diffuse interstitial expansion of fibrosis.

LGE in AS

The physiological basis of the LGE of MF is based on a combination of the increased volume of distribution for the contrast agent and a prolonged washout related to the decreased capillary density within the fibrotic myocardial tissue.[27,28] The increase in gadolinium concentration within fibrotic tissue causes T1 shortening, which appears as bright signal intensity in the CMR image, based on conventional inversion-recovery gradient echo sequences. In the normal myocardium, the contrast concentration in the extracellular space equilibrates rapidly with the blood pool, but in regions of MF, the extracellular space is greater, as a consequence of excessive collagen deposition. Consequently, gadolinium accumulates in these regions, and contrast wash out is delayed, producing differences in signal intensities between normal and abnormal myocardium.[27,29,30]

Focal MF (Figure 1) is a frequent finding in patients with AS,[31,32] usually with a midwall scar pattern different from that of myocardial infarction and is associated with increased myocardial injury, diastolic and systolic dysfunction, and adverse outcomes.[33,34] In 143 patients with moderate-to-severe AS, focal MF was shown to be an independent predictor of death, with a more than an 8-fold increase in all-cause mortality, despite similar severity of AS, and the prognosis worsened with the increasing burden of fibrosis.[31] Focal MF is also a potential marker of increased perioperative risk in AVR, as it was shown to be associated with a significantly higher rate of 30-day mortality and major adverse cardiac and cerebrovascular events in a prospective study of 63 patients undergoing AVR for severe AS.[35] Furthermore, focal MF may be associated with incomplete LV functional recovery and worse cardiovascular outcomes after AVR.[32,35,36] A recent meta-analysis concluded that focal MF assessed by CMR-LGE is a promising risk stratification method as it predicts all-cause and cardiovascular mortality in patients with AS.[37] All of the above studies were relatively small, and a British consortium has recently published a large multicenter CMR study[38] of 674 patients with severe AS undergoing surgical or transcatheter AVR (TAVR). They found that preoperative focal myocardial scars were frequent (>50% of patients) and independently associated with mortality, their presence being associated with a 2-fold higher late mortality.[38]

T1 Mapping in AS

The main limiting factor of LGE-CMR is that the process of fibrosis is often diffuse, and thus normal nonfibrotic myocardium as a frame of reference is often lacking. This can result in underestimation of the true extracellular matrix burden due to interstitial fibrosis. Contrast-enhanced T1 mapping has been developed to address this issue, allowing the quantification of diffuse fibrosis, as it does not rely on contrasting signal intensity.[26,39,40] This is an evolving technique, which improves myocardial characterization by its ability to quantify T1 value for each voxel in the myocardium,[30] generating a parametric T1 map (Figure 2). Various T1 mapping approaches have been investigated and validated against the extent of MF by histology.[41–43] Each has its own advantages and limitations, and the optimal T1 image analysis strategy is still a subject of debate.[39,44,45] In AS, most studies have used native T1 or the extracellular volume (ECV) fraction, which corrects for the blood pool and the plasma gadolinium volume of distribution.[30,39,45–47] According to Chin et al,[48] ECV appears to be a promising measure of diffuse MF, based on its superior reproducibility and ability to differentiate diseases from healthy tissue. However, native T1 and ECV may show major overlap with values in control groups and little difference among patients with mild, moderate, and severe AS.[39,48] To solve this issue, Chin et al[39] developed a novel parameter, the indexed ECV, which modifies the ECV fraction to act as a measure of the total volume of the extracellular compartment in the LV. This parameter might be used to estimate the total burden of MF by multiplying the ECV fraction with the indexed LV myocardial volume normalized to the body surface area and, therefore, combined the prognostic information provided by the ECV fraction, with the improved discrimination between groups associated with indexed LV volume into a single measure.[39] In the same study, the authors proposed a threshold of 22.5 mL/m^2 to differentiate a healthy myocardium from a diseased myocardium infiltrated by diffuse fibrosis. This categorization was of prognostic value with a gradual increase in all-cause mortality.[39] Many studies have demonstrated a correlation between diffuse fibrosis assessed by myocardial T1 mapping and AS severity, LV mass, and cardiac performance.[48–50] Although the prognostic implication of focal MF assessed by LGE in AS has been extensively studied with large numbers of patients, data on the prognostic value of the ECV fraction are currently scarce. According to Lee et al,[46] a high native T1 value on noncontrast T1 mapping CMR may be an independent predictor of adverse outcomes in patients with significant AS providing further risk stratification, regardless of the presence of LGE. Recently, Everett et al[51] reported in a multicenter international study of 440 patients with severe AS awaiting AVR that the ECV fraction is associated with multiple markers of

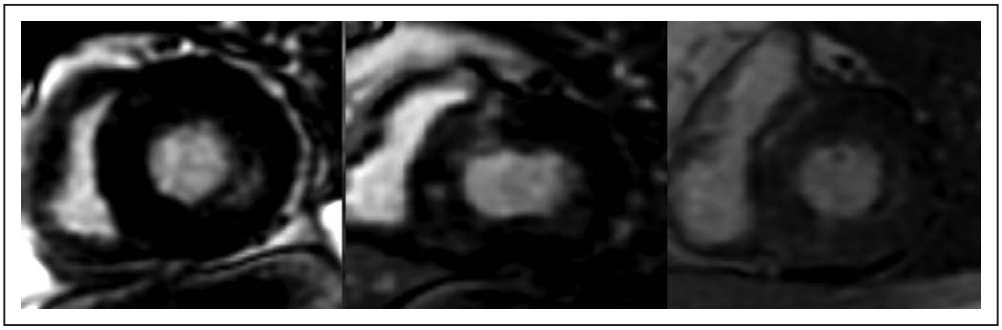

Figure 1. Different type and localization of focal myocardial fibrosis assessed by late gadolinium enhancement in 3 patients with severe aortic stenosis.

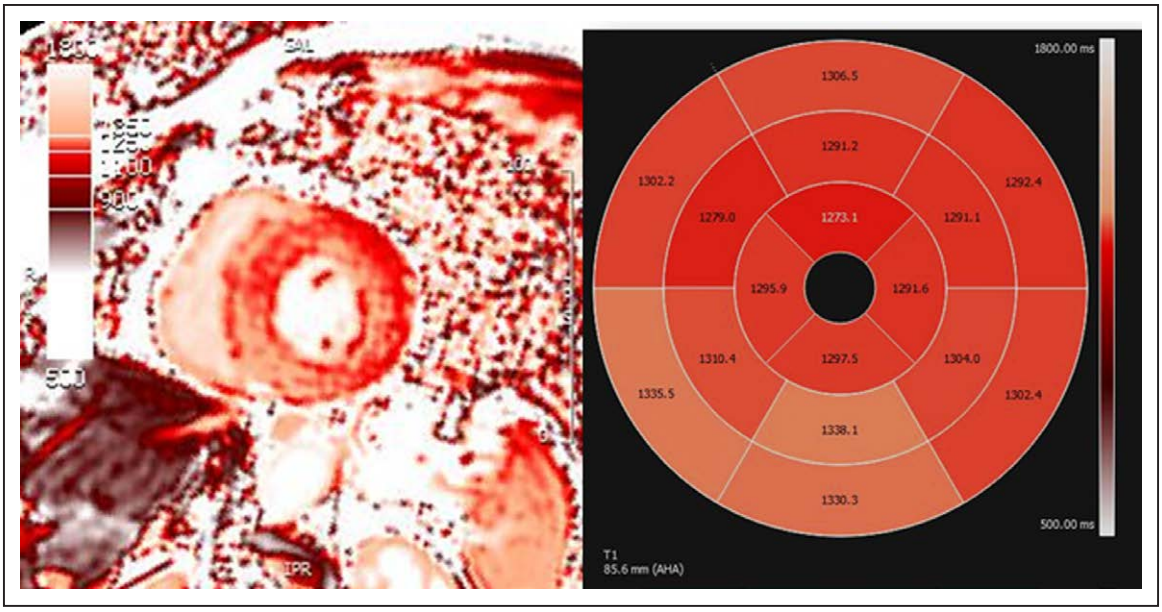

Figure 2. Segmental analysis of T1 maps in a patient with severe aortic stenosis.

LV decompensation including symptoms, atrial volume, LV mass, and lower LVEF and is independently associated with all-cause and cardiovascular mortality.

Unlike focal MF detected by LGE-CMR, which is a common finding in patients with AS, and appears to be irreversible, diffuse interstitial fibrosis may be a potential treatment target,[52–54] and its quantification by T1 mapping could be used to assess the progression of the disease. Interstitial fibrosis is diffusely distributed, reflecting the progressive nature of the disease, and precedes irreversible replacement fibrosis in which cellular damage and cardiomyocyte necrosis/apoptosis appear.[29] There is thus clinical interest in its assessment for the management of patients with AS. Although T1 relaxation time increases with the field strength,[55] T1 mapping combined with LGE could more precisely characterize myocardial tissue characterization, and this combination appears to provide the best stratification of AS patients.[26] This combined multiparametric approach with T1 mapping and LGE may also help to improve our understanding of the disease, monitor AS progression and treatment response, and eventually guide treatment strategies.

Assessment of LV Reverse Remodeling After AVR

According to echocardiographic studies, LV hypertrophy decreases by 20% to 30% 1 year after AVR,[56–58] and this reduction in mass may be associated with better survival.[57,59] CMR appears to be superior to echocardiography for assessing post-AVR regression of LV hypertrophy.[60,61] Whether such regression is cellular, interstitial, or both has been difficult to ascertain until recently.[62] Most CMR studies agree that cellular hypertrophy and diffuse fibrosis may be reversible after AVR, whereas focal MF is irreversible.[44,62] Treibel et al[62] studied 116 patients with severe AS undergoing surgical AVR and showed a 19% reduction in indexed LV mass 1 year post-AVR, caused by a 22% reduction in cellular volume and a 16% decrease in matrix volume. However, focal MF assessed by LGE did not change in absolute terms (LGE in g/m^2) but expressed as a percentage of the regressed LV mass, focal MF (LGE as %) increased post-AVR. Multivariate analysis showed high baseline LV mass, elevated baseline NT-proBNP (N-terminal pro-B-type natriuretic peptide) levels, and high baseline ECV to be independently associated with greater matrix volume regression.[62] Everett et al[45] showed a 19% reduction in the LV mass index and an 11% reduction in indexed ECV at 0.9±0.3 years after surgery in a study of 38 symptomatic AS patients who underwent AVR. In contrast, focal MF did not change post-AVR, with no evidence of regression, even after 2 years. In the same study, 61 asymptomatic AS patients were also followed by systematic CMR, and patients with baseline focal MF demonstrated particularly rapid increases in scar burden (78% increase in LGE mass per year). The authors consequently suggested that, given the adverse prognosis associated with midwall fibrotic burden, prompt AVR at the first sign of focal MF assessed by LGE, or just before its development, may improve long-term patient outcomes.[35] Furthermore, Dobson et al[63] showed that patients with baseline midwall LGE had lower LV mass regression than those without scars in a study of 57 AS patients undergoing TAVR.

Determining the ideal timing of AVR is still the greatest challenge in AS. Ideally, surgery should be performed before irreversible changes occur in the myocardium. Indeed, rather than an isolated valve disease, AS is more

a global disease potentially affecting the entire myocardium. An echocardiographic prognostic classification has been recently proposed, characterizing in 4 stages the extent of anatomic and functional cardiac lesions associated with AS: stage 0, no damage; stage 1, LV damage; stage 2, left atrial or mitral damage; stage 3, pulmonary vasculature or tricuspid damage; and stage 4, right ventricular damage.[64] CMR-based techniques provide additional and reliable information regarding repercussions of AS on the left and right ventricles and could be an essential tool to better determine the stage of cardiac damages in AS. To date, current guidelines[3,4] have not incorporated CMR for risk stratification or the management of patients with AS. Randomized trials are needed to determine whether the use of fibrosis imaging biomarkers can improve outcomes of asymptomatic patients with AS. The EVOLVED-AS study (Early Valve Replacement Guided by Biomarkers of LV Decompensation in Asymptomatic Patients With Severe AS; NCT03094143) is an ongoing trial that should answer this crucial question. This multicenter, randomized controlled trial is assessing whether early valve intervention in patients with asymptomatic severe AS and midwall fibrosis by CMR improves clinical outcomes compared with standard care.

CMR FOR AORTIC STENOSIS QUANTIFICATION

Aortic Valve Planimetry

Classic limitations of TTE are patients with poor acoustic windows, flow alignment difficulties, inaccurate aortic annulus diameter measurement, subvalvular flow acceleration, and mostly discordant or inconclusive findings in the grading of AS severity (AVA <1 cm^2 and mean pressure gradient <40 mm Hg) underscoring the need for a multimodal approach. In these difficult cases, the direct evaluation of the AVA by planimetry can be performed by transesophageal echocardiography, or the Gorlin formula can be used during cardiac catheterization for the evaluation of the AVA. However, these 2 techniques are invasive, and the use of the Gorlin equation to estimate the AVA is associated with several sources of error.[65] CMR planimetry of the AVA is reproducible, observer independent, and correlates well with transesophageal echocardiography measurements[6] but also with Gorlin method.[7] However, the direct planimetry of the stenotic aortic valve (Figure 3) is prone to measurement errors, especially if there is a nonplanar orifice or severe calcified AS, which can cause signal void and make border discrimination of the valve leaflets difficult. Furthermore, ECG gating may be a source of reduction in image quality in patients with arrhythmias. It must also be emphasized that planimetry measures the anatomic orifice area, whereas the continuity equation estimates the effective (functional) orifice area and that these 2 areas may differ markedly, depending on the magnitude of the flow contraction downstream of the valve.[66] Indeed, there is generally an overestimation of the AVA when using direct planimetry compared with the continuity equation,[66] which must be accounted, to avoid an inappropriate grading of AS. Furthermore, there is no validated threshold to define severe AS by planimetry. Consequently, the direct planimetry of the stenotic aortic valve appears useful when its area is <1 cm^2, and no conclusion can be drawn when the planimetry is between 1 and 1.3 cm^2 because the mean differences between the planimetry and the continuity equation are between 0.10±0.17 and 0.11±0.18 cm^2.[7,13] However, one can be reassured about the absence of severe AS when the planimetry is >1.5 cm^2. It is important to underline that to define severe AS, current guidelines recommend the use of the continuity equation sometimes supplemented by the calcium score, which have well-defined thresholds[3] supported by extensive prognostic data. Therefore, CMR anatomic measurements should not be used for clinical decision-making in AS, particularly for referring a patient for AVR as there is no validated prognostic threshold. Thus, to date, a planimetry <1 cm^2 can only be used as a strong argument in favor of severe AS.

Velocity-Encoded CMR for Quantifying AS

Caruthers et al[8] proposed 2-dimensional (2D) CMR velocity-encoded images using the continuity equation to estimate the AVA. They showed in 24 AS patients imaged with CMR and echocardiography excellent correlation coefficients between these 2 modalities for pressure gradients and AVA. It is important to point out that the evaluation of the peak jet velocity is underestimated by CMR due to its lower temporal resolution than echocardiography. Therefore, when the peak jet velocity is recorded on CMR as >4.0 m/s, one can be confident that the AS is severe. In a study by Garcia et al[9] CMR revealed that the shape of the LV outflow tract (LVOT) cross section is typically oval and not circular. As a consequence, TTE tended to underestimate the LVOT cross section relative to CMR, whereas TTE overestimated the LVOT velocity-time integral, and a good concordance was observed between the 2 techniques for estimating aortic jet velocity-time integral, leading to a good correlation and concordance between TTE- and CMR-derived AVA.[9] Hakki formula,[10] which is a simplified version of the Gorlin formula (AVA=cardiac output [L/min]/$\sqrt{}$gradient [mm Hg]),[67] has also been used to treat CMR velocity-encoded images to estimate the AVA. In 2010, Puymirat et al[10] reported excellent correlations between Hakki formula and the continuity equation but also with planimetry.[8] The evaluation of the AVA and hemodynamic parameters in the 3 aforementioned studies was based on manual delineation of the aortic valve and the LVOT, which is subjective

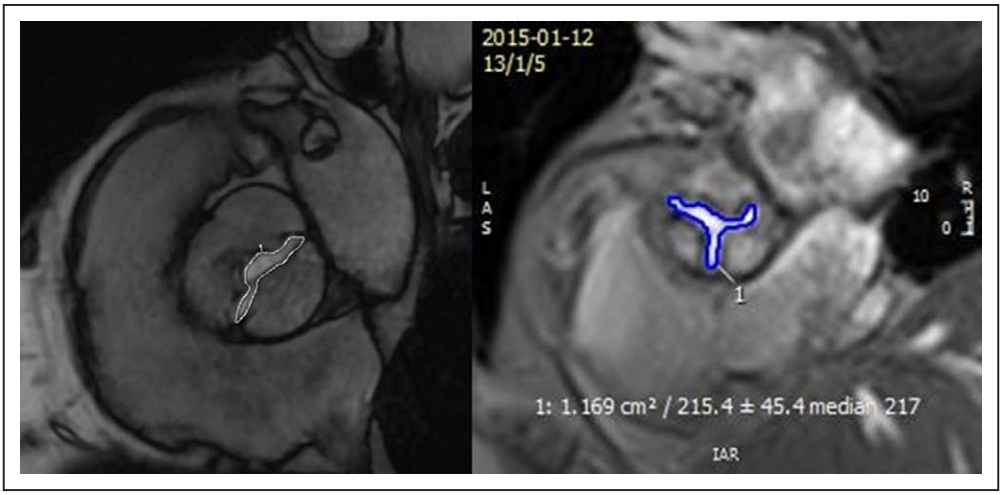

Figure 3. **Aortic valve planimetry in a bicuspid valve aortic stenosis (left) and a tricuspid valve aortic stenosis (right).**

and time-consuming, limiting the utility of CMR for assessing AS in clinical practice. To offset this problem, Defrance et al[11] performed a semiautomated analysis of aortic hemodynamics from phase-contrast CMR providing a reproducible and accurate evaluation of the AVA, aortic velocities, and gradients with values similar to those obtained by TTE. Valenti et al[12] emphasized that the assessment of aortic pressure gradient by using the phase-contrast sequences derived is subject to potential sources of error and tested the ability of an additional noninvasive parameter to estimate pressure gradients in AS by CMR. It consisted of the indirect calculation of the gradient from the cardiac output and AVA, by using the inverse simplified Gorlin formula (cardiac output/AVA)—a method that can be used without the acquisition or analysis of phase-contrast images. They found this parameter to show a higher correlation with LV mass than phase-contrast sequence–derived pressure gradients and to be more reproducible.[12]

These previous studies[6–12] were all performed using 1.5-Tesla CMR systems. However, MRI systems with higher magnetic field strengths (3 Tesla) have become widely available and allow a better signal-to-noise ratio through the use of parallel imaging, along with faster acquisition, that can be used to provide higher spatial or temporal resolution.[55] Levy et al[13] have evaluated the feasibility and reproducibility of the AVA assessment and the concordance between TTE and 3-Tesla CMR for the evaluation of AS severity. They found an excellent inter- and intraobserver reproducibility of the CMR measurements and that direct CMR planimetry tended to overestimate the AVA (bias=0.11±0.18 cm^2), whereas the Hakki formula underestimated it (bias=–0.11±0.17 cm^2) relative to TTE.

Different imaging modalities are available for AS quantification, each with its own advantages and limitations (Table 2). Although echocardiography is still the gold standard for evaluating and quantifying AS, CMR appears to be a feasible, radiation-free, and reproducible imaging modality for estimating AS severity. The continuity equation approach, with the use of velocity-time integral data, is adapted from current echocardiographic methods and appears to be robust and easy to perform. Underestimation of the LVOT diameter by TTE is compensated by overestimation of the LVOT velocity-time integral, resulting in good concordance between TTE and CMR for the estimation of AVA. Thus, CMR provides a noninvasive and reliable alternative to Doppler echocardiography for the quantification of AS severity. However, the use of CMR for the assessment of the severity of AS should be reserved for cases where Doppler echocardiographic calculation of the AVA is difficult and meets limitations (poor acoustic windows, difficulties in LVOT measurements or for alignment of the Doppler probe with the flow, or in case of high subaortic velocities like in the presence of a septal bulge or severe hypertrophy), or when the assessment of the ascending aorta is not possible by TTE, or when the results are discordant (ie, discordance between symptoms and echocardiographic evaluation, low gradient and AVA <1 cm^2). It is important to note that in case of low-flow low-gradient severe AS with normal or reduced ejection fraction, CMR has currently a limited role in terms of diagnosis and is not included in recent position papers or guidelines. Indeed, due to the low-flow condition, the maximum potential valve area may be underestimated by CMR direct planimetry of the stenotic valve. CMR is, therefore, not helpful in differentiating between pseudosevere and severe AS. However, CMR has an essential role in this setting to confirm the low-flow state, to assess the LV systolic, and to help in determining the myocardial substrate using T1 and T2 mapping and LGE.

CMR is not a first-line examination, but its main advantages compared with CT scan are that it is nonirradiating, does not use iodinated contrast agents, and

Table 2. Advantages, Limitations, Threshold for Intervention, and Indication of Different Imaging Modalities to Assess the Severity of AS

	Advantages	Limitations	Threshold for Severe AS	Indication
TTE	Gold standard for AS evaluation	Poor acoustic windows	AVA ≤1 cm^2 or 0.6 cm^2/m^2 using the continuity equation	First-line examination
	Large availability	Difficulties for alignment of the Doppler probe with the flow	Peak aortic jet velocity ≥4 m/s	All patients with AS
	Low cost	Difficulties for LVOT measurements in heavily calcified valves	Mean pressure gradient ≥40 mm Hg	Exercise stress echocardiography may provide prognostic information in asymptomatic AS by assessing the increase in mean pressure gradient and change in LV function during exercise
	Provides information on valve calcification (subjective), valve morphology and mobility, cause, and severity of AS	High subaortic velocities (septal bulge, severe hypertrophy)		
	Provides information on AS consequences on LV function	Assumptions of the continuity equations are not always true (circular LVOT and laminar flow profile)		
	Can be combined with stress/dobutamine to evaluate hemodynamic response to stress			
TEE	High spatial resolution	Invasive	AVA ≤1 cm^2 using the continuity equation	Second-line examination
	Provides information on valve calcification (subjective) and valve morphology and mobility	6-h fasting	Not clear using planimetry (but probably severe when AVA <1 cm^2)	Poor acoustic windows
	Provides additional evaluation of concomitant valvular heart disease	Contraindications to TEE		Difficulties in LVOT measurements/alignment with the flow or in case of high subaortic velocities
	Planimetry of the stenotic valve (better in 3D with multiplanar review)	Good alignment with the flow can be difficult and requires a transgastric view		Imaging aorta if not seen clearly on TTE
	Precise measurement of the LVOT diameter	2D planimetry can be challenging in case of severe calcifications		Discordance in AS grading (AVA <1 cm^2 and mean pressure gradient <40 mm Hg)
	Planimetry of the LVOT area in 3D (with multiplanar review)	More operator- and image quality-dependent than CT		Combined or mixed valvular heart disease
				Before TAVI to evaluate the aortic annulus and the ascending aorta if CT is not feasible
Multislice CT	High spatial resolution	Lower availability than TTE	Likely if calcium score >2000 in men and 1200 in women and likely if >3000 and 1600, respectively	Second-line examination
	Good visualization of the aortic valve	Low temporal resolution	Not clear using planimetry (but probably severe when AVA <1 cm^2)	Poor acoustic windows
	Provides information about the aortic valve morphology, LV dimensions, coronary artery anatomy, coronary ostia localization, leaflet length, aortic annulus size, and aortic root morphology and dimensions	Arrythmias	A cutoff of 1.2 cm^2 by fusion imaging is associated with adverse outcome	Difficulties in LVOT measurements/alignment with the flow or in case of high subaortic velocities
	Objective evaluation of aortic valve calcification by calcium scoring	Irradiating		Imaging aorta if not seen clearly on TTE

(*Continued*)

Table 2. Continued

	Advantages	Limitations	Threshold for Severe AS	Indication
	Accurate measurement of anatomic AVA by planimetry	Injection of iodinated agent for contrast CT		Discordance in AS grading (AVA <1 cm^2 and mean pressure gradient <40 mm Hg)
	Possibility to perform fusion imaging with TTE using the planimetry of the LVOT area by CT	Does not provide information on V_{max} or gradients		Contraindications to TEE or refusal by the patient
				Gold standard before TAVI for procedure planification
CMR imaging	See Table 1 for specific advantages of each CMR modality	See Table 1 for specific limitations of each CMR modality	Not clear using planimetry (but probably severe when AVA <1 cm^2)	Second-line examination
	Accurate measurement of anatomic AVA by planimetry	Low availability	Good correlation between the continuity equation by phase-contrast imaging and by TTE but no data on outcome	Contraindication to CT (severe renal failure or allergy to iodinated contrast agents) or TEE and (1) poor acoustic windows, (2) difficulties in LVOT measurements/alignment with the flow or in case of high subaortic velocities, (3) imaging aorta if not seen clearly on TTE, (4) discordance in AS grading (AVA <1 cm^2 and mean pressure gradient <40 mm Hg)
	Provides noninvasive myocardial tissue characterization	Costs		Need to assess accurately LV function, volumes, or mass or to look for fibrosis
	Provides dynamic quantification of blood flow	Duration of the examination		Assessment of combined AS and aortic regurgitation
	Possibility to perform fusion imaging with TTE using the planimetry of the LVOT area by CMR	Contraindication to CMR		In suspected LFLG AS and preserved LVEF, low-flow state may be confirmed by CMR flow measurements according to ESC Guidelines 2017
	Precise evaluation of myocardial mass and LV function	Claustrophobia		Evaluation of myocardial viability/understanding the etiology of LV dysfunction in LFLG AS with reduced LVEF
	Evaluation of myocardial focal (LGE) and diffuse fibrosis	Does not provide information on calcifications		Suspicion of concomitant amyloidosis
	Precise evaluation of aortic dimensions and measurement of aortic annulus pre-TAVI	Inferior to CT with regard to assessment of inner vessel dimensions and calcifications for pre-TAVI assessment		Before TAVI if CT is contraindicated

2D indicates 2 dimensional; 3D, 3 dimensional; AS, aortic stenosis; AVA, aortic valve area; CMR, cardiac magnetic resonance; CT, computed tomography; ESC, European Society of Cardiology; LFLG, low flow low gradient; LGE, late gadolinium enhancement; LV, left ventricular; LVEF, left ventricular ejection fraction; LVOT, left ventricular outflow tract; TAVI, transcatheter aortic valve implantation; TEE, transesophageal echocardiography; and TTE, transthoracic echocardiography.

provides functional information in addition to anatomic data. However, CMR is clearly inferior to CT scan with regard to assessment of aortic valve calcifications, which are not measurable by CMR. Thus, CMR can be a noninvasive alternative to transesophageal echocardiography or catheterization in certain cases of discordant grading by standard assessment (TTE and calcium scoring by CT scan). It is although noteworthy, that unlike echocardiography, none of the CMR assessments of peak velocity or AVA have been validated against clinical outcomes. Therefore, CMR is not recommended in the current guidelines for assessing the severity of AS, and data are required before using these CMR measurements for clinical decision-making.

4D FLOW MRI IN AORTIC STENOSIS

4D flow MRI, or time-resolved 3-dimensional phase-contrast MRI, is an alternative to TTE and 2D phase-contrast CMR to noninvasively measure blood flow velocities, as it can provide a dynamic quantification of blood flow in both the heart and the great vessels with good spatial and temporal resolutions and with a full access to the tridirectional blood flow velocities

(Figure 4).[68–70] Indeed, velocity data are acquired in an entire volume of interest, enabling blood flow quantification during postprocessing in any desired orientation. This technique is consequently more appropriate for the accommodation of eccentric blood flow jets in the assessment of peak velocity than 2D phase-contrast CMR.[68] In a study of 34 patients with bicuspid aortic valves, Rose et al[68] showed that 4D flow MRI velocity measurements were more accurate than those obtained by 2D phase-contrast CMR and similar to Doppler echocardiography measurements.

The quantification of turbulence kinetic energy (TKE) using 4D flow MRI has been introduced as an alternative method for predicting the turbulence energy loss of the blood flow through the aortic valve. Ha et al[71] suggested in an in vitro study that TKE measurement may provide a potential benefit as an energy loss index to characterize blood flow through the aortic valve; however, in vivo measurements of TKE were not consistent with the transvalvular pressure gradient. Binter et al also found a weak correlation between mean pressure gradient and TKE (R^2=0.26), but it is interesting to note that patients with dilated ascending aorta and those with bicuspid aortic valves had increased TKE measurements due to higher energy losses. They concluded that TKE allows a quantification of the influence of valve morphology and ascending aorta geometry on the hemodynamic burden of AS, information that is not assessable by current echocardiographic measures.[72] Dyverfeldt et al[73] found that TKE values in the ascending aorta are also well correlated to poststenotic pressure loss in AS patients as TKE was significantly higher in patients with AS than in normal volunteers and strongly correlated to index pressure loss (R^2=0.91).

The calculation of the effective aortic valve orifice area using 2D phase-contrast CMR and the continuity equation requires measurements that are susceptible to error. As an alternative, Garcia et al[74] proposed a new method called jet shear layer detection (using a mathematical method that provides an accurate and simple means of separating the jet-like zone from the recirculation zone just downstream of the stenotic valve and then defines the area of the vena contracta, ie, the effective orifice area), allowing a better assessment of the effective valve orifice area. However, this technique can be problematic in cases with highly eccentric flow, such as bicuspid aortic valves, for which accurate placement is not easily feasible. Thus, the same team applied the jet shear layer detection method using 4D flow MRI to assess the effective orifice area and found a good correlation and agreement with 2D phase-contrast CMR measurements.[75]

Finally, a few studies using 4D flow MRI have shown that AS is associated with an abnormal blood flow pattern and increased wall shear stress in the ascending aorta compared with healthy volunteers.[76–78] Guzzardi et al[77] showed in a study of 20 bicuspid patients undergoing ascending aortic resection that these regions of increased wall shear stress assessed by 4D flow MRI correspond with extracellular matrix dysregulation and elastic fiber degeneration in the ascending aorta. Recently Farag et al[79] reported that the extent of increased wall shear stress in the ascending aorta of bicuspid patients is most pronounced in the presence of AS and a nondilated ascending aorta.

4D flow MRI appears to be a promising technique in AS, both for the assessment of difficult cases, especially for bicuspid valves, and a better pathophysiological understanding of this disease, notably the flow dynamics and its repercussion on the aortic wall.

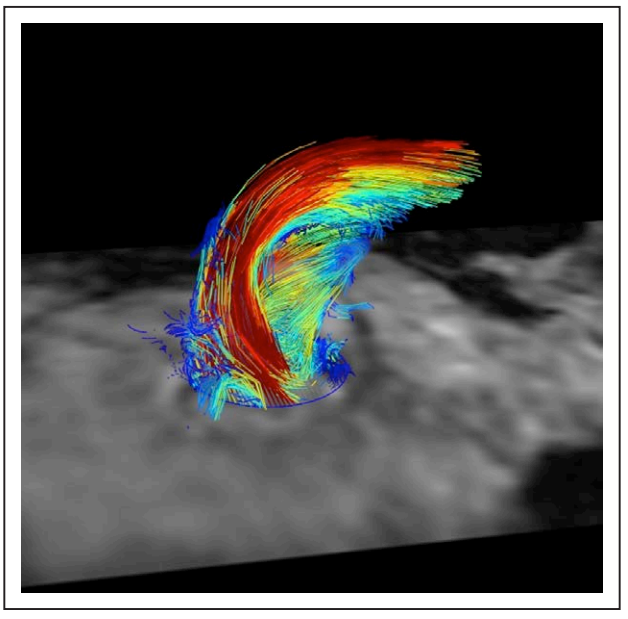

Figure 4. Representative examples of systolic 3-dimensional velocity fields in the ascending aorta obtained by 4-dimensional flow magnetic resonance imaging in a patient with severe aortic stenosis.

OTHER CLINICAL SITUATIONS WHERE CMR MIGHT BE USEFUL IN AORTIC STENOSIS

- Accurate measurement of the aortic annulus is crucial before TAVR for appropriate prosthesis sizing to minimize the risk of paravalvular leak. In daily practice, CT-scan angiography is the most commonly used method. However, some patients may be unsuitable for the administration of iodinated contrast, such as those with severe renal failure. Noncontrast CMR appears to be a promising alternative modality to provide aortic annulus measurements.[80,81] In a study of 133 patients undergoing TAVR, aortic root measurements made by both CMR and CT-scan angiography

were highly reproducible and showed close agreement.[80] Furthermore, CMR could also be considered as an alternative for planning valve-in-valve procedures in patients with preexisting bioprostheses and advanced chronic kidney disease.[81]

- The association of AS with ascending aorta enlargement is common, especially in patients with bicuspid aortic valve.[82] According to the current guidelines, combined aortic and valve surgery is recommended at significantly lower thresholds (45 mm) than for isolated ascending aorta aneurysms (55 mm).[3] The evaluation of valve morphology and accurate aortic diameters is, therefore, crucial. However, the bicuspid or tricuspid character of the aortic valve may be difficult to identify by TTE in cases of severe calcification, and it is sometimes difficult to properly visualize the ascending aorta, especially if there is a poor acoustic window. CMR imaging can depict aortic valve morphology and allows excellent characterization of the valve phenotype in patients with bicuspid valves even in the presence of calcification.[83,84] With its ability to delineate the intrinsic contrast between blood flow and vessel wall, MRI is well suited for aortic measurements. In cases of a diameter >45 mm measured by TTE, a measurement with another imaging modality is indicated.[85] MRI does not require ionizing radiation or iodinated contrast and is, therefore, highly suitable for aortic measurements, especially in cases of serial follow-up studies in (younger) patients with known aortic dilatation. The external diameter should be measured perpendicular to the axis of blood flow for measurements taken by MRI, and the widest diameter, typically at the mid-sinus level, should be used for aortic root measurements.[86]
- The combination of AS and aortic regurgitation is a common condition.[87] However, the assessment of the severity of aortic regurgitation by TTE can be challenging in patients with associated AS because of calcification. CMR provides highly reproducible quantification of aortic regurgitation using phase-contrast velocity-encoded assessment of anterograde and retrograde flow at the sinotubular junction, thereby allowing quantification of the regurgitant volume and regurgitant fraction.[88] In cases of mixed aortic valve disease, the velocity-encoding limit should be changed to a higher value to avoid underestimation of the peak velocity.[89] Aortic regurgitation assessment by comparison of the forward aortic flow and pulmonary forward flow by CMR can also be useful for patients with combined aortic stenosis, in whom the higher velocity encoding leads to underestimation of regurgitant volume.[89]
- Degenerative AS and age-related transthyretin cardiac amyloidosis share common demographic and clinical characteristics. According to Scully et al[90] and Castano et al,[91] 13.9% to 16% of patients undergoing TAVR have occult cardiac amyloidosis diagnosed by technetium-99 m pyrophosphate cardiac scintigraphy. Certain echocardiographic features can be suggestive of this association, such as a low-flow low-gradient AS, inappropriate LV hypertrophy, an average tissue Doppler mitral annular S′ of <6 cm/s, or an apical sparring strain pattern.[90–92] However, confirmation by another imaging technique is required to make this diagnosis. CMR is an excellent way to noninvasively diagnose cardiac amyloidosis. For tissue characterization, the typical CMR findings of cardiac amyloidosis include diffuse subendocardial or transmural LGE on late gadolinium imaging with nulling of the blood pool and elevated native T1 and ECV on T1 mapping sequences (Figure 5).[93,94] The use of T1 mapping for the diagnosis of associated amyloidosis may be challenging in patients with AS.
- CMR may be useful in the situation of low-flow low-gradient severe AS with reduced LVEF to understand the reason for LV dysfunction, which can be due to AS but also to myocardial infarction or other pathologies. In addition, CMR permits the detection and quantification of MF, providing additional prognostic information, which can influence decisions on whether or not to intervene on the stenotic valve. Low-dose dobutamine echocardiography is currently recommended in this setting to assess the presence of LV flow reserve and thus to distinguishing between truly severe AS from pseudosevere AS.[3] According to the study of Rosa et al,[95] patients with low-flow low-gradient AS and reduced LVEF have higher ECV fraction, indexed ECV, and LGE mass compared with high-gradient AS, but the degree of MF is similar in patients with flow reserve to those without flow reserve questioning the independent prognostic value of the flow reserve in these patients.
- In case of asymptomatic severe AS, LVEF has a central place in the current guidelines, and AVR must be performed if LVEF is <50%.[3,4] Indeed, LVEF is a powerful and independent predictor of mortality in these patients.[96] However, LV structural and functional abnormalities may exist despite preserved LVEF,[31,32,39,97] highlighting the need to identify other parameters to assess earlier the LV consequences of AS-related pressure overload. LV global longitudinal strain assessed by TTE is also an independent predictor of outcome in AS.[97,98] According to an individual participant data meta-analysis, LV global longitudinal strain is relatively homogeneous across available published cohorts

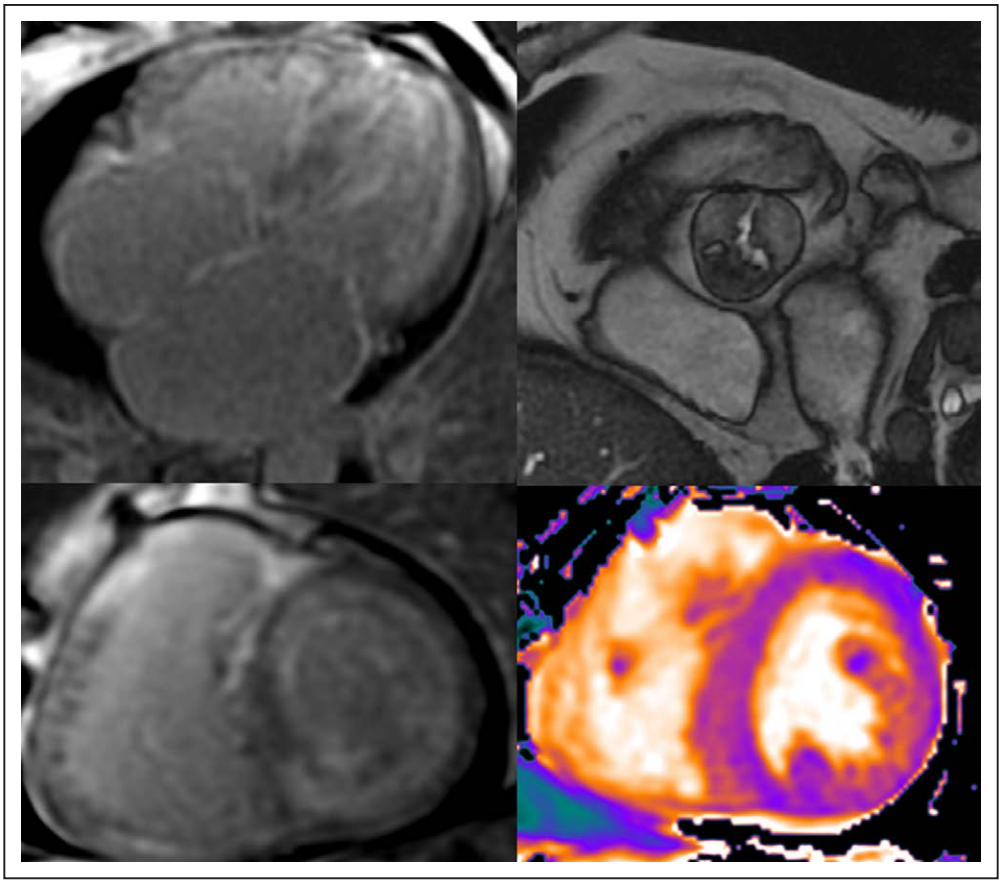

Figure 5. Association of transthyretin cardiac amyloidosis and severe aortic stenosis in a patient of 85 y.
Presence of a diffuse subendocardial and transmural late gadolinium enhancement (**upper left** and **lower left**), elevated native T1 (**lower right**), and limited opening of a tricuspid aortic valve (**upper right**).

of AS patients, and a value >−14.7% is associated with more than a 2.5-fold increase in risk of death even when LVEF is ≥60%.[97] Global longitudinal strain can also be assessed by CMR feature tracking. This technique appears reproducible and is predictive of mortality in dilated cardiomyopathy, besides LVEF and LGE.[99] There are currently still no prognostic data using this technique in AS, but a series of 63 patients with severe AS and preserved LVEF reported an association between preoperative LV global longitudinal strain assessed by CMR feature tracking and LV mass regression post-AVR.[100]

CONCLUSIONS

Echocardiography is, and will probably always be, the cornerstone of AS evaluation. CMR appears to be a good alternative to more invasive techniques (cardiac catheterization and transesophageal echocardiography) in AS, when TTE results are equivocal or in case of poor echocardiographic windows without exposing the patient to ionizing radiation. As disease presentation and progression can vary, the main utility of CMR in AS appears to be its ability to better stratify patients according to their myocardial response in terms of fibrosis and morphological and functional cardiac alterations. 4D flow MRI is a promising technique both for the assessment and understanding of AS pathophysiology, notably flow dynamics and their repercussion on the aortic wall. However, further prospective studies are necessary before patients can be referred for AVR based solely on CMR findings. Despite its relatively low availability and its operator dependency, CMR is expanding, and improvements in techniques and technologies should enhance its utility in routine clinical practice.

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Sources of Funding

This work was supported by the French Government through the National Research Agency Program Investissements d'Avenir (ANR-16-RHUS-0003_STOP-AS).

Disclosures

None.

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