Advanced echocardiography in characterization and management of patients with secondary mitral regurgitation

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Chapter one

General introduction and outline of thesis

"Imaging of the mitral valve: role of echocardiography, cardiac magnetic resonance, and cardiac computed tomography".

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Introduction

Severe mitral regurgitation is one of the most common valvular diseases worldwide [1??]. The advent of transcatheter therapies has influenced the decision making of patients with symptomatic severe mitral regurgitation, particularly those with high-operative risk or contraindications for surgery. These therapies include devices that target the leaflets (MitraClip, Abbott Vascular, Santa Clara, CA; Neochord, Inc., St Louis Park, MN; Pascal, Edwards Lifesciences, Irvine, CA), the mitral valve annulus (Cardioband, Edwards Lifesciences; Carillon Mitral Contour System, Cardiac Dimensions, Kirkland, WA) or replace the mitral valve (apical tethered system – Tendyne [Abbott Vascular]; radial force system – Intrepid [Medtronic, Inc., Redwood City, CA]; and native leaflet engagement – Tiara valve [Neovasc Tiara]) (Fig. 1). Selection of patients for these therapies requires accurate quantification of mitral regurgitation, assessment of the mitral valve anatomy and evaluation of the left ventricular dimensions and systolic function as well as left atrial dimensions. In contrast to surgery, the mitral valve cannot be inspected during the procedure and the interventionalists need to have accurate visualization of the mitral valve apparatus. Three-dimensional-imaging techniques have become indispensable tools to plan and guide these transcatheter interventions: three-dimensional transesophageal echocardiography and computed tomography provide unparalleled views of the mitral valve and the key measurements to select the type and size of the device. In addition, three-dimensional transesophageal echocardiography provides the soft-tissue resolution that can be overlaid on to fluoroscopy to accurately guide the procedure. Cardiovascular magnetic resonance (CMR) is less frequently used but is an excellent imaging modality to quantify left ventricular dimensions and function and the severity of mitral regurgitation. In addition, late gadolinium contrast-enhanced techniques permit tissue characterization of the myocardium and may have important implications in the timing of intervention. This review will discuss the role of different imaging techniques to evaluate patients with mitral regurgitation for transcatheter interventions.

Echocardiography

Two-dimensional transthoracic echocardiography is the imaging modality of first choice in diagnosing mitral regurgitation and assessing its severity. The mechanism of mitral regurgitation can be assessed with two-dimensiontal transthoracic echocardiography; however, the advent of three-dimensional echocardiography has permitted a systematic approach to define the lesion that causes the mitral regurgitation (Fig. 2). In general, mitral regurgitation is divided into primary (when the lesion is primarily of the mitral leaflets) and secondary (when the coaptation failure is because of left ventricular dilation and dysfunction or left atrial dilation but the mitral leaflets are structurally normal). The classification by Dr. Carpentier [2], considering the motion of the mitral valve leaflets, divides the mechanisms of mitral regurgitation into three different types: type I, when the mitral leaflets are structurally normal, the left ventricular systolic function is preserved and mitral annulus dilatation is the only mechanism responsible for mitral regurgitation; type II, when there is excessive motion of the mitral valve leaflets (causing prolapse); and type III, when there is restrictive motion of the mitral valve leaflets (IIIa, with systolic and diastolic restriction due to primary thickening of the mitral valve apparatus; IIIb, with systolic restriction due to tethering of the leaflets by dilation and severe dysfunction of the left ventricle). When there is primary damage of structurally normal leaflets, such as perforation because of endocarditis, the mechanism is also considered type I. Grading mitral regurgitation needs the integration of qualitative, semiquantitative, and quantitative echocardiographic parameters (Fig. 2). However, in very eccentric regurgitant jets or in patients with secondary mitral regurgitation, the criteria may be discordant and grading the severity of mitral regurgitation becomes challenging. In those situations, three-dimensional echocardiography or CMR may help to discern between severe and nonsevere mitral regurgitation.

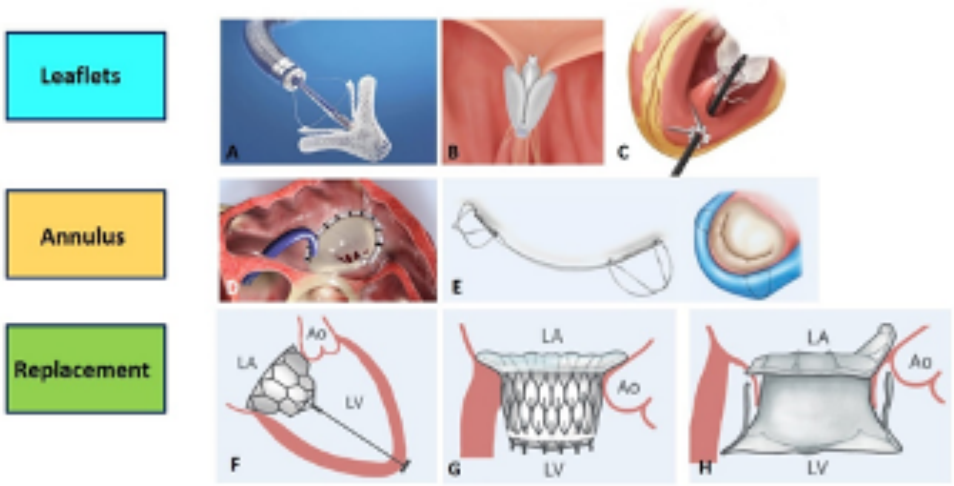

Figure 1: Transcatheter mitral valve therapies. Mitral valve devices targeting the mitral valve leaflet (Panel a = MitraClip device, Abbott Vascular, Santa Clara, California (courtesy of Abbott Vascular); panel b = Pascal, Edwards Lifesciences, Irvine, California (courtesy of Edwards Lifesciences); panel c = NeoChord, Inc., St Louis Park, Minnesota (courtesy of Neochord), mitral valve annulus (panel d = Cardioband, Edwards Lifesciences) (Courtesy of Edwards Lifesciences); panel e = Carillon Mitral Contour System, Cardiac Dimensions, Kirkland, Washington (reproduced with permission from Witte et al. [29]) and total mitral valve replacement (panel f = apical

tether system; panel g = annular winglets system; panel h = native leaflet engagement system (reproduced with permission from Regueiro et al. [30]).

		Primary MR			**Secondary MR**	
MR mechanism according to Carpentier classification		Type I *Normal leaflet motion (i.e. leaflet perforation)*	Type II *Excessive leaflet motion (i.e. mitral valve prolapse or flail)*	Type IIIa *Restricted opening during systole and diastole (i.e. rheumatic heart disease)*	Type I *Normal leaflet motion (i.e. annular dilation)*	Type IIIb *Restricted closure during systole (i.e. due to tethering of the leaflets secondary to LV dysfunction and dilation)*
Severe MR	**Qualitative**	Flail leaflet, ruptured papillary muscle, large perforation			Large coaptation defect	
		Very large central jet or eccentric jet adhering, swirling and reaching the posterior wall of the left atrium			Very large central jet or eccentric jet adhering, swirling and reaching the posterior wall of the left atrium	
	Semiquantitative measurements	Vena contracta width ≥7mm (>8 mm for biplane)			Vena contracta width ≥7mm (>8 mm for biplane)	
		Systolic pulmonary vein flow reversal			Systolic pulmonary vein flow reversal	
		E-wave dominant ≥1.5 m/s (according to AHA/ACC guidelines >1.2m/s)			E-wave dominant ≥1.5 m/s (according to AHA/ACC guidelines >1.2m/s)	
	Quantitative measurements	EROA ≥40 mm²			EROA ≥20 mm² (according to AHA/ACC guidelines EROA ≥40 mm²)	
		Regurgitant volume ≥60 mL/beat			Regurgitant volume ≥30 mL/beat (according to AHA/ACC guidelines RVol ≥60 mL/beat)	
		Regurgitant fraction ≥50%			Regurgitant fraction ≥50%	

Figure 2: Mechanisms of and criteria for the definition of severe mitral regurgitation [2,5,7,23]. EROA, Effective regurgitant orifice area; MR = mitral regurgitation RVol, regurgitant volume.

Three-dimensional transesophageal echocardiography has been shown to provide better information on valve morphology and function [3,4–7]. Morphological assessment of the mitral valve is key in the evaluation of patients with severe mitral regurgitation who may be candidates for transcatheter therapies (Fig. 3). For transcatheter edge-to-edge repair therapies, the leaflet coaptation depth and length (in secondary mitral regurgitation) and the width and height of the flail (in primary mitral regurgitation) need to be measured. The Neochord device is an appropriate therapy for primary mitral regurgitation preferably because of prolapse of the central scallop of the posterior mitral leaflet and with enough length of the leaflets relative to the mitral annulus dimensions to ensure proper coaptation. When evaluating patients for transcatheter mitral annuloplasty, the dimensions of the mitral annulus should be assessed. Three-dimensional transesophageal echocardiography is superior to two-dimensional transthoracic echocardiography to assess the mitral annulus perimeter and area.

Furthermore, three-dimensional transesophageal echocardiography has shown good agreement with CMR to quantify the effective regurgitant orifice area and the regurgitant volume [8–11]. Postprocessing of the three-dimensional color Doppler data using multiplanar reformation planes permits the measurement of the three-dimensional vena contracta and the anatomic regurgitant orifice area (Fig. 4). Choi et al.[12] compared mitral regurgitation quantification with the two-dimensional and three-dimensional echocardiographic proximal isovelocity surface area (PISA) methods and demonstrated that the two-dimensional PISA method significantly underestimated the mitral regurgitant volume compared with the three-dimensional PISA method (52.4 ± 19.6 ml versus 59.5 ± 25.6 ml; P = 0.005). In addition, in the subgroup of individuals with CMR data, the mitral regurgitant volume obtained by three-dimensional PISA method showed a better agreement with phase-contrast CMR than two-dimensional PISA (r = 0.97 versus 0.84, respectively).

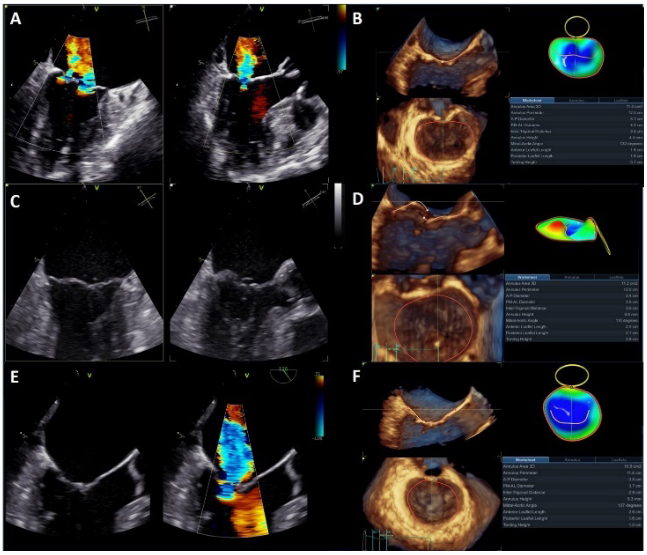

Figure 3: Examples of three-dimensional transesophageal echocardiography images of patients with suitable anatomy for various transcatheter interventions. Panels a and b demonstrate a patient suitable for cardioband, with mitral regurgitation caused by annulus dilation (annulus area of 11.4 cm2). Panels c and d demonstrate a patient suitable for Neochord, with primary mitral regurgitation because of prolapse of the central scallop of the posterior mitral leaflet and enough leaflet length (anterior leaflet length of 2.0 cm and posterior leaflet length of 2.1 cm). Panels e and f demonstrate a patient with secondary mitral regurgitation with suitable anatomy for edge-to-edge therapy device (tenting height of 1.0 cm and anterior and posterior leaflet length of 2.6 and 1.6 cm, respectively).

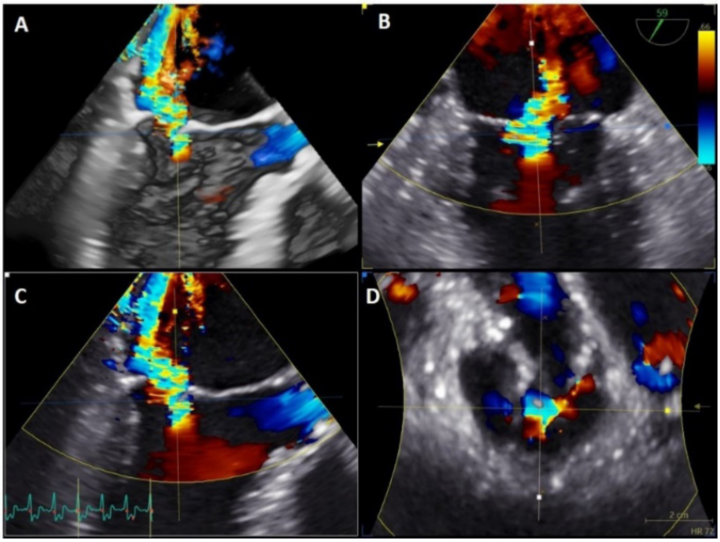

Figure 4: Three-dimensional transesophageal echocardiography color Doppler data for mitral regurgitation quantification. The multiplanar reformation planes are aligned to obtain the three-dimensional vena contracta (1.0 cm) and EROA (0.90 cm2). Panel a displays the three-dimensional rendering of the mitral valve. Panel b displays the reconstructed bicommissural mitral view, whereas panel c shows the reconstructed long-axis view. Panel d displays the transversal plane of the mitral valve at the level of the coaptation line where the anatomical vena contracta can be planimetered. EROA, effective regurgitant orifice area; mitral regurgitation, mitral regurgitation.

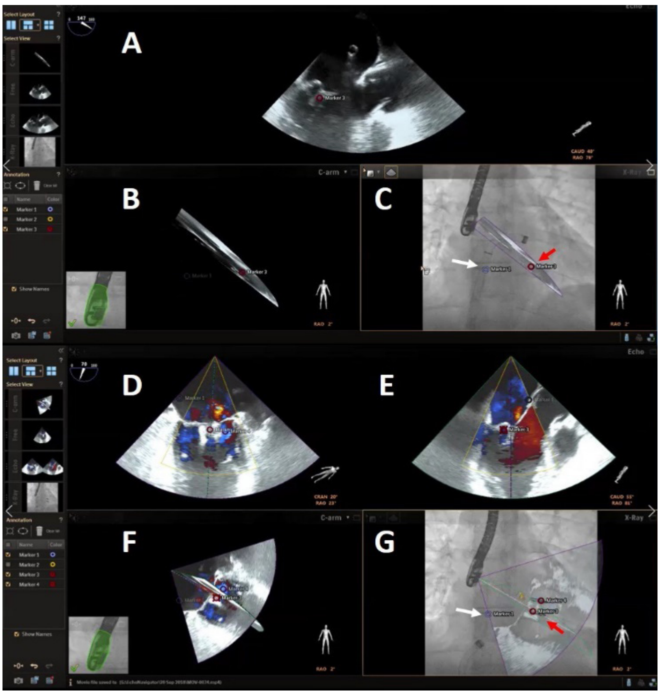

Figure 5: Fusion image of echocardiography and fluoroscopy, facilitating the procedural guidance during the MitraClip procedure. Panel a demonstrates real-time transesophageal image during the procedure whereas panel b shows the spatial orientation of that two-dimensional view based on the fluoroscopic projection. The probe is detected indicating that the position of the probe relative to the C-arm has been detected leading to the overlaid of the transesophageal echocardiographic view

on to the fluoroscopy image with markers placed at the level of the transseptal puncture to introduce the guiding catheter (Panel c, arrow) and where the MitraClip device should be positioned (Panel c, arrow). Panels d and e display the simultaneous biplane color Doppler views of the mitral valve during the MitraClip device implantation which are oriented relative to the C-arm in Panel f. Panel g demonstrates the fusion image with fluoroscopy showing the markers of the transseptal puncture and guiding catheter (arrow) and where the MitraClip device is placed (arrow).

Finally, two-dimensional and three-dimensional TEE are very important in the procedural guidance. Fluoroscopy does not have good soft-tissue resolution and needs the combination of echocardiography to guide the procedure. Current advances permit live fusion of echocardiography and fluoroscopy, facilitating the procedural guidance in key steps such as transseptal puncture and orientation of the device during the deployment of the device (Fig. 5).

Computed tomography

Multidetector row computed tomography (MDCT) is crucial to anticipate the feasibility of specific transcatheter mitral valve repair techniques. MDCT provides information on the mitral valve anatomy and geometry and its spatial relationship with surrounding structures [13,14]. When MDCT data are acquired along the entire cardiac cycle, the movement of the mitral valve leaflets can be characterized and the anatomical lesion causing the dysfunction can be identified. In addition, the narrowest three-dimensional anatomical vena contracta can be assessed by aligning the multiplanar reformation planes at the level of the tips of the mitral leaflets during systole [15].

MDCT is the imaging technique of choice to select patients and plan transcatheter therapies that target the mitral valve annulus or replace the valve. The key information that needs to be assessed with MDCT prior to transcatheter mitral annuloplasty includes the dimensions of the mitral valve annulus, the location of the coronary sinus and circumflex coronary artery relative to the mitral annulus and the presence of extensive mitral annulus calcifications, particularly at the anterolateral level (P1) where the first three anchors of the Cardioband device are implanted (Fig. 6). The size of the mitral valve annulus will determine the size of the annuloplasty device. The location of the coronary sinus relative to the mitral annulus is important when considering devices that indirectly cinch the mitral annulus (Carillon Mitral Contour System). In addition, the course of the circumflex coronary artery is important to predict the risk of impingement of this artery by the device (Fig. 6).

In the selection of patients for transcatheter mitral valve replacement, the dimensions and calcification of the mitral valve annulus should be assessed as well as the dimensions of the left ventricle and left ventricular outflow tract (LVOT). The mitral valve annulus has a characteristic saddle shape which may be difficult to conform for a tubular transcatheter expandable valve. Blanke et al.[16] proposed an MDCT-based simplified annulus description consisting of a D-shaped mitral annulus which is defined as being limited anteriorly by the intertrigonal distance, excluding the aortomitral continuity (Fig. 7). When measuring the mitral valve annulus according to the saddle shape, the area was significantly larger than when considering the D-shaped annulus (13.0 ± 3.0 cm2 versus 11.2 ± 2.7 cm2). In addition, the three-dimensional perimeter of the saddle-shaped annulus was significantly larger than the two-dimensional projected perimeter of the D-shaped annulus (136.0 ± 15.5 mm versus 128.2 ± 14.8 mm).

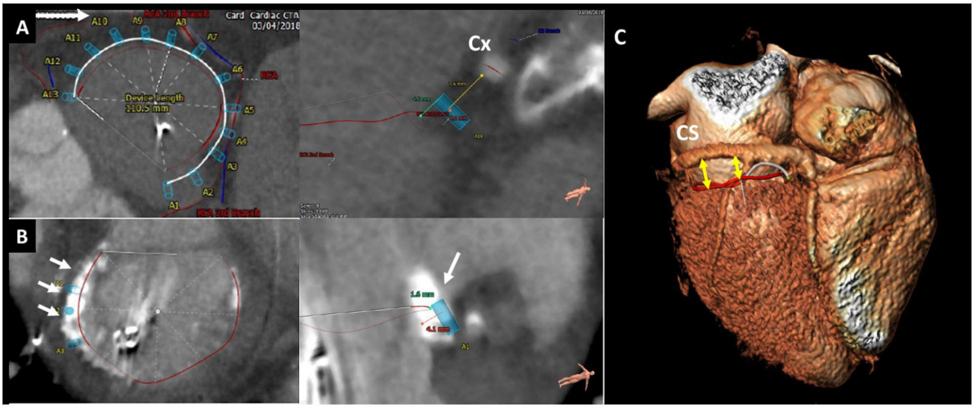

Figure 6: Multidetector row computed tomography to assess the anatomical suitability for transcatheter mitral valve annuloplasty. Panel a demonstrates a patient suitable for Cardioband. The left part shows the anchoring planning (arrow) in the mitral valve annulus. At the right is the distance measured between the anchoring and annulus (4.0 mm) and distance between anchoring and circumflex coronary artery (Cx, 7.6 mm). Panel b shows an example of a patient with unsuitable anatomy for Cardioband with massive mitral annulus calcification (arrows). In the left the anchoring would be in the calcified mitral valve annulus at the level of P1 (arrow). For indirect transcatheter mitral annuloplasty technique, the distance between the coronary sinus and the mitral annulus is relevant to efficiently reduce the size of the annulus. From three-dimensional volume rendering, the coronary sinus can be visualized coursing in this patient too high above the mitral annulus (line) as pointed out by the double arrowheads (panel C).

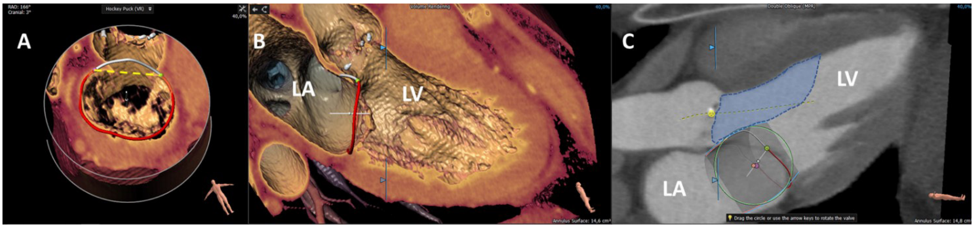

Figure 7: Mitral annulus assessment with MDCT in preprocedural planning of transcatheter mitral valve replacement. The D-shape mitral annulus reconstruction is shown in panel a with the dotted line indicating the intertrigonal distance. Panel b shows the long-axis view of the left ventricular outflow tract (LVOT) and the mitral annulus with the highest point anteriorly in relation with the aortic root. The corresponding computed tomography sagittal view shows the simulation of a tubular transcatheter mitral valve fitted in the mitral annulus and showing the LVOT clearance (or neo-LVOT, shaded area).

More important is the prediction of LVOT obstruction when considering transcatheter mitral valve replacement and that can be performed by calculating the neo-LVOT area [16–18]. Blanke et al.[16] noticed that when considering the saddle-shaped mitral valve annulus, the clearance of the LVOT was smaller than when considering the D-shaped annulus. In addition, it is also important to establish how to measure the neo-LVOT. Meduri et al.[19⍰⍰] hypothesized that the current standard MDCT-assessment performed on end-systolic images might underestimate the neo-LVOT area. Of 33 patients considered for transcatheter mitral valve replacement who were screened for the Intrepid Global Pilot Study and had high risk of LVOT obstruction based on end-systolic measurements, 11 would have been eligible if the neo-LVOT area was measured throughout the entire cardiac cycle (multiphase average) or if the neo-LVOT area was measured at early systole. Therefore, the potential enrollment would have increased by 33% if multiphase average or early systolic measurements would have been performed. In addition, in nine patients who were considered having high risk of LVOT obstruction based on end-systolic assessment, the Intrepid valve was eventually successfully implanted after the multiphase average measurements showed that the area of the neo-LVOT was acceptable [19⍰⍰]. Prediction of LVOT obstruction is also important when transcatheter mitral valve replacement is considered for patients with failed mitral bioprosthetic valves (valve-in-valve), annuloplasty rings (valve-in-ring), and mitral annular calcification (valve-in-MAC). Yoon et al.[18] showed that patients undergoing valve-in-MAC had worse prognosis as compared with patients undergoing mitral valve-in-valve or valve-in-ring. On MDCT, these patients showed the smallest predicted neo-LVOT area, which was associated with LVOT obstruction after transcatheter mitral valve replacement needing conversion to surgery and higher mortality. The neo-LVOT was computed at two device locations: where the device is largest in diameter and at the most ventricular portion of the device. The minimum value of the two measured locations was reported as the end-systolic minimum neo-LVOT area [19??]. A substantial proportion of patients would have been not eligible for TMVR after this screening.

In addition, MDCT is useful to plan the transseptal and transapical implantation routes [14]. The transseptal puncture for mitral valve interventions is usually located 3.5–4 cm above the plane of mitral leaflet coaptation. From MDCT data, the multiplanar reformation planes can be aligned across the interatrial septum, the fossa ovalis can be detected and the transseptal puncture location can be drawn in a coaxial plane 3.5–4 cm above the mitral annulus [14]. The optimal fluoroscopic projection will be defined by the superimposition of the coaxial plane and the mitral annulus plane. For the planning of transapical procedures, the fusion of MDCT data and fluoroscopy helps to locate the puncture site with adequate distance from the left anterior descending coronary artery [20]. For transcatheter mitral valve replacement, the coplanar fluoroscopic projection angles that ensure a coaxial device deployment are derived from a compromise between the projection where the intertrigonal distance and the projection where the septal to lateral distance of the mitral annulus can be assessed. The mitral annular plane is oriented anterior and superiorly with pronounced tilting to the right leading to an S-shaped optimal projection curve that crosses the X axis (i.e., 0° cranio-caudal) at an average 38.8 ± 11.5° right anterior oblique [21].

Cardiac magnetic resonance

In the evaluation of mitral regurgitation, current guidelines recommend CMR when echocardiography is inconclusive in grading the severity of mitral regurgitation [22,23]. In the preprocedural planning of transcatheter mitral valve interventions, CMR is currently used in the assessment of mitral regurgitation severity and left ventricular volumes and function. Furthermore, CMR provides information on tissue characterization (myocardial scar/fibrosis) by using late gadolinium contrast-enhanced (LGE) techniques. However, the impact of myocardial scar/fibrosis assessment with LGE-CMR on the decision making remains unclear.

Quantification of the mitral regurgitant volume and fraction are the key parameters to assess the severity of mitral regurgitation. Several methods can be used to quantify the mitral regurgitant volume [24??]:

(1) By calculating the difference between the left ventricular stroke volume measured

on cine steady-state, free-precession images using planimetry of the left ventricular cavity and the aortic forward volume measured on phase-contrast images. This is the most frequently used method and is not affected by the presence of concomitant regurgitant valve lesions.

(2) By calculating the difference between the left ventricular stroke volume and the right ventricular stroke volume measured using planimetry of the left and right ventricular cavities on cine steady-state, free-precession images. This method cannot be used when concomitant regurgitant valve lesions or significant shunts are present.

(3) By calculating the difference between the mitral inflow stroke volume and the aortic forward volume measured on phase-contrast images.

(4) Using four-dimensional flow CMR data with retrospective mitral valve tracking.

The mitral regurgitant fraction is calculated as the coefficient between the mitral regurgitant volume and the left ventricular stroke volume × 100. Quantification of mitral regurgitation with CMR provides important prognostic data. In 109 asymptomatic patients with moderate or severe mitral regurgitation, Myerson et al.[25] showed that a mitral regurgitant volume more than 55 ml and a regurgitant fraction more than 40% identified the patients who developed indications for surgical intervention during the following five years with a sensitivity of 72 and 76%, respectively, and a specificity of 87 and 74%, respectively. More recently, Penicka et al.[26⍰⍰] showed that the majority of the discrepancies between CMR and two-dimensional echocardiography in mitral regurgitant volume quantification occurred among patients with late systolic or multiple regurgitant jets and that patients with moderate mitral regurgitation based on two-dimensional echocardiography but with severe mitral regurgitation based on CMR analysis had higher rates of all-cause mortality or developed earlier indication for surgery as compared with patients with moderate mitral regurgitation assessed both with CMR and two-dimensional echocardiography.

The consequences of chronic severe mitral regurgitation on the left ventricular dimensions and function can be also assessed with CMR. Particularly, the presence of replacement fibrosis as assessed with LGE-CMR has been described in patients with primary mitral regurgitation. In the study by Kitkungvan et al.[27] patients with mitral valve prolapse had increased regional left ventricular replacement fibrosis, particularly in the segments adjacent to the posteromedial papillary muscle. The presence of replacement fibrosis may be further related to increased symptomatic ventricular arrhythmic events in patients with mitral valve prolapse [27]. In patients with secondary mitral regurgitation where the remodeling and dysfunction of the left ventricle is frequently the underlying pathophysiological mechanism of mitral malcoaptation, assessment of extent of myocardial fibrosis/scar has important prognostic implications (Fig. 8). Cavalcante et al.[28] showed in a cohort of 578 patients with ischemic cardiomyopathy and a mean mitral regurgitant fraction of 18% that patients with significant mitral regurgitation (defined by a regurgitant fraction ≥35%), that the presence of a myocardial scar size at least 30% of the left ventricular was associated with a hazard ratio of 5.41 for the combined endpoint of all-cause mortality or heart transplant.

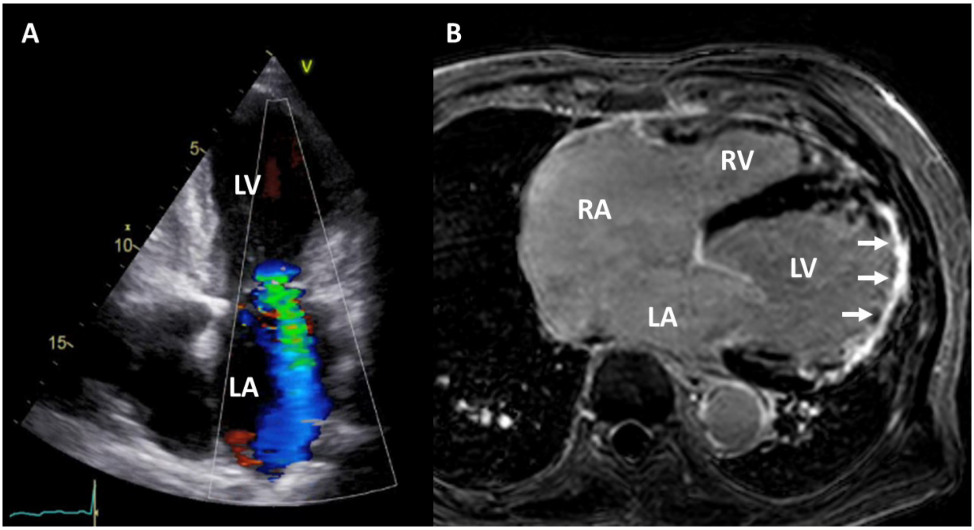

Figure 8: Late gadolinium contrast-enhanced cardiovascular magnetic resonance in patient with ischemic mitral regurgitation. Panel a shows the apical four-chamber view with severe mitral regurgitation based on color flow Doppler data. On late gadolinium contrast-enhanced cardiovascular magnetic resonance, the presence of myocardial scar extent can be assessed (arrows).

Conclusion

The growing prevalence of patients with severe mitral regurgitation and a high surgical risk or contraindications for surgery has opened the field for transcatheter therapies, which are evolving rapidly. Preprocedural imaging with three-dimensional imaging techniques, such as transesophageal echocardiography, computed tomography, and cardiac magnetic resonance, provide the anatomic and functional information needed to determine the underlying mechanism and severity of mitral regurgitation and define the most appropriate transcatheter therapy. In addition, advances in fusion imaging, where noninvasive three-dimensional imaging modalities can be overlaid on to fluoroscopy, facilitate the communication between imagers and interventionalists and procedural guidance.

Outline of this thesis

The objective of this thesis was to evaluate the role of advanced echocardiography for the risk stratification and treatment guidance of patients with secondary mitral regurgitation.

Part I describes epidemiological characteristics of patients with mitral regurgitation and how these effect treatment and outcome. **Chapter 2** evaluates the sex differences in secondary mitral regurgitation and how it impacts outcome.

Part II focuses on the role of echocardiography and advanced echocardiography (speckle tracking) in defining predictors of outcome in patients with secondary mitral regurgitation. **Chapter 3** evaluates the incremental prognostic value of LV GLS over LVEF in secondary mitral regurgitation. **Chapter 4** has analyzed the ratio between mitral regurgitant volume and LV end-diastolic volume as a predictor of outcome in secondary mitral regurgitation. **Chapter 5** evaluates geometrical mitral valve differences in patients with secondary mitral regurgitation treated with transcatheter mitral valve repair. **Chapter 6** evaluates an echocardiographic marker for right ventricular-arterial coupling in patients with significant secondary mitral regurgitation and it association with outcome.

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