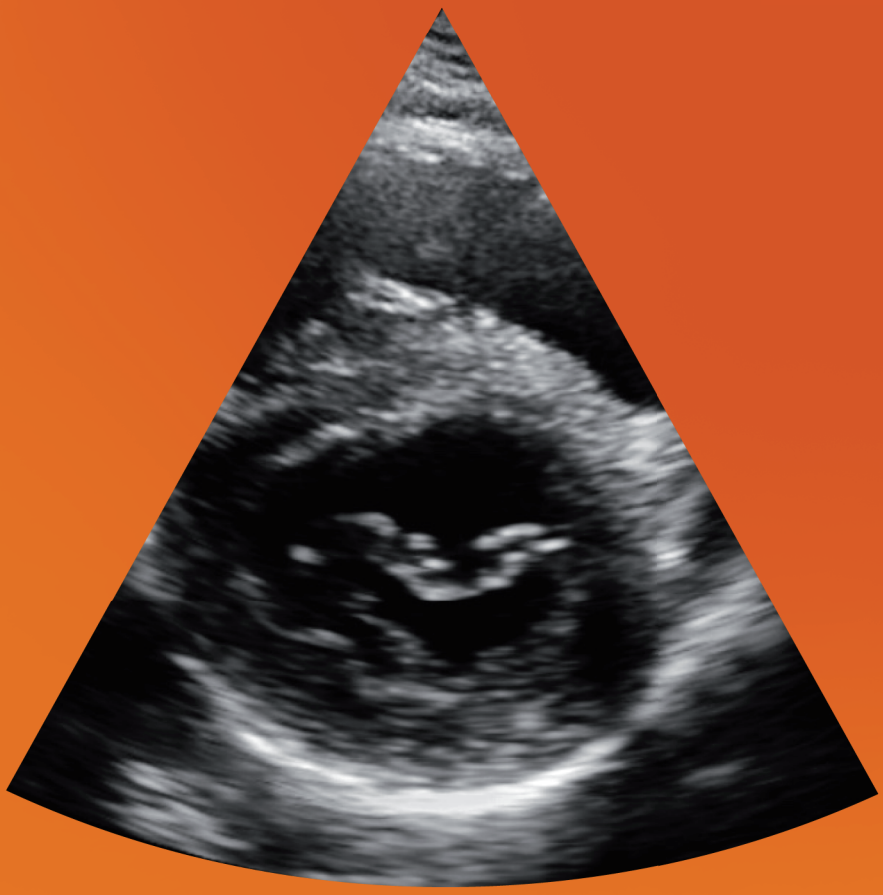
Echocardiographic and clinical aspects of mitral regurgitation



LOTTE E. DE LAAT

Echocardiographic and Clinical Aspects of Mitral Regurgitation

Lotte Elisabeth de Laat

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Echocardiografische en klinische aspecten van mitralisklepinsufficiëntie

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Voor Michael, Tim en Isabelle

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General Introduction and Outline of the Thesis

GENERAL INTRODUCTION

Mitral valve and regurgitation

Valvular regurgitations are among the most frequent heart diseases [1,2] and mitral regurgitation (MR) is considered the most common valve disease with a prevalence of 2-3% having significant regurgitation in the general population [2]. MR is defined as systolic regurgitation of blood from the left ventricle (LV) to the left atrium (LA) and results from incomplete mitral valve (MV) closure and a pressure gradient between the LV and LA. Incomplete MV closure results from dysfunction of one of the components of the MV apparatus, which includes the mitral annulus, leaflets, chordae tendineae, papillary muscles and the underlying LV wall (Figure 1).

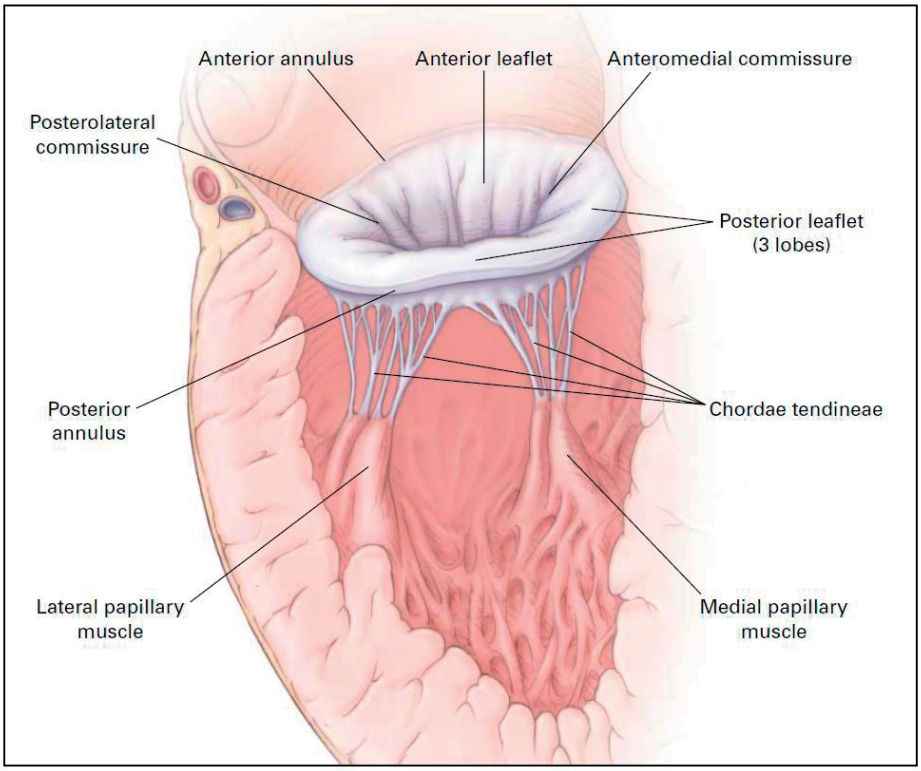

Figure 1. Mitral valvular apparatus. *Reproduced with permission from Otto CM. Evaluation and management of chronic mitral regurgitation.* N Engl J Med. *2001;345:740-746, Copyright Massachusetts Medical Society.*

The mitral annulus is a highly complex saddle-shaped anatomical and functional entity, which is directly related to hemodynamic changes subsequent to muscle contraction of the LV, LA and motion of the aortic root throughout the cardiac cycle [3]. It plays an important

role in leaflet coaptation, in unloading MV closing forces and in promoting LA and LV filling and emptying. Enlargement of the annulus is mostly seen secondary to LV cavity dilatation in dilated cardiomyopathy or in remodeling as result of scar formation after myocardial infarction [4]. Primary mitral annular remodeling is also seen in patients with MV prolapse or atrial fibrillation [5,6].

The leaflet part of the MV apparatus consists of two leaflets with a larger and usually thicker anterior leaflet with a trapezoid or dome-shape. The posterior leaflet is crescent-shaped with a shorter radial length but longer circumferential base that is attached to the posterior mitral annulus [7]. Both leaflets can be dived into three parts with a lateral (A1/P1), central (A2/P2) and medial scallop (A3/P3), with demarcating indentations and slits only seen in the posterior leaflet (Figure 2). Additional commissural leaflet tissue can be found at the anterolateral and posteromedial commissures.

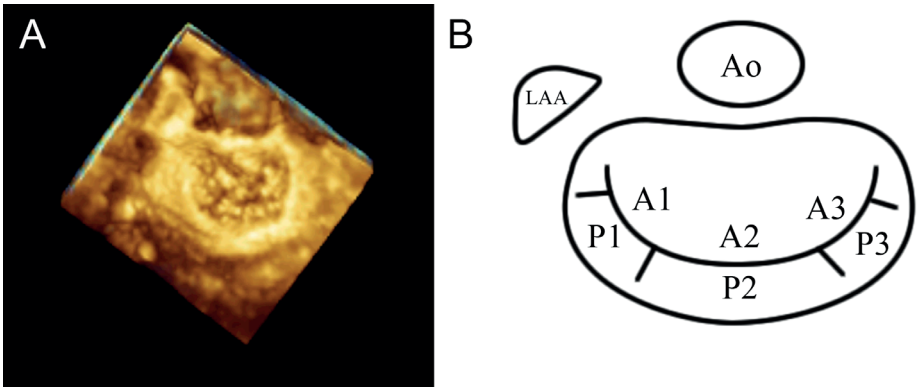

Figure 2.
A. En-face view of a normal mitral valve with 3D echocardiography
B. Schematic representation of the anterior (A1/A2/A3) and posterior (P1/P2/P3) mitral valve scallops. LAA: left atrial appendage, Ao: aorta

The leaflets are connected with the papillary muscles and the LV wall by chordae tendineae. From each papillary muscle, chordae attach to the ipsilateral half of both MV leaflets. The primary chords attach to the free margins of the leaflets and secondary chordae insert close to the rough zone of the leaflets. The tertiary chords arise directly from the LV wall or from the trabeculae carnae and insert exclusively into the posterior leaflet [8]. Primary and secondary chordae have different functions with primary chordae to maintain leaflet apposition and secondary chordae to maintain normal LV size and geometry [9]. Elongation or rupture of the primary chordae leads to significant MR. Secondary chordae rarely rupture and are not critical to maintaining coaptation [7].

Two papillary muscles are present: the anterolateral and posteromedial. Their location is variable, but they are most commonly attached to the middle third of the LV wall avoiding

the interventricular septum and are designated by their projected relationship to the lateral and medial mitral commissures [10]. In most cases, the lateral papillary muscle has a single head and dual blood supply whereas the medial papillary muscle has commonly two heads and single blood supply by the right coronary artery or the circumflex, based on coronary dominance [7].

According to etiology and pathophysiology, MR can be divided somewhat artificially into a primary or organic and a secondary or functional categories [11,12]. In primary lesions, one or more of the components of the MV itself are deranged. Acute MR will occur in case of traumatic, papillary muscle rupture usually associated with a myocardial infarction or infective endocarditis with leaflet perforation or chordal rupture. With the reducing prevalence of rheumatic fever and increased lifespan nowadays degenerative MV disease, leading to leaflet prolapse due to chordal elongation or rupture, is the most common etiology for primary chronic MR in Europe [1]. Barlow's disease with myxomatous degeneration is seen more in a younger population whereas older populations more often present with fibro-elastic deficiency in which lack of connective tissue leads to chordal rupture. Other less common causes of primary chronic MR are infective endocarditis, connective tissue disorders, congenital cleft and radiation heart disease. In secondary lesions geometric and/or functional changes of the LV are the core of the problem with idiopathic cardiomyopathy and coronary artery disease as main causes. MR results from tethering (apical and lateral papillary muscle displacement, annular dilatation) and reduced closing forces due to LV dysfunction (reduced contractility and/or LV dyssynchrony) [11].

In 1983 Carpentier distinguished in his classical report about the pathophysiologic classification of the MV three types of pathology on the basis of a functional approach: in type I there is a normal leaflet motion, type II is associated with increased leaflet motion and type III is associated with restricted leaflet motion [13]. More recently, Shah and Raney proposed an updated classification based on echocardiography in order to provide a more comprehensive and detailed assessment of MV disorders which may be more relevant to modern MV repair techniques [14,15].

Echocardiography

The MV was the first of the four cardiac valves to be evaluated with echocardiography. Over the last fifty years conventional two-dimensional (2D) echocardiography has served as a valuable clinical tool and is still the imaging modality of choice for the diagnosis and management of MR [11,12]. For accurately assessing MV morphology, 2D transthoracic echocardiography (TTE) and transesophageal echocardiography (TOE) are often used. Although 2D-echocardiography is a non-ionizing and cost-effective technique, the cardiologist has to reconstruct mentally the complex structure of the heart, resulting in geometrical assumptions, which in turn could underestimate the validity of clinical findings. With the introduction of three-dimensional (3D) echocardiography there is now a feasible technique

for rapid and accurate identification of MV pathology and in some studies it has been shown to be superior to 2D in patients with MR [16,17].

MR severity depends on the degree of leaflet malcoaptation: it can range from trace to severe and increases over time [18]. Echocardiographic assessment of MR severity consists primarily of colour Doppler flow imaging. To quantify MR severity, measurement of the vena contracta (Figure 3A) and proximal isovelocity surface area (PISA) (Figure 3B) are recommended [19]. The vena contracta is measured as the narrowest width of the MR jet just distal to the leaflet tips. It is a simple linear measurement of the regurgitant orifice and is relatively independent of loading conditions. Three-dimensional measurements of the vena contracta may be more accurate, in particular in asymmetric regurgitant orifices seen in functional MR, because the effective regurgitant orifice area is now measured without geometric assumptions [20]. The PISA method is based on a geometric assumption of a hemispherical flow shape distal to the regurgitant orifice. Just as the vena contracta, the PISA method is also subject to research in 3D echocardiography [21]. However, all these 3D approaches have not yet found their way into clinical routine application.

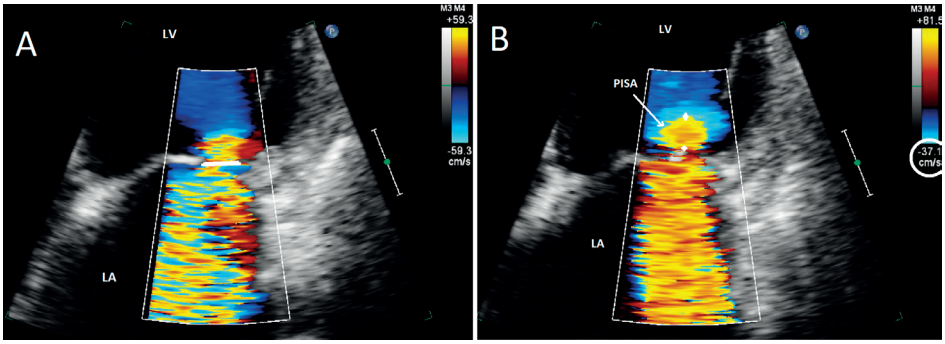

Figure 3.
A. Vena contacta measurement (white line)
B. PISA method: measurement of the radius (between white dots) to calculate the PISA after optimizing by decreasing the depth, narrowing the sector, using zoom mode and adjusting the aliasing limit to a value between 20-40 cm/s with shifting the baseline downward. LV: left ventricle. LA: left atrium.

Surgical and percutaneous treatment of MR

In multiple studies impaired long-term survival in patients with MR has been reported, which led to a worldwide consensus and acceptance of surgical repair of the MV to prevent LV dysfunction and mortality [11,12,22]. Through preservation of normal valvular tissue and the subvalvular apparatus, MV repair optimizes postoperative LV function and is preferred over MV replacement. Compared with MV replacement, MV repair has a lower surgical mortality risk and provides better survival, in particular in patients with degenerative MV disease [23,24]. In MV surgery for secondary MR, MV repair was considered the gold standard, but reports of high recurrence rates raised doubts. Comparing MV repair with replacement

Acker et al. observed no significant difference in left ventricular reverse remodeling or survival at 12 months [25].

MV repair may combine different techniques as annuloplasty, resection, sliding plasty or chordal replacement according to etiology. Repair of disease of the anterior leaflet is more challenging than repair of disease of the posterior leaflet, mostly prolapse, with the anterior leaflet to be more important to retain geometry and mobility.

Open chest procedures with a full sternotomy are the gold standard for MV surgery, but over the last few years the use of minimally invasive techniques for MV repair with a partial sternotomy approach or with minimally invasive, video-assisted, surgery through the right thoracic cavity have steadily increased. These techniques are associated with equivalent mortality and major morbidity, but with superior cosmetics, faster recovery, reduced hospital costs and lower risk of atrial fibrillation and bleeding [26]. Especially in young and in asymptomatic patients these arguments help to convince these patients to undergo MV repair [27].

For patients at high risk for surgical treatment there are currently also percutaneous alternatives. Although numerous percutaneous annuloplasty techniques are being tested in clinical trials [28], the MitraClip® system is the main technique used in clinical practice. By a transseptally introduced catheter system, a metallic clip covered with a polyester fabric is guided towards the MV. The clip is able to grasp and approximate the free edges of the MV leaflets, analogue to the surgical Alfieri stich technique [29]. The clip can be removed or re-positioned if the immediate result is not satisfactory, or an additional clip can be implanted. The safety, feasibility and echocardiographic results of this MitraClip® system were demonstrated in the Endovascular Valve Edge-to-Edge Repair Study (EVEREST) trials [30,31]. Also, in real-world registries good clinical outcomes have been described, particularly the COAPT and MITRA-FR trials are relevant in this regard and will be discussed in the final chapter of this thesis, but questions about the most appropriate patient population to treat and at what time to treat still need to be answered [32-34].

OUTLINE OF THE THESIS

The aims of this thesis are to investigate the role of echocardiography in identification of MR mechanism and quantifying MR severity and to evaluate MR outcome. For this purpose, the thesis is divided into three main parts.

Identification of MR mechanism

A new, updated echocardiographic classification of MR mechanisms with special attention to the added value of three-dimensional (3D) echocardiography is described in **Chapter 2**. The optimal echocardiographic measurement of mitral annulus size, one of the main

mechanisms of MR, is discussed in **Chapter 3**. In **Chapters 4** and **5** the role of new echocardiographic techniques such as 2D xPlane imaging and 3D echocardiography for the evaluation of the site and extent of MV prolapse is discussed.

Quantification of MR severity

To determine the severity and need for intervention, quantification of MR is recommended. In **Chapter 6** errors in calculating MR volume according to present methods are discussed. In **Chapter 7** the gap between guidelines and real-world practice in echocardiographic quantification of MR in patients referred for MV surgery is discussed.

Evaluation of MR outcome

In this part of the thesis we report outcome of MR treated conservatively, with MV surgery and the MitraClip® system. The results of optimization of heart failure therapy on secondary moderate-to-severe MR is reported in **Chapter 8**. Outcome after minimal or conventional MV surgery in asymptomatic and symptomatic patients with MR is reported in **Chapters 9** and **10**. The role of the anatomy of the MV complex and outcome after transcatheter MV intervention with the MitraClip® system is discussed in **Chapters 11** and **12**. Finally, in **Chapter 13** we reflect on and discuss the most important findings of this thesis.

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Chapter 2

A Modified Echocardiographic Classification of Mitral Valve Regurgitation Mechanism: The Role of Three-dimensional Echocardiography

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René Frowijn, Frans B. Oei and Marcel L. Geleijnse.

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ABSTRACT

In this report, we provide an overview of a new, updated echocardiographic classification of mitral regurgitation mechanisms to provide a more comprehensive and detailed assessment of mitral valve disorders. This is relevant to modern mitral valve repair techniques, with special attention to the added value of 3D-echocardiography.

INTRODUCTION

Pre-operative echocardiographic assessment of MV pathology has become of crucial importance with the transition from prosthetic mitral valve (MV) replacement to MV repair in the last decades. This has more recently been facilitated by development of newer echocardiographic techniques such as three-dimensional (3D) imaging [1,2] and simultaneous biplane imaging [3,4].

Communication between the cardiologist and the surgeon is as important as the obtained echocardiographic information. Therefore, in 1983, Carpentier proposed a clearly defined, universal MV leaflet terminology [5]. The normal MV is comprised of an anterior leaflet connected on either side through the anterolateral and posteromedial commissures to the posterior leaflet. The anterior leaflet occupies two-thirds of the valve area, whereas the posterior leaflet occupies only one-third, and the latter leaflet is connected to two-thirds of the annulus. The posterior leaflet consists of three scallops or segments: the lateral scallop is labeled P1, the middle scallop P2, and the medial scallop P3. Although the anterior leaflet is smooth without natural scallops, the leaflet parts opposing the corresponding posterior leaflet scallops are accordingly labeled A1, A2, and A3. Because the P2 scallop is relatively large, it may be divided into lateral and medial halves (P2L and P2M) or even divided into three parts: centro-lateral (P2CL), central (P2C), and centro-medial (P2CM). The two commissures are usually also composed of small scallops and may be designated as the lateral commissural scallop (CL) and medial commissural scallop (CM) [6]. The chordae arising from the anterolateral papillary muscle are attached to CL, A1, P1, A2L and P2L, whereas those arising from the posteromedial papillary muscle are attached to CM, A3, P3, A2M, and P2M.

In addition to the leaflets and their scallops, the MV apparatus includes an annulus, chordae tendineae, papillary muscles, and the left ventricle (LV). Mitral regurgitation (MR) may develop when any part of the MV apparatus becomes abnormal. Carpentier described the pathophysiologic classification of the three types of MV pathology on the basis of a functional approach that were linked to specific repair techniques [5]. Type I involves normal leaflet motion, type II is associated with increased leaflet motion, and type III is associated with restricted leaflet motion.

More recently, Shah and Raney proposed a modified echocardiographic classification of MR mechanisms to provide a more comprehensive and detailed assessment of MV disorders that is relevant to modern MV repair techniques [7,8]. In this report, we give an overview of the Shah and Raney pathological MR classification (Table 1), with special attention to the added value of 3D-echocardiography. The focus is on trans-esophageal 3D imaging because, in our experience, 3D transthoracic imaging of the MV has limited accuracy even in the hands of experts [3,9-11].

Table 1. Echocardiography-based classification of mitral valve pathology

Type I: Normal leaflet motion
A. Leaflet perforation
B. Congenital cleft
C. Dilated annulus (without leaflet tethering)
Type II: Increased leaflet motion
A. Localized prolapse or flail scallop
B. Billowing leaflets with prolapse
C. Billowing leaflets with a flail segment
Type III: Restricted leaflet motion
A. Systolic and diastolic restriction
B. Symmetric systolic restriction
C. Asymmetric systolic restriction
Type IV: Systolic anterior motion (SAM)
A. Hypertrophic cardiomyopathy
B. Post–mitral valve repair
C. Hemodynamically-induced (hypovolemia, inotropic stimulation)
Type V: Hybrid conditions
Examples
- Prolapse of a leaflet combined with systolic anterior motion or a restricted leaflet
- Intrinsic pathology with super imposed infective endocarditis lesion

Modified from Shah and Raney [7,8]

CLASSIFICATION OF MV PATHOLOGY

Type I: Normal leaflet motion

This type of pathology is the same as in the original Carpentier classification. The MV leaflets have normal excursions and subannular leaflet coaptation without a tenting or tethering appearance. Underlying pathologies for MR of this type are now sub-categorized as leaflet perforation (Type I-A), congenital cleft deformity (Type I-B), and pure annular dilatation without leaflet tethering (Type I-C).

MV leaflet perforation can be the result of trauma but is most commonly caused by localized infective tissue destruction. Other than primary MV endocarditis, aortic valve endocarditis can also directly extend toward the anterior MV leaflet via the anatomically shared fibrous trigones or be transmitted via the aortic valve regurgitation blood jet [12]. Three-dimensional echocardiography provides added benefit to traditional two-dimensional (2D) imaging because of its ability to provide en-face visualization of the MV, allowing more precise anatomical localization and measurement of the size of the leaflet perforation, as seen in Figure 1 [13].

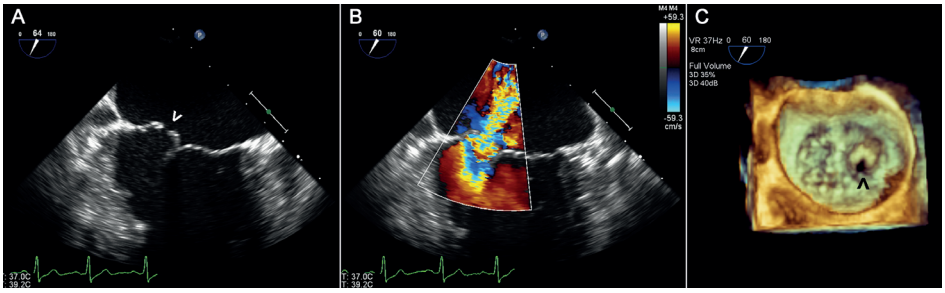

Figure 1. Mitral valve perforation in the medial part of the anterior leaflet, identified with 2D grayscale (A, see arrowhead), 2D colour (B) and with 3D echo from the left atrial (surgical) view (C, see arrowhead).

A congenital cleft of the MV is most commonly seen in association with an atrioventricular canal defect, but an isolated cleft of the anterior or posterior MV leaflet has also been described [14]. In this subtype, 3D echocardiography provides superior diagnostic accuracy and may improve surgical results [15,16]. An MV cleft can be easily seen on the 3D image from both the atrial (Figure 2A) and ventricular (Figure 2B) aspects of the MV, whereas it is often extremely challenging to make the correct diagnosis with 2D echocardiography. It is important to differentiate true clefts from drop-outs (facilitated by the use of color Doppler) and pseudo clefts from deep folds in myxomatous MV disease, particularly in post-MV repair.

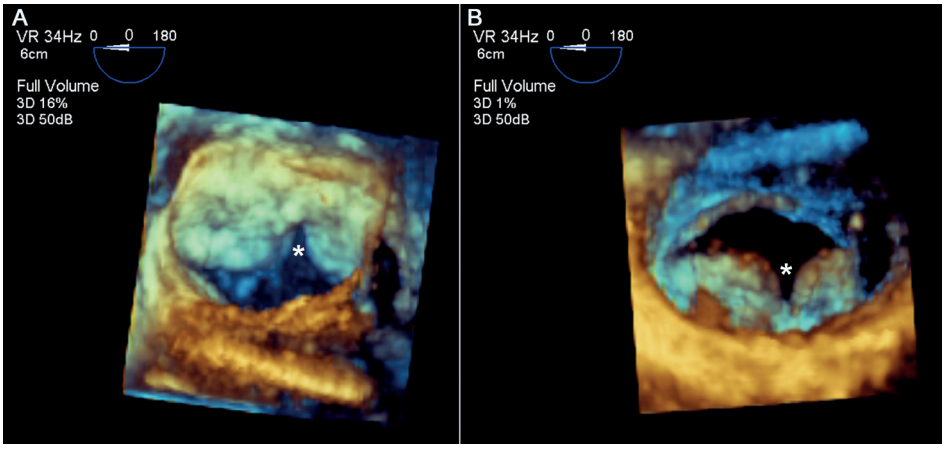

Figure 2. Three-dimensional echocardiographic surgical view of an anterior mitral valve leaflet cleft seen from the left atrial (surgical) view (A, see asterisk) and left ventricular view (B, see asterisk).

Mitral annulus dilatation is usually seen in combination with the later described types II and III MR [17]. Pure or isolated mitral annulus dilatation in the absence of leaflet tethering or prolapse is mainly seen in patients with chronic atrial fibrillation but also in patients with heart failure with preserved LV function [18]. The location of MV leaflets coaptation with

respect to the annulus is normal, but the zone or surface of coaptation is reduced, resulting in central MR. The definition of annulus dilatation with 2D echocardiography is limited by lack of clear data regarding the best echocardiographic view in which it should be measured [19,20]. The apical 4-chamber view is recommended in some instances [21], although it is well known that this view does not represent a consistent or reproducible axis of the mitral annulus [22-24]. In contrast, 3D echocardiography provides an en-face view of the mitral annulus from which multi-planar reconstruction or modeling of the MV enables precise measurements not only of the major and minor axes, but also of the complete annular circumference (Figure 3).

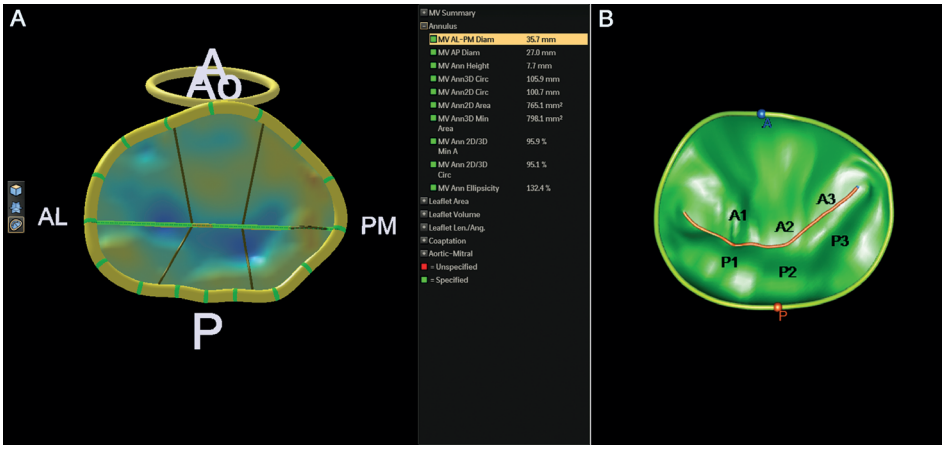

Figure 3. Three-dimensional echocardiographic surgical view reconstruction of the mitral annulus with software from Philips QLAB (A) and TomTec (B).

Type II: Increased leaflet motion

This type is characterized by MV leaflets exhibiting excess excursion into the left atrium and is also the same as in the original Carpentier classification but now has three subtypes. In type II-A there is typically fibro-elastic deficiency with thin and friable chordae that lead to a prolapsing segment due to chordal elongation, eventually resulting in a flail leaflet prolapse due to chordal rupture (Figure 4A). Acute flail leaflet prolapse may also be the result of chordal rupture in acute endocarditis or (less often) papillary muscle rupture due to acute myocardial infarction (Figures 4B to 4E) . The MR jet in this type is always eccentric: anteriorly directed in posterior MV leaflet prolapse and posteriorly directed in anterior MV leaflet prolapse. A late-systolic central jet may be seen in billowing leaflets due to chordal elongation (Type II-B, Figures 5A to 5C). In its extreme form, there is significantly increased diffuse redundant and thickened leaflet tissue due to myxoid infiltration and annulus dilatation with multiple central and eccentric regurgitant jets known as myxomatous Barlow's disease (Figure 5D and 5E). In patients with more severe chordal elongation, the

regurgitant jets may occur earlier in systole. The combination of these two types results in a third subtype consisting of billowing leaflets with associated flail due to chordal rupture that also results in multiple jets (Type II-C).

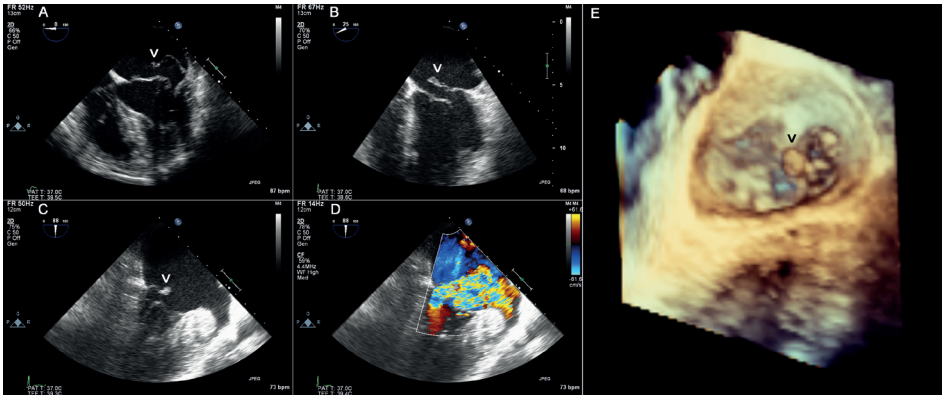

Figure 4. Type II-A mitral valve prolapse due to fibro-elastic deficiency with chordal rupture (A, see arrowhead). Acute flail mitral valve leaflet prolapse due to antero-lateral papillary muscle rupture (B, see arrowhead) and postero-medial papillary muscle rupture (C: gray-scale , see arrowhead, D: color Doppler, E: 3D image, see arrowhead).

Of note, the terms of flail, prolapse, and billowing MV are often used differently, especially between cardiologists and surgeons. Billowing refers to passing of only the body of the MV leaflet above the mitral annular plane (Figures 5A to 5C), whereas prolapse means that the leaflet tips are also above the mitral annular plane. Prolapse, unlike billowing, is always associated with MR. A flail MV leaflet is an extreme form of prolapse associated with chordal rupture (Figure 4A) or extreme chordal elongation without rupture.

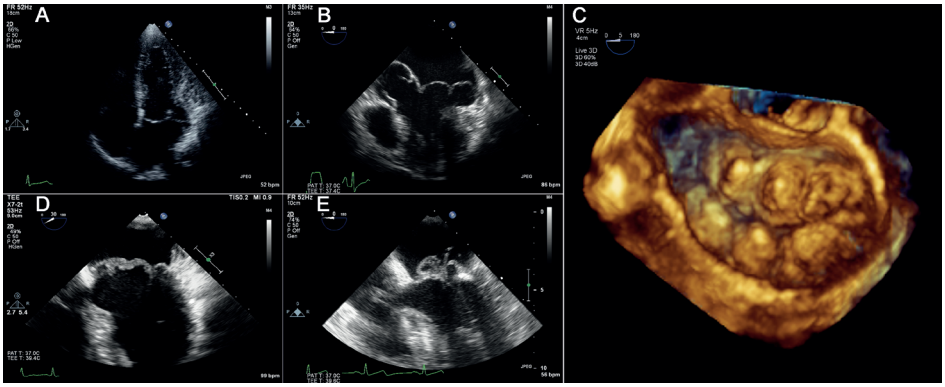

Figure 5. Type II-B billowing mitral valve leaflets due to chordal elongation seen with 2D transthoracic (A), 2D trans-esophageal (B), and 3D echocardiography (C: surgical view). Diffuse redundant and thickened leaflet tissue known as myxomatous Barlow's disease is seen with trans-esophageal echocardiography without (D: type II-B) and with chordal ruptures (E: type II-C) .

The presence, location and extent of prolapse are of crucial importance in defining the likelihood of successful MV repair [25,26]. Compared to 2D imaging, 3D echocardiography obviates the need to mentally reconstruct the MV in three dimensions from multiple 2D images to understand the underlying MV anatomy. The entire MV can be visualized in a single image, making it possible to examine both leaflets from the left atrial (surgical) perspective, which allows more definitive identification of the localization (Figure 6) and extent (Figure 7) of prolapse. This technique may also be less operator dependent because it does not require the finesse of probe manipulation to delineate MV pathology. Several studies have

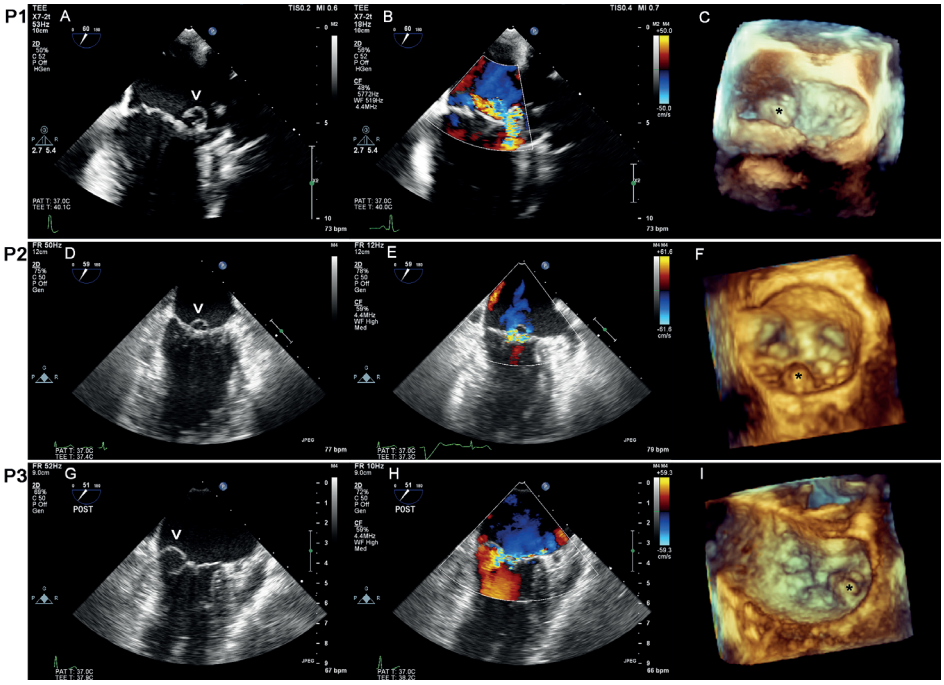

Figure 6. Mitral valve prolapse site identification with trans-esophageal commissural view 2D imaging (left column), color-imaging (middle column) and 3D imaging (right column). Seen are prolapses (asterisks and arrowheads) of the P1 (top row A-C), P2 (middle row D-F), and P3 (bottom row G-I) scallops.

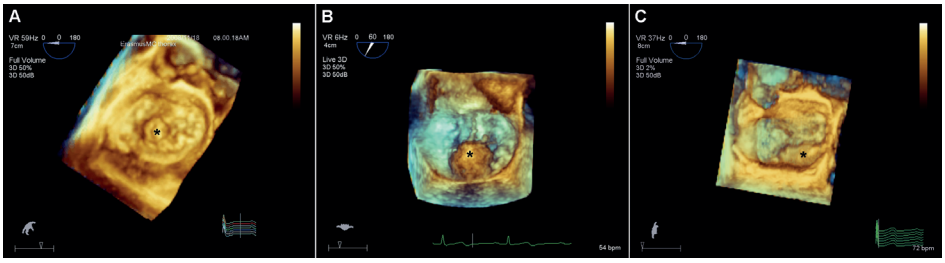

Figure 7. Three-dimensional echocardiographic surgical view of mitral prolapse extent: small P2 prolapse (A), broad P2 prolapse (B) and P2-P3 prolapse (C). The sites of prolapse are indicated with arrowheads.

shown that time to diagnosis was considerably faster and diagnostic accuracy improved with 3D echocardiography, in particular for identification of P1 and P3 prolapse [6].

Type III: Restricted MV leaflet motion

In the original Carpentier classification, type III was divided into two subtypes: IIIA with restricted opening and IIIB with restricted closure. Shah and Raney proposed division of this type into three subtypes [5,8].

Type III-A is characterized by systolic and diastolic restriction as seen in rheumatic and other inflammatory pathologies and is associated with commissural fusion, chordal shortening and fibrosis. The leaflets are thickened and shortened, resulting in inadequate coaptation and regurgitation (Figure 8A and 8B). The main role for 3D echocardiography in this subtype is the assessment of the MV area, and this has become the reference method of classifying MV stenosis [27,28] (Figure 8C) because it facilitates imaging of the true narrowest opening of the MV orifice. Still, it should be recognized that this measurement is – as the 2D measurement – challenging by the presence of severe calcification. The use of a 3D Wilkins score may improve the traditional 2D Wilkins score for selection of patients suitable for MV plasty [29,30].

In types III-B and III-C, there is systolic restriction with one or more tethered leaflets. Tethering on echocardiography is characterized by systolic displacement of one or more leaflets from the annular plane [31,32]. The closure and position of mitral leaflets are determined by the balance between two forces acting on them: the closing forces generated by the LV systolic contraction, which effectively closes the valve, and the tethering forces, which restrain the leaflets to prevent leaflet prolapse. When tethering is increased by outward displacement of the papillary muscles and the closure forces are reduced by LV dysfunction, the equilibrium between these two forces is disrupted in favor of tethering forces, with displacement of the coaptation point of leaflets in the ventricle.

Two tethering patterns have been described [33] and in the new approach classified as type III-B symmetric (Figure 8D and 8E) and type III-C asymmetric (Figure 8F and 8G) restriction. Systolic symmetric tethering with central MR is seen in dilated or chronic global ischemic cardiomyopathy with outward displacement of the papillary muscles and annulus dilatation with the point of coaptation remaining at the leaflet tips but displaced toward the apex and with a reduction in coaptation zone [33]. The severity of this type of MR is greatly related to dynamic changes in loading conditions seen in treatment with diuretics, afterload reducing agents or general anesthesia [34] (Figure 9). 3D Echocardiography may quantify dynamic changes that occur in the mitral annular surface and its 3D longitudinal displacement and characterize the complex geometric relationship between the papillary muscles and the MV apparatus [35]. Some have advocated measurement of the tenting pattern, especially regional 3D tethering of segment P3, as a predictor for long-term prognosis in patients with dilated cardiomyopathy [36] or as predictor for recurrent ischemic MR after undersized mitral ring annuloplasty [37].

Asymmetric systolic restriction as seen in type III-C (Figure 8F and 8G) typically occurs in patients with a localized posterior wall motion abnormality and results in tethering of the corresponding leaflet, whereas the other normal leaflet overrides the point of coaptation without going above the annular plane. It is important to recognize that this latter leaflet is thus not prolapsing but only overriding a restricted opposite leaflet.

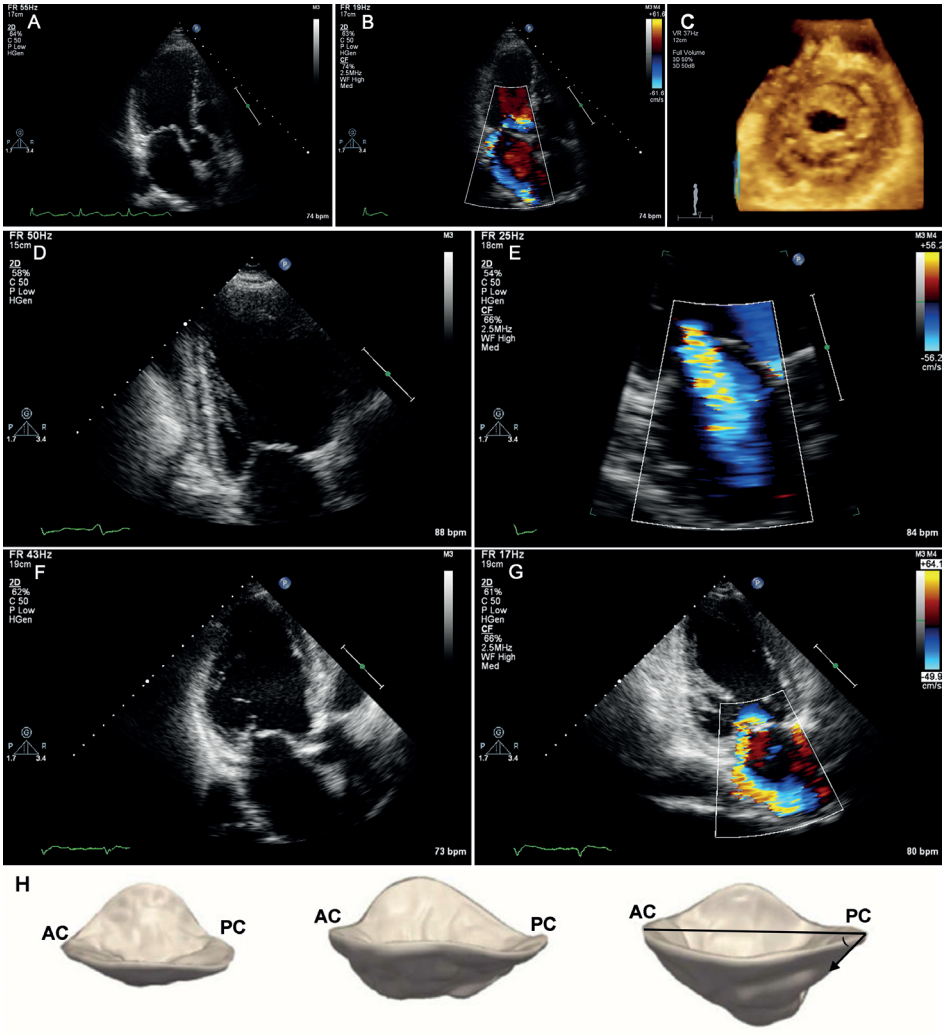

Figure 8. Mitral valve restriction seen with 2D trans-thoracic gray scale and color imaging in rheumatic disease with systolic and diastolic restriction (A and B, C showing the 3D surgical view with reduced valve opening), in dilated cardiomyopathy with symmetric systolic restriction (D and E) and ischemic cardiomyopathy (F and G) with asymmetric systolic restriction. In the bottom panel (H), 3D echocardiographic virtual models are seen from the commissure-to-commissure view. The 3D tenting area and tethering angle of segment P3 (arrow-line) may predict recurrent mitral regurgitation after annuloplasty. AC denotes anterior commissure and PC denotes posterior commissure. Reproduced with permission from Bouma et al. [37].

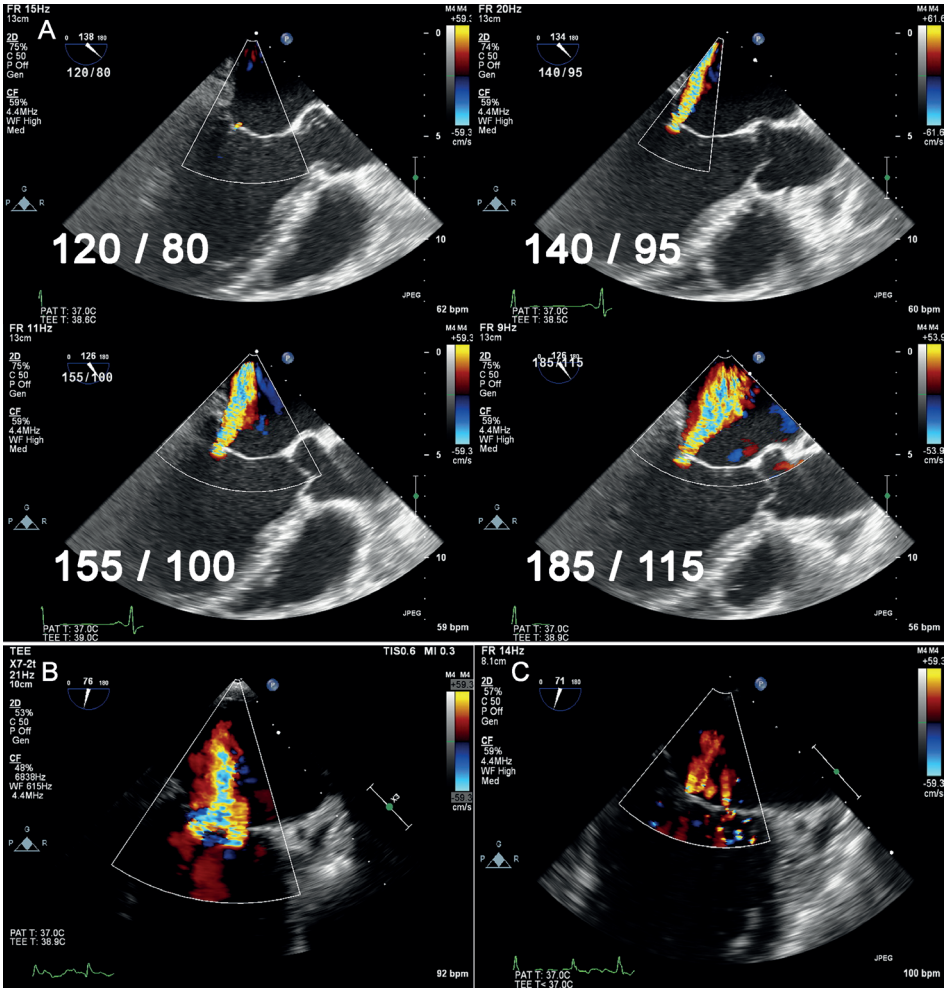

Figure 9. Influence on the severity of trans-esophageal assessment of mitral regurgitation by peri-operative blood pressure changes (A) and general anesthesia (B: significant mitral regurgitation in the outpatient clinic, C: minimal mitral regurgitation under general anesthesia).

Type IV: Systolic anterior motion (SAM)

Systolic anterior motion (SAM) of the MV may lead to significant MR and is seen in different circumstances. In general, the role of 3D echocardiography in recognition of SAM is minimal.

Type IV-A is seen in hypertrophic cardiomyopathy characterized by anteriorly displaced papillary muscles elongated MV leaflets with a residual portion of the anterior MV leaflet extending beyond the point of coaptation [38]. This portion is not constrained by the left atrial – ventricular pressure differences but freely moves with the flow in the LV outflow

tract. In particular, in patients with a relatively short posterior MV leaflet, SAM causes an eccentric MR jet directed laterally and posteriorly (Figure 10A).

Type IV-B is seen after MV repair. Pathologic motion of the distal MV leaflet as described above may be simulated by a disproportionate reduction of the MV annulus compared to the size of post-repair MV leaflet tissue (Figure 10B and 10C).

Type IV-C is seen in a hypovolemic, hyperdynamic LV. Typically it is seen during dobutamine stress [39] or with excess doses of inotropics in hypotensive states, paradoxically worsening hypotension.

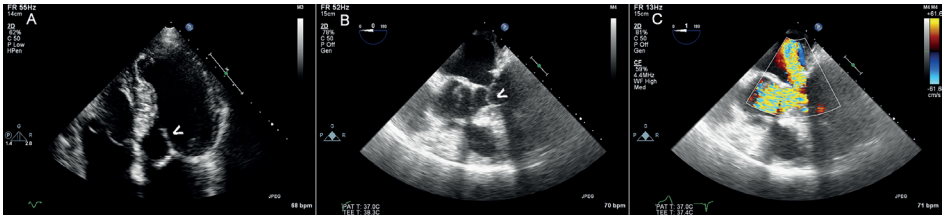

Figure 10. Mitral regurgitation due to systolic anterior motion (see arrowheads) in hypertrophic cardiomyopathy (A) and after mitral valve annuloplasty (B: gray-scale and C: color Doppler).

Type V Hybrid motion in co-existing pathologies

Hybrid pathologies include combinations of more than one pathology in a patient. Examples include intrinsic pathology with a superimposed infective endocarditis lesion and restrictive posterior leaflet pathology combined with anterior leaflet prolapse or SAM.

SPECIFIC ROLES OF 3D COLOR IMAGING IN ASSESSMENT OF MV PATHOLOGY

The main application of 3D color imaging for assessment of MV pathology is in assessment of paravalvular leakage after MV surgery [40]. Evaluation of the extent and shape of the leaking orifice and the site of annulus detachment is critical in assessment of paravalvular leakage and may best provided by the surgeon's en-face view of the prosthetic MV from the left atrium (Figure 11). In addition, color 3D imaging may facilitate the differentiation of 3D drop-out artifacts from true defects [41].

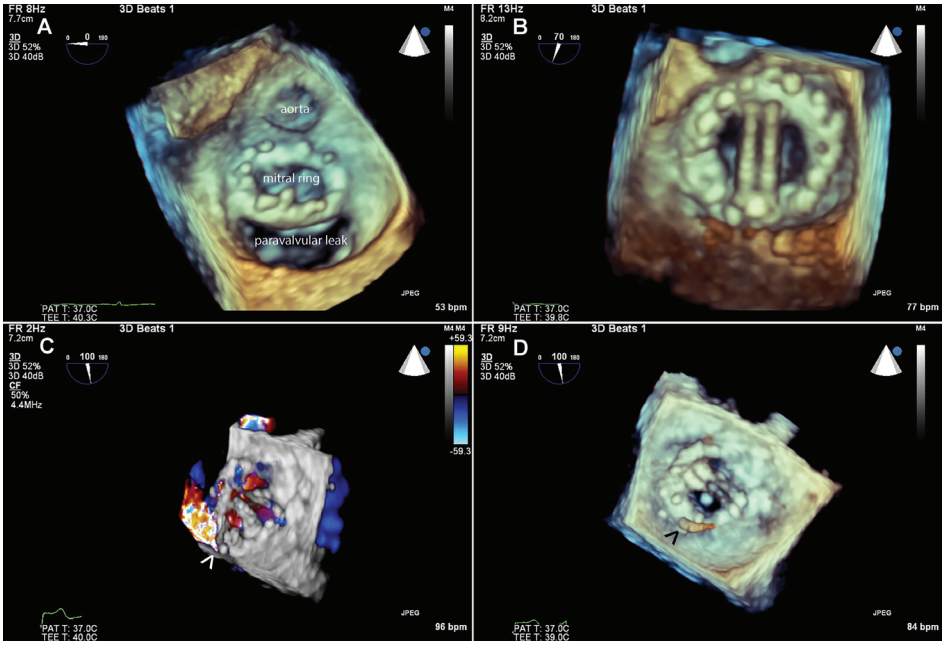

Figure 11. Three-dimensional echocardiography showing mitral ring dehiscence (A) and replacement with a mechanical prosthesis (B). In the lower panel shows localization of smaller paravalvular leakage after implantation of a mechanical prosthesis by the origin of the 3D color Doppler jet (C, arrowhead), facilitating wire passage (D, arrowhead) and thus placement of a closure device.

CONCLUSION

Accurate description of the MR mechanism is crucial for the determination of the need for and type of MV surgery. Addition of 3D echocardiography may be particularly helpful in identification of MV leaflet perforation, cleft, or prolapse and a more reproducible definition of MV annulus dilatation. The described modified classification by Shah and Raney provides a more comprehensive and detailed assessment of MV disorders. Further studies should investigate whether this modified classification has an impact on surgical techniques and outcome.

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Chapter 3

How to Measure Mitral Annulus Size with Two-dimensional Transthoracic Echocardiography

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ABSTRACT

Aim

Dilatation of the mitral annulus (MA) is a main mechanism of mitral regurgitation (MR). Unfortunately, there is a lack of recommendations in which transthoracic two-dimensional echocardiographic view and specific time point in the cardiac cycle MA size should be measured.

Methods

The MA was measured during different time points in the cardiac cycle in 50 subjects (40 patients with MR and 10 healthy subjects). Measurements were done in the parasternal long-axis (PSLAX) and apical 2, 3, and 4-chamber views. Validation was done against measurements of the 3D transoesophageal echocardiographic (TOE) MA area.

Results

MA annulus dimensions were significantly different in the different views. The difference in MA dimension between control subjects and patients with mitral regurgitation was best recognized in the PSLAX view: enlargement 36.5% versus 21.3% in the 2-chamber view, 28.8% in the 3-chamber view and 26.5% in the 4-chamber view. In end-diastole the respective correlations against the 3D TOE MA area were for the 4CH, 2CH, 3CH and PS LAX views were 0.404, 0.620, 0.625 and 0.625, respectively. In end-systole these numbers were 0.595, 0.499, 0.555 and 0.559, respectively. Normal MA values in the PSLAX view were in end-systole 28.2 ± 3.0 mm and in end-diastole 25.5 ± 2.8 mm.

Conclusion

MA measurement with 2D-echocardiography should be done in the PSLAX view at a fixed time point in the cardiac cycle. Because of the functional component of the MA the end-systolic time-point may be preferred with an upper limit of normal of 35mm.

INTRODUCTION

The mitral annulus (MA) is an anatomically well-defined D-shaped fibrous structure [1,2]. It is a vital component of the mitral valve apparatus [3] and dilatation of the MA is one of the main mechanisms of mitral regurgitation (MR) [4]. Because the MA is not circular in shape [1,3], dilates in an asymmetric manner [5] and is dynamic in the cardiac cycle [6], it seems essential to define the transthoracic echocardiographic cross-sections and the specific time point in the cardiac cycle at which the MA diameter should be measured. However, in most echocardiographic textbooks there is no recommendation where to measure the MA diameter [7,8]. Alternatively, it is recommended to use the apical 4-chamber view [9], although it is well known that this view does not represent the true major or minor axis of the MA [10-12] and may be more prone to variation in acquisition, or the parasternal long-axis view [13]. Intriguingly, also in none of the echocardiographic textbooks a recommendation is given at which specific time point in the cardiac cycle the MA diameter should be routinely measured. This is a potentially important issue because the normal MA is a dynamic structure with a continuously changing area during the cardiac cycle [6]. This study sought to establish which transthoracic two-dimensional echocardiographic view and specific time point in the cardiac cycle are the most reproducible in terms of inter-observer variability, accurate compared to a gold standard and representative for dilatation direction of the MA diameter.

METHODS

Fifty subjects (28 men, mean age 61 ± 12 years) were analysed: 40 consecutive patients (23 men, mean age 63 ± 11 years) with moderate or severe MR, and 10 healthy subjects (5 men, mean age 51 ± 9 years). Healthy subjects were recruited from our department (personnel), or were family members or friends of the authors. All had normal left atrial and left ventricular (LV) dimensions, normal systolic and diastolic LV function, and no valvular abnormalities. None of these healthy subjects used cardiovascular medications, and all had a normal 12-lead electrocardiogram. Normal values of the 3D MA area were assessed in 10 subjects referred for analysis of a cardiac source of embolus but with normal cardiac findings (4 men, mean age 49 ± 14 years) with optimal 2D and 3D quality images. All echocardiograms in these subjects were made by one single, highly experienced sonographer (JMG). In the standard parasternal long-axis (PSLAX) and apical 2, 3, and 4-chamber views one physician (LGL) assessed the overall image quality defining it as good (quality score 1), moderate (quality score 2) or poor (quality score 3). Good image quality was defined as a clear definition of both sides of MA attachment / hinge points on a moving image in the whole cycle. Moderate image quality was defined when one of both sides of MA attachment / hinge points on the moving image was less visible in a part of

the cycle. Poor image quality was defined when one or both sides of the MA attachment / hinge points on a moving image were not visible in a part of cycle. The presence of MA calcification was noted. To study MA dynamics, the MA diameter was measured at six different time points in the cardiac cycle: early systole (ES) the frame after MV closure, late or end systole (LS) the frame before MV opening, mid systole (MS) midway between ES and LS, early diastole (ED) the frame after MV opening, late or end diastole (LD) the frame before mitral valve closure and mid diastole (MD) midway between ED and LD. Subsequently, a second physician (BR) also scored the overall image quality, the presence of MA calcification, and the MA diameter from the identical images (frames).

Validation of the 2D MA measurements with 3D echocardiography

In the 3D MA validation study, 30 of the 40 subjects (17 men, mean age 63 ± 11 years) with moderate or severe MR and same-day adequate three-dimensional (3D) transoesophageal echocardiographic (TOE) images of the mitral annulus available, and 10 subjects (4 men, mean age 49 ± 14 years) that underwent two-dimensional (2D) and 3D transthoracic echocardiography (TTE) and TOE because of analysis of source of emboli with normal findings were included. To validate the 2D mitral annular measurements, the end-diastolic and end-systolic frames were correlated to 3D mitral annular areas (Figure 1).

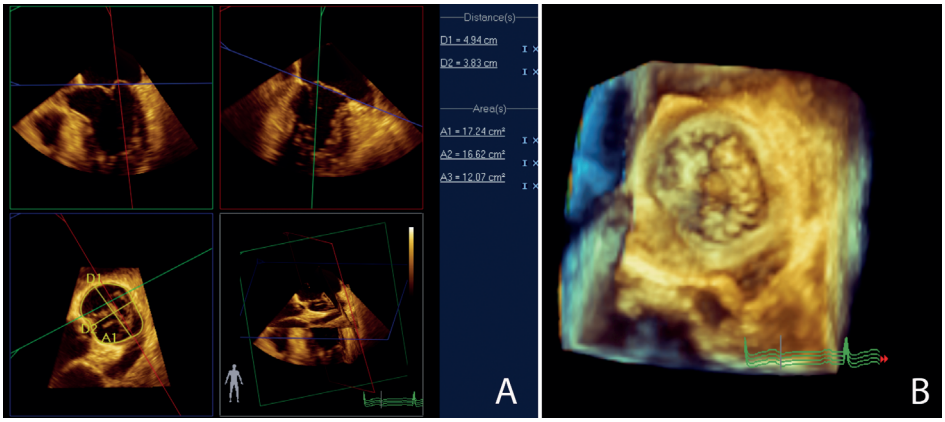

Figure 1. Measurements of the mitral annular area and major and minor dimension from 3D TOE in end-systolic frame. The 3D dataset (B) is displayed as three orthogonal images of the mitral annulus (A). The blue plane shows the "en face" view of the mitral annulus in which the inner border of the cross-sectional area was traced manually.

Three-dimensional TOE imaging was performed using the iE33 ultrasound system with the X7-2t matrix-array transducer. Electrocardiographically gated full-volume data sets were acquired at the midesophageal level during breath-hold with the ultrasound focus on the MV in the four-chamber view. Care was taken to include the complete mitral annular circumferences throughout the acquisition. Each full-volume data set was digitally stored

and exported to QLAB 9.0 3DQ software (Philips Medical Systems) for offline analysis. The "en face" views of the MA was revealed at time points during the cardiac cycle similar as for the 2D TTE measurements. Subsequently, the major-axis and minor-axis diameters of the MA were measured.

Normal MA values

After definition of the optimal MA measurement normal values were established in 50 healthy subjects (26 men, mean age 49 ± 12 years). Also, these healthy subjects had normal left atrial and LV dimensions, normal systolic and diastolic LV function, and no valvular abnormalities.

Statistical Analysis

Categorical data are presented as numbers and percentages. Normality of continuous variables was evaluated by Shapiro-Wilk tests, and data were then presented as mean ± standard deviation (SD) or median and interquartile range (IQR) in case of a significant test.

Interobserver variability was defined as the absolute difference between measurements divided by the mean. To compare this interobserver variability between two different echocardiographic views paired Student-T tests or, if the distribution was not normal, Wilcoxon signed-rank test was used. We compared also the MA dimension in these views by the same tests. The mean values of the MA dimension in MR patients were compared with healthy controls by unpaired Student-T tests. Correlations between the 2D annular measurement and the 3D mitral annular areas were performed using the Pearson correlation test.

All statistical tests were two-sided and a p-value <0.05 was considered statistically significant. Analyses were performed using SPSS version 21.0.0.1 (SPSS, IBM, Armonk, NY).

RESULTS

MA dimensions in the different views

Average (all time points) values of the MA annulus in the 4 different cross sections in the 50 subjects were 34.0 ± 6.2 mm in the PSLAX, 35.7 ± 6.5 mm in the 2-chamber view, 32.9 ± 6.2 mm in the 3-chamber view and 37.0 ± 6.6 mm in the 4-chamber view. All MA annulus dimensions were significantly different ($P <0.001$).

Differences in MA dimensions in normal subjects and mitral regurgitation patients

As seen in Figure 2, in all views the MA was larger in patients with mitral regurgitation compared to control subjects. The difference in MA dimension between control subjects and patients with mitral regurgitation was best recognized in the PSLAX view: enlargement 36.5% versus 21.3% in the 2-chamber view, 28.8% in the 3-chamber view and 26.5% in the 4-chamber view.

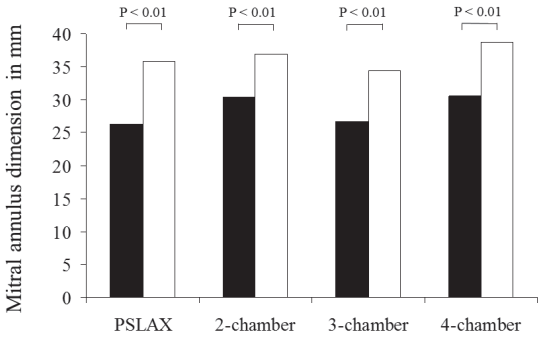

Figure 2. Measurements of mitral annular dimension in patients with mitral regurgitation (white bars) and control subjects (black bars).

MA dimensions during the cardiac cycle

As seen in Figure 3, the MA showed in the PSLAX and apical 3 and 4 chamber views a progressive decrease in size during diastole and a progressive increase in size during systole, whereas changes in size in the apical 2-chamber view were not significant.

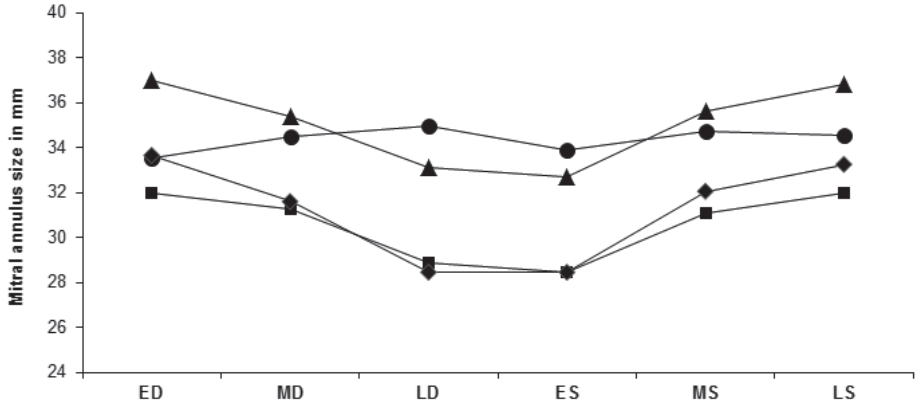

Figure 3. Measurements of mitral annular dimension in 6 phases of the cardiac cycle: early, mid and late diastole (ED, MD, and LD) and systole (ES, MS, LS) in the parasternal long-axis (diamonds) and three apical views: 2-chamber view (dots), 3-chamber view (squares), and 4-chamber view (triangles).

Interobserver variability in MA measurements

As seen in Figure 4, when considering all available views the apical 4-chamber view showed the best inter-observer variability in MA dimensions (6.2% vs. 9.1% for the PSLAX view, 8.7% for the apical 2-chamber view, and 9.0% for the apical 3-chamber view). As seen in Figure 5, there were no significant differences in inter-observer variability between the different time points in the cardiac cycle. This was true when all views were taken together but also for the view with the best inter-observer variability, the apical 4-chamber view.

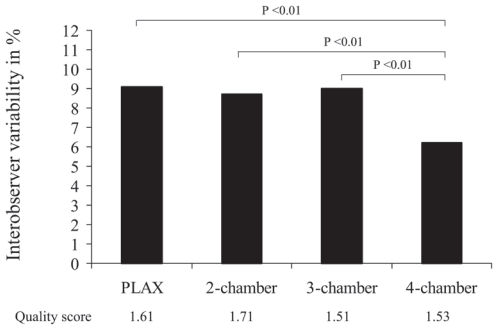

Figure 4. Interobserver variability of mitral annular measurements in the parasternal long-axis (PLAX), apical 2-chamber, apical 3-chamber, and apical 4-chamber views. Image quality score: 1 = good, 2 = moderate, 3 = poor.

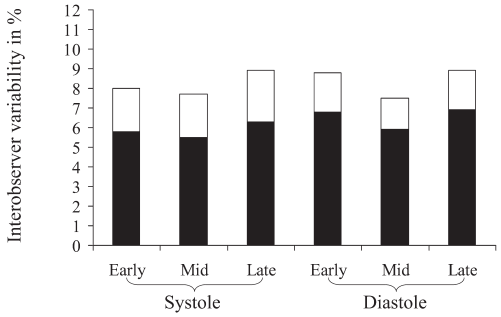

Figure 5. Interobserver variability of mitral annular measurements in the different time points in the cardiac cycle (white bars: average of all views, black bars: apical 4-chamber view).

Validation of the 2D MA measurements with 3D echocardiography

In end-diastole the respective correlations of the 2D annular measurement with the 3D mitral annular areas for the 4CH, 2CH, 3CH and PSLAX views were 0.404, 0.620, 0.625 and 0.625. In end-systole these numbers were 0.595, 0.499, 0.555 and 0.559, respectively.

Normal MA values

Normal MA values in the PSLAX view were in end-systole 28.2 ± 3.0 mm and in end-diastole 25.5 ± 2.8 mm.

DISCUSSION

According to Carpentier *et al.* [4] dilatation of the MA is one of the main mechanisms of MR. Because the MA is not circular in shape [1,2], is dynamic in the cardiac cycle [6] and dilates asymmetrically [5], it seems essential to define the transthoracic echocardiographic cross-sections and the specific time point in the cardiac cycle at which the MA diameter should be measured. The main finding of this study is that in the PSLAX view enlargement of the MA is best identified and correlation to the 3D MA area is also optimal whereas the specific measurement time point in the cardiac cycle seems less relevant.

It is well known that the MA is not circular but oval in shape [1,2,12]. In our study different values were consequently seen in the different views. Surprisingly, in the 4-chamber view the largest values were measured. The MA in this particular view is, however, variably in between the shortest (best identified in the PSLAX view) and largest (best identified in the 2-chamber view) axes of the oval MA [12]. The actual measurement can thus only be explained by a mistake in measurement in this view (which seems unlikely since this measurement showed actually the best inter-observer variability) or a structural MA underestimation in the 2-chamber view. Indeed, when the 2D 2-chamber measurements were compared to the major-axis of the 3D annulus a bias of -12mm was found (in contrast the 2D 3-chamber measurements showed compared to the minor-axis of the 3D annulus only a bias of -1mm).

Some have claimed that the MA dilates mostly in the anterior-posterior direction [5] and in one study control subjects could be differentiated from patients with functional mitral regurgitation in all cross-sections apart from the so-called “intervalley” distance, equaling the diameter in the 2-chamber view [14]. Indeed in our study in the PSLAX view (best representing the anterior-posterior direction) the greatest MA enlargement in patients versus control subjects was seen. Providing further arguments to measure the MA in the PSLAX view.

As seen in this study and described by others, the MA is a dynamic structure changing in size during the cardiac cycle, in particular in the non-commissural (2-chamber) views [6,15]. Although discrepant findings have been reported, the progressive increase in MA size during systole described in our study was also seen in studies by others [6,15]. In our study there were no differences in inter-observer variability between any of the six time points during the cardiac cycle. The most commonly used end-diastolic and end-systolic time-points seems most attractive because of their clear, uniform definitions. In our opinions the end-systolic time-point has the additional advantage that it intuitively seems very attractive

from a functional point of view combining information of both MA size and function (which is very important during mitral regurgitation) we therefore suggest to use the end-systolic MA diameter from the PSLAX view as the preferred one. Based on our normal values the upper limit of normal of the PSLAX end-systolic MA diameter is 35mm.

Limitations

Our study concentrated on real-world measurements of the MA with 2D echocardiography. 3D-echocardiography clearly offers a better, "en-face" view of the MA [1,2,12] and may be the optimal way of measuring the MA, not only providing representative dimensions but also a circumference or area rather than a dimension with unknown exact representation. However, in daily routine practice and certainly the initial assessment is virtually always done with 2D echocardiography.

CONCLUSIONS

MA measurement with 2D-echocardiography should be done in the PSLAX view at a fixed time point in the cardiac cycle. Because of the functional component of the MA the end-systolic time-point may be preferred with an upper limit of normal of 35mm.

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Chapter 4

Transthoracic Two-dimensional xPlane and Three-dimensional Echocardiographic Analysis of the Site of Mitral Valve Prolapse

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ABSTRACT

Aim

This study sought to assess the value of two-dimensional (2D) transthoracic echocardiography (TTE), 2D xPlane imaging and three-dimensional (3D) TTE for the definition of the site and the extent of mitral valve (MV) prolapse.

Methods

Fifty patients underwent transthoracic 2D, 2D xPlane and 3D echocardiography. With 2D xPlane a segmental analysis of the MV was performed, by making a lateral sweep across the MV coaptation line as seen in the parasternal short-axis view.

Results

Inter-observer agreement for specific scallop prolapse was for 2D xPlane excellent (97 %, kappa = 0.94) and for 3D TTE moderate (85 %, kappa = 0.67). The respective sensitivities of standard 2D TTE, 2D xPlane, and 3D TTE for the identification of the precise posterior scallop prolapse were for P1 92, 85, and 92 %, for P2 96, 96, and 82 %, and for P3 86, 81, and 71 %. In total, 5 (8 %) prolapsing MV scallops were missed by 2D TTE, 7 (12 %) by 2D xPlane, and 12 (20 %) by 3D TTE. The sensitivity of 3D TTE was significantly lower than standard 2D imaging (80 % versus 93 %, $P < 0.05$). The extent of P2 prolapse was under or over- estimated in 5 patients with 2D xPlane and in 9 patients with 3D TTE.

Conclusion

2D xPlane imaging is an accurate, easy to use (compared to 3D TTE) and easy to interpret (compared to 2D and 3D TTE) imaging modality to study the site and the extent of MV prolapse.

INTRODUCTION

Mitral valve (MV) prolapse (MVP) is one of the most common valvular abnormalities in industrialized countries [1]. The site and extent of the prolapse is essential in defining the suitability for MV repair [2]. Many physicians are of the opinion that two-dimensional (2D) transthoracic echocardiography (TTE) is not reliable enough to provide the surgeon with the essential pre-operative information and consider transesophageal echocardiography (TEE) obligatory. However, it should be recognized that newer technology (beam formers and har- monic imaging) has improved TTE quality and TEE is a semi- invasive imaging technique not totally without procedural risk [3-5]. More recently, three-dimensional (3D) TTE has been developed; a technique that is thought to be able to define more precisely the site and extent of the prolapse in a non-invasive manner [6,7]. However, 3D imaging requires expertise and suffers from limited temporal and spatial resolution [8].With the 3D matrix transducer, it is also possible to identify the prolapse site and the extent from multiple 2D xPlane views taken from a standard parasternal short axis view of the MV by simultaneous multiplane imaging (SMPI) [9,10]. This technique requires less expertise and the spatial resolution is only minimally reduced compared to 3D imaging. Therefore, this study sought to assess the value of 2D TTE, 2D xPlane imaging and 3D TTE for the definition of the site and the extent of MV prolapse in patients that underwent MV surgery.

METHODS

Study population

Between May 2012 and August 2013, 57 consecutive patients with MVP were referred to our center for surgical MV repair because of isolated severe mitral regurgitation (MR). The institutional review board approved the study and informed consent was obtained from all patients.

Prior to surgery a transthoracic 2D, 2D xPlane and 3D echocardiogram in harmonic imaging was performed using an iE33 ultrasound system (Philips Medical Systems, Best, The Netherlands) equipped with an X5-1 matrix probe composed of 3040 elements, with a 1–5 MHz extended operating frequency range, with the patient in the left lateral decubitus position.

2D echocardiography

As recommended, four standard 2D imaging planes were used: the parasternal long-axis and short-axis views and the apical four- and two-chamber views [5].

2D xPlane mode

A segmental analysis of the MV was performed with SMPI in xPlane mode, by making a lateral sweep across the MV coaptation line as seen in the parasternal short-axis view (Figure 1). In the xPlane mode an orthogonal view can be acquired through the midline of a primary image and dis- played as a secondary image. From the midline, additional secondary images can be obtained by a lateral tilt of up to a maximum of +30° to -30° allowing precise visualization of the prolapsing scallop in the secondary image which will resemble a parasternal long axis view. A clear example of a P1, P2 and P3 prolapsing scallop is seen in Figure 2. The smallest sector able to encompass the mitral valve should be used because in the xPlane mode frame rate will be half of the frame rate of the original image [10]. Mean xPlane frame rate was 37 ± 6 frames per second.

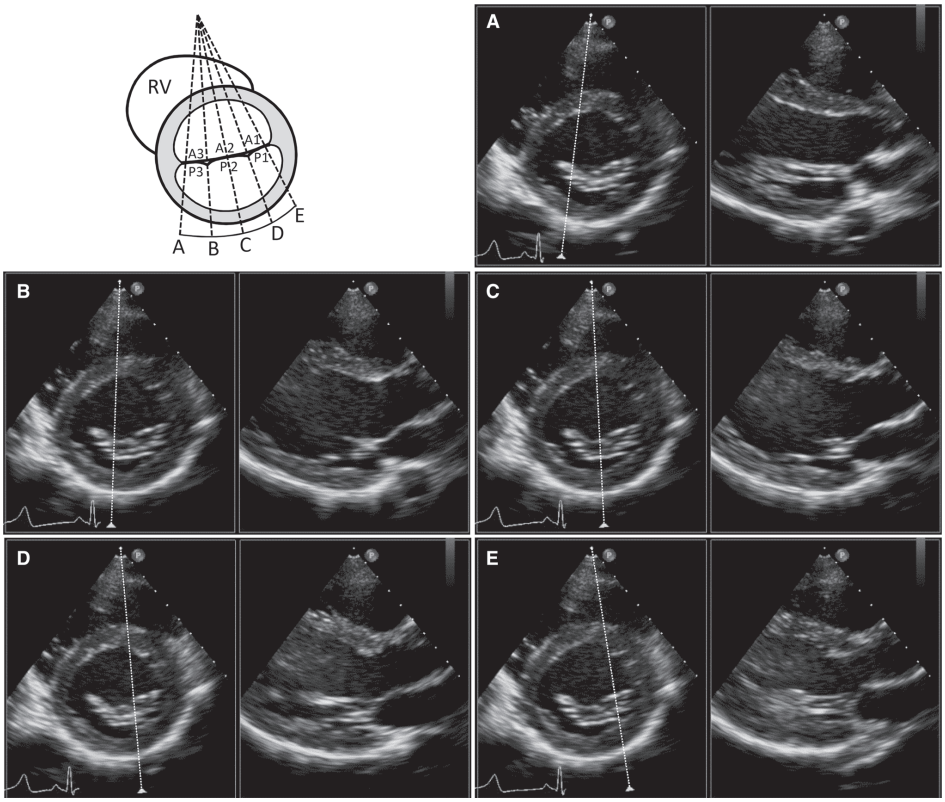

Figure 1. Segmental sweep analysis of the mitral valve scallops with 2D xPlane imaging with lateral tilt. A–E correspond to the P3, P2 medial, P2 central, P2 lateral and P1 scallops.

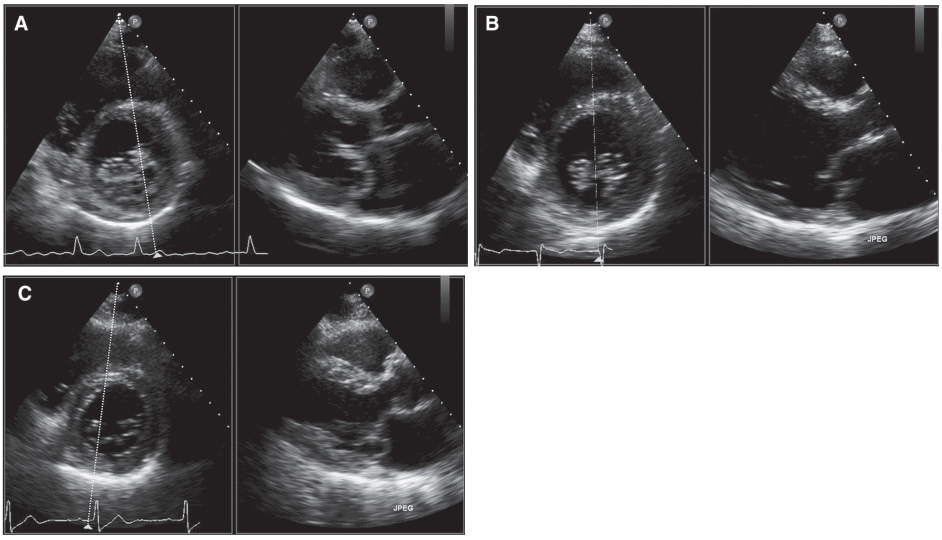

Figure 2. Segmental analysis of the mitral valve scallops with 2D xPlane imaging with lateral tilt. aP1 prolapse b P2 prolapse c P3 prolapse.

3D echocardiography

In patients in sinus rhythm a full-volume data set from four to six R-wave gated sub-volumes during a single end-expiratory breath-hold was acquired and in patients with atrial fibrillation a live 3D data set was acquired to avoid the concerns about stitching artefacts. All full-volume and live 3D data sets were taken from a parasternal or an apical window [11,12]. The 3D data set was manipulated, off- line, using QLAB version 9 (Philips Medical Systems, Best, The Netherlands) to show an 'en-face' or 'surgical' view of the MV as seen from the left atrium. The mean 3D volume rate was 36 ± 16 volumes per second.

Scoring protocol

A senior cardiologist with extensive experience in 2D and 3D echocardiography and MV disease analyzed all echocardiographic data sets blinded to other patient infor- mation with at least 10 days between each specific analysis in a random order. MV prolapse and segmental visualiza- tion of the affected scallop was classified according to the Carpentier nomenclature [13]. The extent of P2 prolapse was only assessed with 2D xPlane and 3D echocardiography since standard 2D echocardiography is not capable of doing so. The surgical findings served as the gold standard. However, in 6 cases the surgeon only described a P2 prolapse without a clear description on the specific extent of the prolapse. In these 6 cases, intra-operative 3D trans-esophageal data were used as supplementary gold standard data to describe the extent of the P2 prolapse.

The sensitivity of scoring a P1, P2 or P3 prolapse was calculated as the positive findings of the different modalities divided by the positive surgical findings. The specificity

was calculated as the negative findings of the different modalities divided by the negative surgical findings.

The identification of the extent of the P2 prolapse examined with 2D xPlane and 3D TTE was split up into five categories and compared with the surgical finding. The five categories are; Barlow disease (including P1 and P3 prolapse), broad P2 (central, including the centro-medial and centro-lateral edges of the P2 scallop but without P1 or P3 prolapse), small P2 (only central prolapse without incorporation of the centro-medial and centro-lateral edges), asymmetric P2 (central and only one edge) and edge P2 (one centro-medial or centro-lateral part only).

Statistical analysis

Prolapse site sensitivity and specificity were calculated according to standard formulas.

The degree of inter-observer agreement between the two blinded observers (MLG and JSMcG) for specific scallop prolapse using 2D xPlane and 3D echocardiography was assessed by calculating the Kappa coefficient (a value > 0.80 indicating excellent agreement).

RESULTS

Of the 57 patients referred for surgical repair, 7 patients (12 %) were excluded because a 3D TTE was not possible due to inadequate 2D image quality. In the remaining 50 patients mean age was 61 ± 16 years and 33 (66 %) were men. Forty (80 %) patients were in sinus rhythm and 10

(20 %) in atrial fibrillation. Eleven patients (22 %) had Barlow's disease involving both the anterior and posterior mitral valve leaflet. In 24 patients (48 %) the prolapse was confined to one or more posterior mitral valve scallops (P1 in 1, P2 in 13, P2 + P3 in 2, P3 in 8 patients). In the remaining 15 patients (30 %) no prolapse was seen and MR was due to mitral annular dilatation with or without retraction in 10 patients (20 %), endocarditis in 3 patients (6 %), and rheumatic disease in 2 patients (4 %).

Anterior mitral valve scallop

In 16 patients, a prolapsing anterior MV leaflet was seen. In the eleven patients with Barlow disease all prolapsing anterior MV leaflets were recognized with all techniques, apart from one patient in which 3D echocardiography missed the prolapse. In the 5 remaining patients the pro- lapse was confined to the A2 part in one patient, the A2–A3 part in one patient and the A3 part in three patients. Standard 2D analysis detected anterior MV leaflet prolapse in all patients although distinction between the specific scallops was problematic. 2D xPlane identified the specific prolapse part in all patients where as 3D echocardiography missed the prolapse in two patients with A3 prolapse.

Localization of posterior mitral valve scallop

As seen in Figure 3a, the respective sensitivities of 2D TTE, 2D xPlane, and 3D TTE for the identification of the precise posterior scallop prolapse were for P1 92, 85, and 92 %, for P2 96, 96, and 82 %, and for P3 86, 81, and 71 %. In total, 5 (8 %) prolapsing MV scallops were missed by 2D TTE, 7 (12 %) by 2D xPlane, and 12 (20 %) by 3D TTE. The sensitivity of 3D TTE was significantly lower than standard 2D imaging (80 vs. 93 %, $P < 0.05$). As seen in Figure 3b, the respective specificities of 2D TTE, 2D xPlane, and 3D TTE for the identification of the precise posterior scallop prolapse were for P1 100, 97, and 97 %, for P2 100, 91, and 91 %, and for P3 100, 97, and 97 %.

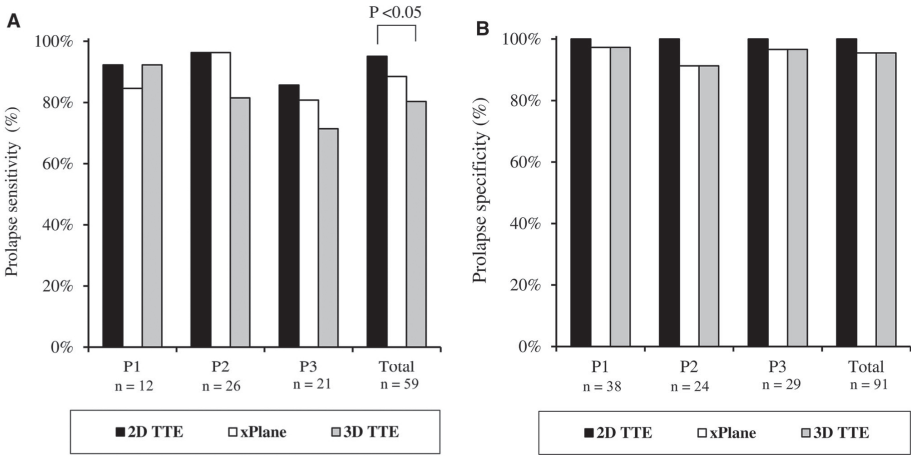

Figure 3. Sensitivity (a) and specificity (b) for the identification of posterior mitral valve scallop prolapse by the different echo techniques.

Identification of the extent of the P2 prolapse

The results of 2D xPlane and 3D TTE for accurately diagnosing the extent of the P2 prolapse are shown in Table 1. All 11 patients with a Barlow MV (that is involvement of the complete anterior and posterior MV leaflet) were correctly diagnosed by both modalities. Seven patients had a broad P2 prolapse. With 2D xPlane 4 were identified correctly and in 3 patients, a prolapsing P2 was seen, but the extent of prolapse was to some extent underestimated (one edge was missed). Whereas with 3D TTE, one was missed completely and 3 were underestimated (in two patient's one edge was missed and in one patient only a prolapsing edge was identified). Five patients had a small central P2 prolapse, 2D xPlane identified three correctly, overestimated one (that is one edge was also scored as prolapsing) and missed one. 3D TTE identified two correctly and missed three. In the three patients with asymmetric P2 prolapse (center and one edge), all three were correctly diagnosed with 2D xPlane, but two were underestimated (only a prolapsing edge was identified in one patient and only a prolapsing central part in one other patient) with 3D TTE. One patient

had a P2 one edge only prolapse that was diagnosed correctly with 2D xPlane and missed by 3D TTE. So, in total 4 and 9 scallop parts were missed or underestimated with 2D xPlane and 3D, respectively.

Table 1. Identification of the extent of P2 prolapse with transthoracic xPlane and 3D echocardiography.

Surgical findings / Echo findings	Barlow N = 11		Broad P2 (central + 2 edges) N = 7		Small P2 (central) N = 5		Assymetric P2 (central + 1 edge) N = 3		Edge P2 (1 edge only) N = 1	
	xPlane	3D	xPlane	3D	xPlane	3D	xPlane	3D	xPlane	3D
Broad	**11**	**11**	**4**	**3**	0	0	0	0	0	0
Small	0	0	0	0	**3**	**2**	0	**1**	0	0
Assymetric	0	0	**3**	**2**	**1**	0	**3**	**1**	0	0
Edge only	0	0	0	**1**	0	0	0	**1**	**1**	0
Negative (missed)	0	0	0	**1**	**1**	**3**	0	0	0	**1**

Colour legend: □ = correct, ■ = overestimation, ■ = underestimation, ■ = missed.

Inter-observer agreement

Seven additional 3D TTE were excluded because the second observer determined the 3D quality too poor to reliably assess the site of MV prolapse. Inter-observer agreement for specific scallop prolapse is shown in Figure 4. For 2D xPlane the agreement was excellent (97 %, kappa = 0.94). For 3D TTE the agreement was moderate (85 %, kappa = 0.67).

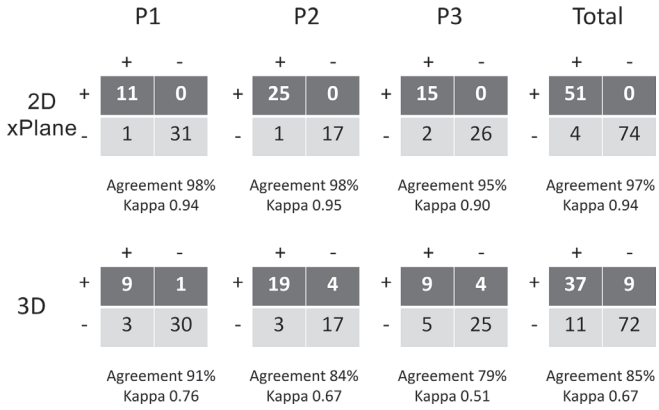

Figure 4. Interobserver variability in assessment of posterior mitral valve scallop prolapse by 2D xPlane and 3D echocardiography.

DISCUSSION

In this study we sought to assess the relative value of transthoracic standard 2D imaging, 2D xPlane imaging, and 3D imaging for the definition of the site and extent of MV prolapse. The main results of the study are (1) transthoracic 2D imaging has excellent diagnostic value in detection of the prolapsing MV scallop, (2) 2D xPlane and 3D imaging do not improve detection of the prolapsing MV scallop, (3) the extent and asymmetry of P2 prolapse can, however, only be assessed by xPlane and 3D imaging, and (4) 2D xPlane imaging may be superior to en-face 3D imaging in this latter aspect because it is (a) easier to implement as it is a 2D technique, (b) has a better inter-observer agreement, and (c) misses less prolapsing MV scallop parts because of less artifacts (dropouts and side-lobe artifacts) and better spatial resolution.

The definition of the site and extent of MV prolapse plays a crucial role not only in surgical referral but also for the operative plan since different pathology require different levels of surgical expertise based on the complexity of lesions seen with echocardiography [14,15]. Some authors have reported poor sensitivities of 2D TTE for the identification of prolapse [16], and in particular of the not centrally-located P1 and P3 scallops [4,17,18]. Minardi et al. reported sensitivities of 64, 99 and 50 % for respectively P1, P2, and P3 scallop prolapse (although they claimed overall sensitivity was excellent since the middle scallop P2 ‘‘represents almost the totality of prolapses’’). Also, Beraud et al. reported a correct description in only 22 % in patients with a prolapse other than isolated P2 prolapse. Pepi et al. reported a sensitivity of 40 % for the antero-lateral commissure and 54 % for the postero-medial commissure.

In contrast, Monin et al. reported sensitivities of 95 and 93 % for respectively the central P2 prolapse and the not centrally-located P1 and P3 scallops based on a similar 2D analysis. Our results of sensitivities of 92, 96, and 86 % for respectively P1, P2, and P3 prolapse are in line with these results of Monin et al. Of note, like in our study the echo studies were performed by dedicated ‘‘senior’’ sonographers and analyzed by a cardiologist with extensive experience in MV assessment. As a result of the excellent transthoracic 2D diagnostic results 2D xPlane and 3D imaging was not able to add diagnostic value. On the contrary, 2D-xPlane imaging and in particular 3D imaging resulted in more false negative results.

In the literature there is some controversy over the accuracy of 3D TTE for the evaluation of the site and extent of the MV prolapse. All investigators stated that 3D TTE is a feasible technique in the majority of patients. This was confirmed in our study as in only 7 patients (12 %) the 3D images were deemed not possible because of image quality by the sonographer and in another 7 patients the 3D image quality was found to be inadequate for analysis by one of the two observers. Several investigators stated that the accuracy of 3D TTE for the identification of scallop prolapse is high [7,17-20] and may even be superior to 2D TTE [17-19] or even 2D TEE [7]. Although Gutie´rrez- Chico already noted imperfect results for

the not centrally-located (lateral and medial) scallops [20], Zekry et al. pointed out clearly the difficulty in using 3D TTE to localize mitral valve segmental disease especially for the not centrally-located scallops: sensitivities were 7, 93, and 29 % for respectively P1, P2, and P3 scallop prolapse [21]. In our 3D study the sensitivity for the detection of P3 prolapse was also somewhat lower. Of note, Agricola et al. and Beraud et al. used a combination of en-face ''surgical'' views and 3 to 5 reconstructed longitudinal views (''rep- resenting the A1–P1, A2–P2, A3–P3 scallops and the two commissures'') and it was claimed to be, in particular, helpful in patients with commissural prolapse, although results were still sub-optimal.

The identification of 3D volume-rendered images may be difficult even for the experienced observer since a pro- lapsing scallop should be identified as a convexity or bulge, and often as a bright area when compared with the rest of the mitral valve. Despite exclusion of patients with poor echocardiographic images, the current spatial and temporal resolution of 3D transthoracic transducers in our opinion still limits the interpretation of images. This was evidenced not only by the 12 missed prolapsing scallops (compared to 5 and 7 with respectively 2D TTE and 2D xPlane), but also by the underestimation of P2 scallop extent by 3D.

2D xPlane imaging

With the introduction of 2D xPlane imaging it is possible to identify not only a prolapsing MV leaflet but also to assess, like 3D imaging, in a systematic manner the extent of MV prolapse. It is important to realize that the xPlane technique in fact mimics the 3D multiplane reconstruction with as opposite to 3D imaging only a minimal impact on spatial resolution compared to standard 2D imaging with a 2D transducer. Compared to the surgical findings 2D xPlane was a sensitive technique (overall 2D xPlane sensitivity 88 vs. 80 % for 3D) to identify MV prolapse and the inter- observer agreement for identification of the prolapsing MV scallop was excellent. Also, the sensitivity of 2D xPlane imaging for the identification of MV prolapse was not lower than standard 2D imaging, whereas 3D TTE was significantly lower compared to standard 2D imaging. In addition, good results were seen in the identification of the extent of P2 prolapse.

Any sonographer will be able to perform an accurate, rapid, online segmental analysis of the entire coaptation line of the MV with xPlane imaging. Virtually the images do not suffer from a loss in spatial resolution and rhythm irregularities will not affect the data. Although in the pre- sent study the identification of MV prolapse presence was not superior to standard 2D imaging it should be realized that the 2D images were interpreted by a senior cardiologist highly experienced in MV evaluation.

Clinical implications

Although not discussed in this article, 2D and 3D TEE imaging are excellent imaging tools to describe the MV geometry and mechanism of regurgitation and to guide the surgical ap-

proach. However, TEE is a semi-invasive imaging technique not totally without procedural risk [3,22]. Because 2D xPlane is an easy, accurate and noninvasive imaging modality we suggest standard 2D supplemented with 2D xPlane to be used in the outpatient clinic for optimal assessment of MV geometry and mechanism of regurgitation. Only in the few patients in whom doubt persists (in particular the involvement of the para-commissural scallops) 2D and/or 3D TEE imaging should be performed in the outpatient's clinic. Finally, preoperative TEE in the operating room (the ideal circumstance for studying the geometry and mechanism of the MV) may further refine the diagnosis and guide the surgical approach.

Limitations

The spatial resolution of the X5-1 matrix transthoracic probe remains somewhat inferior to the stand-alone 2D transducer and in addition the frame rate (temporal resolution) drops by half when entering the xPlane mode. This drop in temporal resolution however, does not seem very important in the assessment of the site and extent of MV prolapse and can be brought to a minimum by ensuring that the smallest sector able to encompass the MV is used.

Care must be taken with the interpretation of the extent of prolapse from the standard parasternal short axis view analysis since the motion of the heart throughout the cardiac cycle may result in the reference line not transecting the same region of interest at any time point in the heart cycle.

The echo studies were performed by dedicated ''senior'' sonographers and analyzed by a cardiologist with extensive experience in MV assessment. Therefore, our results may not be generalized to less experienced centers. In addition, TEE imaging was not considered in the design of the study because the aim of the study was to assess the relative value of transthoracic standard 2D imaging, transthoracic 2D xPlane imaging, and transthoracic 3D imaging for the definition of the site and extent of MV prolapse defined by the surgical standard.

Finally, the anatomical findings at surgery served as the gold standard. It should be recognized that surgeons assess an immobile valve in a flaccid heart whereas echocardiography assesses a dynamic valve. Unfortunately, there is no practical alternative to this approach.

CONCLUSION

2D xPlane imaging is an accurate, easy to use (compared to 3D TTE) and easy to interpret (compared to 2D and 3D TTE) imaging modality to study the site and the extent of MV prolapse.

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Chapter 5

The Role of Experience in Echocardiographic Identification of Location and Extent of Mitral Valve Prolapse with 2D and 3D Echocardiography

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ABSTRACT

Background

Contradiction exists on the incremental value of two-dimensional (2D) and 3D transoesophageal echocardiography (TOE) over 2D transthoracic echocardiography (TTE) for the detection of mitral valve (MV) prolapse in readers with different echocardiographic experience.

Methods

Twenty patients and five healthy persons were retrospectively identified who had undergone 2D-TTE, 2D-TOE and 3D-TOE. Fifteen (75%) patients had surgical evidence of prolapse of the posterior MV leaflet and five patients (25%) had a dilated MV annulus without prolapse. Three reader groups with different echocardiographic expertise (novice, trainees, cardiologists) scored thus in total 675 posterior scallops.

Results

Overall there was an improvement in agreement and Kappa values from novice to trainees to cardiologists. Diagnostic accuracies of 2D-TOE were higher than those of 2D-TTE mainly in novice readers. The incremental value of 3D-TOE over 2D-TOE was mainly seen in specificities. Time to diagnosis was dramatically reduced from 2D to 3D-TEE in all reader groups (all $P < 0.001$). 3D-TOE also improved the agreement (+12 to +16%) and Kappa values (+0.14 to +0.21) in all reader groups for the exact description of P2 prolapse.

Conclusion

Differences between readers with variable experience in determining the precise localization and extent of the prolapsing posterior MV scallops exist in particular in 2D-TTE analysis. 3D-TOE analysis was extremely fast compared to the 2D analysis methods and showed the best diagnostic accuracy (mainly driven by specificity) with identification of P1 and P3 prolapse still improving from novice to trainees to cardiologists and provided optimal description of P2 prolapse extent.

INTRODUCTION

Mitral valve (MV) prolapse is the leading cause of mitral regurgitation and the most frequent reason for MV surgery in the industrialized world [1]. Localisation of the prolapse is crucial for planning surgical management [2]. Two-dimensional (2D) transthoracic and transoesophageal echocardiography (TTE and TOE) are at this moment in most hospitals still the imaging modality of choice for assessment of the MV scallop(s). It is well recognized that a high level of expertise is required for accurate acquisition and interpretation of the 2D images. More recently, in several studies it has been demonstrated that 3D-TOE may be more easy and accurate to identify the locations of MV prolapse [3-6]. However, the generalizability of 3D-TOE publications has been questioned since the observers were usually highly experienced experts working in academic referral centers. Reproducibility is crucial for validation of the general concept that 3D-TOE is the superior imaging technique in non-experts. Currently, sparse data are available on this topic with contradictory results [7,8]. The current study was undertaken to assess the value of 2D-TTE, 2D-TOE and 3D-TOE in three groups of readers with different experience in TOE for the identification of posterior MV scallop prolapse.

METHODS

Patients population

Twenty patients who had undergone 2D-TTE, 2D-TOE and 3D-TOE before MV repair were retrospectively identified. Also five persons with suspected cardiac embolic source but normal MV anatomy who had undergone the same echocardiographic research were identified. The localization and extent of MV pathology (prolapse) in the 20 patients was defined by surgical exploration: isolated P1 in 0 patients, P1-P2 in 2 patients, P2 in 12 patients, P2-P3 in 2 patients, and isolated P3 in 4 patients.

Image acquisition and analysis

All TTE and TOE studies were performed by one single expert echocardiographer (JMcG and MLG respectively) using a Philips iE 33 ultrasound system (Philips Medical Systems, Best, the Netherlands), equipped with a S5-1 transducer for TTE and X7-2t matrix array transducer for TOE. 2D-TTE imaging included at least all the standard MV cross-sections as published by Monin et al. [9], 2D-TOE imaging included at least all the standard MV cross-sections as published by Foster et al.[10].

The 3D-TOE images were acquired in the zoomed mode, with a pyramidal volume allowing the highest temporal and spatial resolution, apart from a few patients in whom only a full volume dataset was available. The 3D loops were presented to the observers as the

surgical intraoperative “en-face” left atrial view of the MV, with the aortic valve rotated to the 12 o’clock position (Figure 1A).

Observers

Nine readers with different echocardiographic expertise scored all the 2D-TTE, 2D-TOE and 3D-TOE images in a random order. For all cases the observers noted the location of MV prolapse according to the Carpentier nomenclature: P1, P2 and P3 for the lateral, middle and medial scallops, respectively [11]. In addition, in case of identified P2 prolapse it was noted whether only the central part of P2 was prolapsing (small central P2 prolapse) or also the centro-medial and/or centro-lateral parts (broad P2 prolapse or asymmetric P2 prolapse) . The time for scoring the study was also noted in seconds.

Group 1 (novice) consisted of three medical students with no experience in echocardiography. These students were given a lecture on the anatomy of the MV scallops, in particular discussing schematic images of the MV anatomy displaying the scallops in standard recordings in 2D-TTE [9], 2D-TOE [10], and 3D-TOE (see Figure 1B).

Group 2 (trainees) consisted of three cardiologists in training with basic knowledge of 2D-TTE and 2D-TOE (but not 3D-TOE) echocardiography (number of 2D-TOE studies <75). These trainees received no formal lecture but the same schematic images as mentioned above of the 2D and 3D MV anatomy were provided.

Group 3 (cardiologists) consisted of three cardiologists with advanced knowledge of 2D-TTE, 2D-TOE and 3D-TOE echocardiography (number of independent 2D/3D-TOE studies >75).

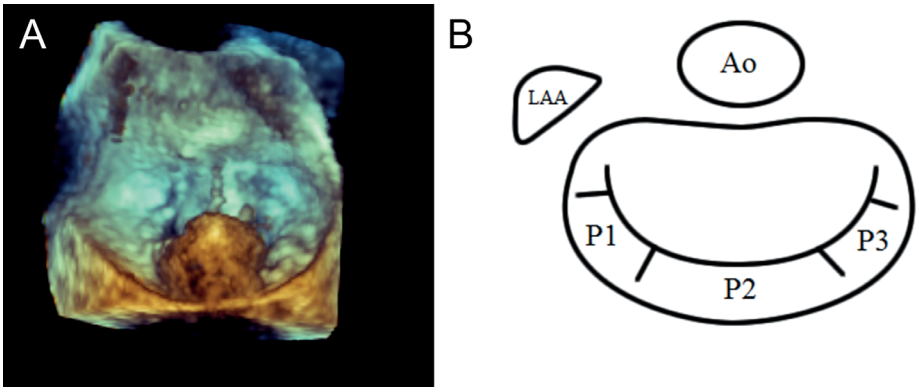

Figure 1
A = En-face view of the mitral valve with 3D echocardiography with a broad P2 prolapse
B = Schematic representation of the posterior mitral valve scallops.

Statistical analysis

Statistical analysis was performed using SPSS version 21.0.0.1 (SPSS, IBM, Armonk, NY). Categorical data are presented as numbers and percentages, whereas continuous data are summarized as mean ± standard deviation (SD) or median value with range. Comparisons of proportions (sensitivities, specificities, accuracies) were done with a one-sided Z test. A Wilcoxon signed ranks test was done for comparisons of time. P-values <0.05 were considered significant.

RESULTS

The study population of 20 patients and five normal subjects consisted of 15 men and 10 woman with mean age 60 ± 14 years. Six persons (including five normal MV) were in NYHA class I, 7 persons in NYHA class II and 11 and 1 person in NYHA class III and class IV, respectively. Six patients had also significant coronary artery disease.

Diagnostic accuracies of the different readers

The diagnostic sensitivities, specificities, accuracies (or agreement) and Kappa values are all displayed in Table 1. Overall (when all individual scallops were summated) there was an improvement in agreement and Kappa values from novice to trainees to cardiologists. This was most clearly seen for 2D-TTE and least clearly for 2D-TOE. With 2D-TTE sensitivity improved from novice to experts from 58% to 82% (P <0.005), specificity from 78% to 90% (P <0.005) and diagnostic accuracy from 72% to 88% (P <0.001). With 3D-TOE specificity increased from 89% to 95% (P <0.05) and diagnostic accuracy from 86% to 92% (P <0.05). The diagnostic improvement seen in more experienced readers was in particular caused by better identification of P3 prolapse (Kappa values increased from 0.19 to 0.47 to 0.73 for 2D-TTE, from 0.45 to 0.65 to 0.70 for 2D-TOE and from 0.52 to 0.72 to 0.85 for 3D-TOE). With 2D-TTE sensitivity increased from 33% to 72% (P <0.05), specificity from 84% to 96% (P <0.05) and diagnostic accuracy from 81% to 95% (P <0.005). With 3D-TOE specificity increased from 84% to 96% (P <0.05) and diagnostic accuracy from 81% to 95% (P <0.01). For the other scallops results were more ambiguous, apart from a better diagnostic accuracy in P1 scallop prolapse detection with 3D-TOE (Kappa values increased from 0.53 and 0.41 to 0.71).

Value of 2D-TOE over 2D-TTE in the different observer groups

The incremental value of 2D-TOE over 2D-TTE can also be appreciated from Table 1. Sensitivities, specificities and accuracies of 2D-TOE were higher than those of 2D-TTE in novice readers. The increments in these readers were 21% (P <0.01), 6% (P = NS), and 10% (P <0.01), respectively. Kappa values increased from 0.36 to 0.61. The increment in

sensitivity was driven by better detection of both P2 (increment 27%, P <0.001) and P3 (increment 11%, P = NS) scallop prolapse, the increment in specificity was driven by better exclusion of both P3 (increment 11%, P <0.05) and P1 (increment 6%, P = NS) scallop prolapse. The respective increments in intermediate readers were 6, 1, and 2% (all P = NS). The non-significant increment in sensitivity was driven by better detection of P1 and P3 scallop prolapse (all P = NS). In cardiologists no incremental value was seen.

Table 1. Diagnostic accuracy (agreement) and Kappa values for the detection of mitral valve scallop prolapse localization.

		Sensitivity			**Specificity**			**Accuracy**			**Kappa**		
		N	T	C	N	T	C	N	T	C	N	T	C
P1	2D-TTE	67	33	67	77	86	91	75	81	89	0.21	0.13	0.44
	2D-TOE	67	50	50	83	88	91	81	85	88	0.28	0.28	0.34
	3D-TOE	67	50	67	94	94	99	92	91	96	0.53	0.41	0.71
P2	2D-TTE	67	88	88	70	74	74	68	83	83	0.35	0.62	0.62
	2D-TOE	94	79	79	63	74	74	83	81	77	0.60	0.60	0.52
	3D-TOE	85	85	85	85	96	85	85	88	85	0.69	0.75	0.69
P3	2D-TTE	33	72	72	84	89	96	72	81	91	0.19	0.47	0.73
	2D-TOE	44	89	89	95	89	88	83	87	88	0.45	0.65	0.70
	3D-TOE	72	89	89	84	91	96	81	89	95	0.52	0.72	0.85
All	2D-TTE	58	75	82	78	85	90	72	82	88	0.36	0.59	0.72
	2D-TOE	79	81	79	84	86	87	82	84	84	0.61	0.65	0.65
	3D-TOE	81	81	85	89	93	95	86	89	92	0.69	0.75	0.81

Abbreviations: C = cardiologist, N = novice, T = trainee

Value of 3D-TOE over 2D-TOE in the different observer groups

The incremental value of 3D-TOE over 2D-TOE can also be appreciated from Table 1. Kappa values increased from 0.61 to 0.69 in novice, from 0.59 to 0.65 in trainees and from 0.65 to 0.81 in cardiologists. Minor non-significant improvements were seen in sensitivity to detect scallop prolapse [a significant effect on sensitivity was only seen in the novice group for P3 prolapse (increment 28%, P <0.05)]. The respective increments in specificity were: for novice readers 5% (P <0.10), for intermediate readers 7% (P <0.05) and for cardiologists 8% (P <0.01). The increments in specificity were in all groups driven by better exclusion of P1 and P2 scallop prolapse (it was only in cardiologists also driven by better exclusion of P3 scallop prolapse). In Figure 2 the standard views of all three

echocardiographic techniques in a patient are shown. In the 2D-TTE views it was difficult to see the prolapse. The P3 prolapse was clearly visualized with 2D-TOE (Figure 2B) and optimal with 3D-TOE (Figure 2C).

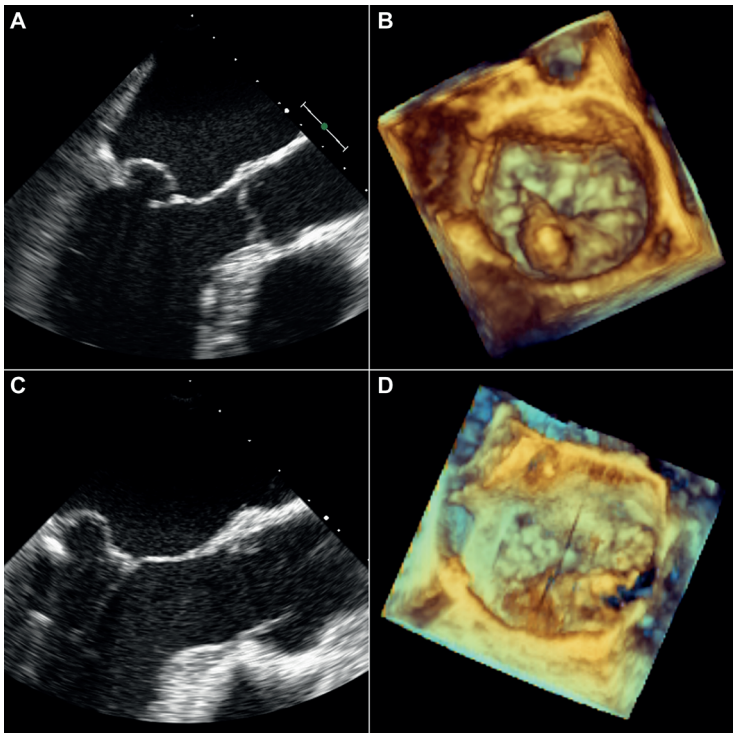

Figure 2
Visualization of mitral valve prolapse with the three different echocardiographic techniques.
A = Two-dimensional TTE with the mitral valve in the four standard views: parasternal long-axis, four chamber, two chamber and three chamber views.
B = Two-dimensional TOE with the mitral valve in three standard views: four chamber, bi-commissural (tilted more posterior in the first image) and long-axis views.
C = Three-dimensional TOE en-face view of the mitral valve with clear visualisation of the P3 prolapse.

Value of 3D-TOE over 2D-TOE in identification of exact P2 prolapse localization and extent

In the 16 patients with P2 prolapse the prolapse was defined by the surgeon as small centrally located in three patients, a broad (involving the centro-medial and central and centro-lateral parts) in six patients and asymmetric (involving the centro-medial or centro-lateral part with or without central location) in seven patients. As seen in Table 2, 3D-TOE improved the agreement and Kappa values in all reader groups. An example of improved identification of the P2 prolapse localization and extent is given in Figure 3.

Table 2. Identification of P2 prolapse according to the precise localization or extent (broad, small central, or eccentric)

Readers	2D agreement (%)	3D agreement (%)	2D Kappa	3D Kappa
Novice	47	59 (+12)	0.28	0.42 (+0.14)
Trainees	55	67 (+12)	0.36	0.53 (+0.17)
Cardiologists	48	64 (+16)	0.29	0.50 (+0.21)

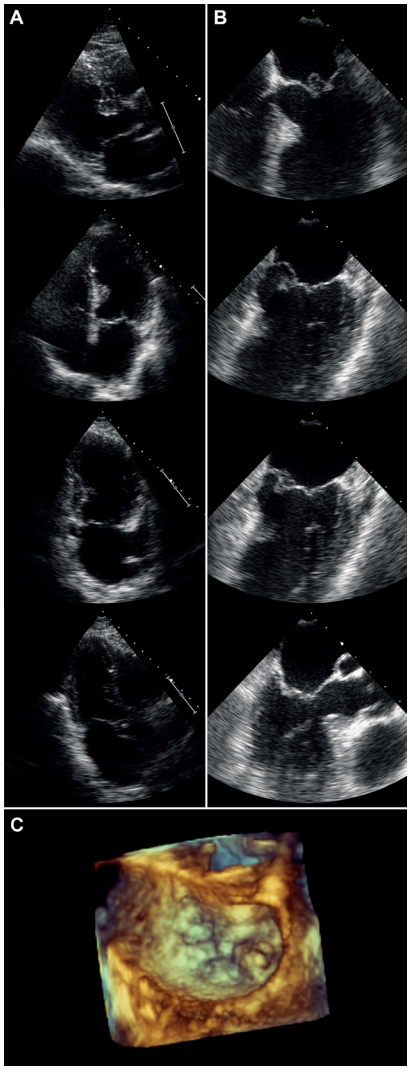

Figure 3
Two-dimensional TOE with prolapse of the posterior mitral valve leaflet (A and C)
Three dimensional TOE with different prolapse of the posterior mitral valve leaflet: broad P2 prolapse (B) and asymmetric P2 (centro-medial) in addition to a P3 prolapse (D).

Analysis time

As seen in Table 3, students needed more time to diagnose the lesion for both 2D-TTE (107 ± 57 vs. 65 ± 33 msec in trainees, P <0.001 and 86 ± 62 msec in cardiologists, P <0.02) and 2D-TEE (99 ± 64 vs 62 ± 26 msec in trainees, P <0.001 and 82 ± 57 msec in cardiologists, P <0.10). The time to diagnosis was dramatically reduced from 2D to 3D-TEE in all reader groups (all P <0.001). No differences in time to diagnosis existed for 3D-TEE between the reader groups (students 15 ± 11 msec, trainees 16 ± 12 msec and cardiologists 17 ± 13 msec).

Table 3. Time in seconds to diagnosis for the different observer groups

Readers	Novice	Trainee	Cardiologist
2D-TTE	107 ± 57	65 ± 33	86 ± 62
2D-TOE	99 ± 64	62 ± 26	82 ± 57
3D-TOE	15 ± 11	16 ± 12	17 ± 13

DISCUSSION

In this study we sought to assess the advantage of 2D and 3D-TOE over 2D-TTE to determine the precise localization and extent of the prolapsing segments of the posterior MV leaflet in readers with different levels of experience in echocardiography. The main findings of the present study were 1) the diagnostic accuracy of 2D-TTE for the identification of posterior mitral valve scallop prolapse increased from novice to trainees to cardiologists, 2) the diagnostic accuracy of 2D-TOE was higher than that of 2D-TTE for novice readers only, 3) with 3D-TOE time to diagnosis was much shorter and best diagnostic accuracy (mainly driven by specificity) was seen, and 4) identification of P1 and P3 prolapse with 3D-TOE still improved from novice to trainees to cardiologists.

The presence, location and extent of prolapse is of crucial importance in defining the likelihood of successful MV repair [2,12]. As seen in this study, more experienced observers - but not less experienced - may identify the prolapsing MV scallops quite satisfactorily with 2D-TTE. Others and us also have shown that experts, certainly in patients with good transthoracic windows, with current transducer technology and standardized acquisition and analysis of planes may have an excellent diagnostic accuracy in assessment of posterior MV leaflet prolapse [9,13]. Traditionally, however, 2D-TOE has been regarded as the gold standard to define MV anatomy. However, it should be recognized that multiplane 2D-TOE is highly operator dependent since it requires manual manipulation of the transducer in the esophagus to acquire views of all parts of the MV leaflets. This process may even be complicated by factors such as distortion of left ventricular geometry, mitral annular dilatation, and aortic root enlargement that can change all of the orientation of the ultrasound plane in relation to MV anatomy, resulting in scallop misidentification. More important,

identification of the prolapsed segment is also highly operator dependent, because it requires the operator to be skilled at mentally reconstructing the MV in three dimensions from multiple 2D-TOE images to understand the underlying MV anatomy. This mental reconstruction often requires information obtained through live probe manipulation that is not permanently recorded. Thus, once the TOE study is completed, this information is not available to another reviewer at a later time as only limited views are saved. The importance of this limitation is difficult to assess but it should be noticed that in our study even novice readers showed good diagnostic results with 2D-TOE, albeit not optimal. With 3D-TOE, the entire mitral valve can be visualized in a single image, making it possible to examine both leaflets from the left atrial (surgical) perspective, allowing more definitive identification of prolapse of individual scallops and segments. Thus, mental reconstruction is no longer critical for localization of MV pathology.

Compared with 2D-TOE, 3D-TOE is less operator dependent and does not require the finesse of probe manipulation to delineate MV pathology. Good quality 3D-TOE "en-face" views of the MV obviate the need for the process of mentally reconstructing the MV and therefore such images may be very helpful, in particular, in less-experienced observers.

However, interpretation of 3D echocardiographic images also requires a learning curve and even with 3D images false identification of segmental lesions may occur, in particular in the commissural regions [14]. The generalizability of 3D-TOE publications has also been questioned since the observers (usually only a single one) were highly experienced experts working in academic referral centers. Reproducibility is crucial for validation of the general concept that 3D-TOE is superior to 2D-TOE in non-experts. Unfortunately, conflicting data were reported for the incremental value of 3D "en-face" analysis of MV scallops. In the study of Hien et al. six patient cases were analyzed by 21 physicians without clinical experience in TOE and 15 physicians certified at an expert level. Significant benefits were seen for 3D-TOE in both novice persons without experience with TOE and experts [7]. In contrast, in a study by Tsang et al. 50 patient cases were scored by 10 readers with different experience in echocardiography but sensitivity nor specificity for the detection of MV scallop prolapse improved, actually the observers had even greater difficulty with 3D-TOE compared with 2D-TOE data (in their study only 3D parametric maps made by experts improved diagnostic accuracy) [8]. In our study small improvements were seen in all reader groups, mainly based on improvements in diagnostic specificity. Importantly, 3D-TOE also improved the agreement and Kappa values in all reader groups for the exact description of P2 prolapse.

Limitations

The images used for this study were acquired by expert TTE and TOE echocardiographers resulting in high-quality images. This may have influenced both the lack of additional value of 2D-TOE over 2D-TTE in the more-experienced readers, as reported also by others [9],

and the relatively high diagnostic accuracy of the less-experienced observers. Also, only posterior scallop prolapse was analyzed in this study. This was done because such lesions constitute the most common localized form of prolapse and most importantly a scallop subdivision of the anterior MV leaflet is artificial since this leaflet has no indentations. The study population was composed of persons without any MV disorder and patients who were referred for MV repair, which give a bias of including pathology that is severe and also more amenable to surgical repair. However, this cannot be avoided when an independent gold standard is necessary. It should also be recognized that a surgical gold standard may overcall prolapse because when the mitral valve is inspected and the heart volume is small. However, the results of this study in comparing different expertise would still be valid.

3D-TTE images were not included in the present study because it is well agreed that even in the hand of experts 3D-TTE has limited accuracy in prolapse identification [3,13-15]. Finally, each reader group consisted of only a small number of readers. However, the total number of analyses scallops was with 675 analyses not small.

CONCLUSION

Differences between readers with variable experience in determining the precise localization and extent of the prolapsing posterior MV scallops exist in particular in 2D-TTE analysis. 3D-TOE analysis was extremely fast compared to the 2D analysis methods and showed the best diagnostic accuracy (mainly driven by specificity) with identification of P1 and P3 prolapse still improving from novice to trainees to cardiologists and provided optimal description of P2 prolapse extent.

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Chapter 6

Geometric Errors of the Pulsed-Wave Doppler Flow Method in Quantifying Degenerative Mitral Valve Regurgitation: A Three-dimensional Echocardiography Study

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ABSTRACT

Aim

The aim of this study was to estimate geometric errors made by the two-dimensional (2D) transthoracic echocardiographic (TTE) pulsed-wave Doppler flow (PWDF) method in calculating regurgitant volume (RVol) and effective regurgitant orifice area (EROA) in degenerative mitral regurgitation (MR) by comparison with the three-dimensional (3D) transesophageal echocardiographic (TEE) PWDF method.

Methods

RVol and EROA were calculated in 22 patients with degenerative MR using the conventional 2D TTE PWDF method on the basis of monoplanar dimensions and a circular geometric assumption of the crosssectional areas (CSAs) of the mitral annulus (MA) and the left ventricular outflow tract (LVOT) and the 3D TEE PWDF method, in which the CSAs of the MA and LVOT were measured directly in ''en face'' views. Diameters of the MA and LVOT were also measured in similar views as with TTE imaging in 3D TEE data sets.

Results

Both the MA and LVOT were oval. Mean MA diameters were 41 ± 4 mm (3D TEE major axis), 31 ± 4 mm (3D TEE minor axis), 39 ± 5 mm (2D TTE imaging), and 38 ± 5 mm (2D TEE imaging). Mean LVOT diameters were 29 ± 4 mm (3D TEE major axis), 21 ± 2 mm (3D TEE minor axis), 22 ± 2 mm (2D TTE imaging), and 23 ± 2 mm (2D TEE imaging). Compared with 3D TEE measurements, mitral annular CSA was overestimated by 13 ± 12% on 2D TTE imaging and by 7 ± 14% on 2D TEE imaging, while LVOT CSA was underestimated by 23 ± 10% and 17 ± 10%, respectively. Mean values of RVol were 95 ± 43 mL (3D TEE PWDF), 137 ± 56 mL (2D TTE PWDF), 120 ± 45 mL (2D TEE PWDF), and 111 ± 49 mL (flow convergence). Mean EROAs were 69 ± 34 mm^2 (3D TEE PWDF), 98 ± 45 mm^2 (2D TTE PWDF), 88 ± 42 mm^2 (2D TEE PWDF), and 79 ± 36 mm^2 (flow convergence). Observer variability for 3D TEE imaging was better than for 2D imaging.

Conclusion

The 2D TTE PWDF method overestimates mitral RVol and EROA significantly because monoplanar 2D measurements represent mitral annular major-axis diameter and LVOT minor-axis diameter, and assumed circular CSAs of the MA and LVOT are oval.

INTRODUCTION

Quantification of mitral regurgitation (MR) is essential to determine the severity of MR and clinical outcomes [1,2] .The two most used quantitative parameters are regurgitant volume (RVol) and effective regurgitant orifice area (EROA), which may be calculated by the flow convergence method and the pulsed-wave Doppler flow (PWDF) method as previously recommended [1,3]. However, both of these methods suffer from geometric limitations of two-dimensional (2D) echocardiography. The flow convergence method potentially underestimates RVol and EROA in functional MR, because the shape of the flow convergence zone may be elliptic instead of hemispheric in this situation [4-11]. In the PWDF method, important geometric errors are made in calculating the cross-sectional areas (CSAs) of the mitral annulus (MA) and left ventricular outflow tract (LVOT), because of the monoplanar measurements and geometric assumption [12]. In this study, we sought to ascertain the geometric errors made by the traditional 2D transthoracic echocardiographic (TTE) PWDF method in calculating RVol and EROA in patients with degenerative MR, by comparison with the three-dimensional (3D) transesophageal echocardiographic (TEE) PWDF method. Using the latter method, the CSAs of the MA and LVOT were measured directly in state-of-the-art ‘‘en face’’ views on 3D TEE imaging.

METHODS

Study Population

From November 2009 to September 2011, we prospectively enrolled 96 consecutive patients referred to our center for potential mitral valve (MV) repair who had undergone baseline TTE and TEE examinations. In the present study, we included patients with (1) degenerative MR according to preoperative TTE findings, (2) P2 scallop prolapse confirmed by both 3D TEE examination and surgery, and (3) good 3D image quality, with complete regions of interest and without stitching artifacts. The exclusion criteria were (1) MR due to other etiologies or mechanisms (e.g., endocarditis, functional MR; $n = 39$), (2)

prolapse of other scallops ($n = 19$), (3) a severely calcified MA ($n = 11$), (4) more than trivial aortic valve regurgitation ($n = 3$), and (5) poor general image quality ($n = 2$). Eventually, 22 patients (12 men; mean age, 64 ± 10 years) were included in the study. The protocols were approved by the institutional review board, and informed consent was obtained from all patients.

PWDF Method

2D TTE Measurements. Two-dimensional TTE imaging was performed using the iE33 ultrasound system (Philips Medical Systems, Best, The Netherlands) with the S5-1 trans-

ducer. The pulsed-wave Doppler sample was carefully placed as parallel as possible (angle < 20^{0}) to the blood flow in the apical four-chamber and three- chamber views to obtain the Doppler spectral profiles of the MA and LVOT [13]. The mitral annular diameter was measured between the inner edges of the base of posterior and anterior leaflets in early to mid diastole at maximal MV opening in the apical four-chamber view; the LVOT diameter was measured just below the aortic valve in early to mid systole in the parasternal long-axis view [3,13]. Both diameters were measured at the level at which the volume sample had been placed. The modal velocity profile on Doppler recordings was traced to obtain the velocity-time integral (VTI) (Figure 1). The regurgitant VTI was averaged from measurements in the apical four-chamber and three-chamber views. All measurements were averaged over three cardiac cycles.

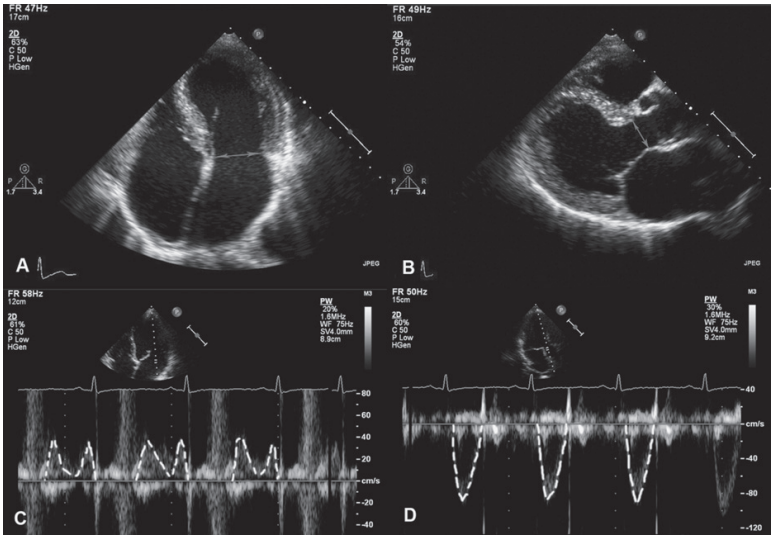

Figure 1.
Measurements of the 2D TTE PWDF method. (A) The diameter of the MA was measured between the inner edges of the base of the posterior and anterior leaflets in early to mid diastole at the maximal opening of the MV (two to three frames after the MV opened) in the apical four-chamber view. (B) The diameter of the LVOT was measured just below the aortic valve in early to mid systole in the parasternal long-axis view. (C) Mitral annular inflow pulsed-wave Doppler was traced to obtain the VTI of mitral inflow. (D) LVOT pulsed-wave Doppler was traced to obtain the VTI of ventricular outflow.

3D TEE Measurements. Three-dimensional TEE imaging was performed using the iE33 ultrasound system with the X7-2t matrix-array transducer. Electrocardiographically gated full-volume data sets (built from seven subvolumes) were acquired at the midesophageal level during breath-hold with the ultrasound focus on the MV in the four-chamber view and on the LVOT in the long-axis view. Care was taken to include the complete mitral annular and LVOT circumferences throughout the acquisition. Each full-volume data set

was digitally stored and exported to QLAB 8.0 3DQ software (Philips Medical Systems) for offline analysis. The en face views of the MA and LVOT were revealed at time points during the cardiac cycle similar as for the 2D TTE measurements and adjusted to the level at which the pulsed-wave Doppler volume sample had been placed in the 2D TTE examinations. Subsequently, the inner border of the cross-sectional planes of the MA and LVOT as well as the major-axis and minor-axis diameters were measured (Figure 2).

2D TEE Measurements. By adjusting the orthogonal multiplanar reconstruction views of the 3D TEE data sets, the diameter of the MA was measured in the four-chamber view in early to mid diastole at the maximal opening of the MV, and that of the LVOT was measured in early systole in the long-axis view (Figure 2). Both diameters were measured at the level at which the volume sample had been placed. Using the same VTI_{MR}, VTI_{MA}, and VTI_{LVOT} values obtained during the 2D TTE examinations, the 2D TTE, 3D TEE, and 2D TEE measurements of the diameters or CSAs were used in the following formulas to calculate the RVol and EROA:

$$RVol = SV_{MA} - SV_{LVOT} = \pi r^2_{MA} \times VTI_{MA} - \pi r^2_{LVOT} \times VTI_{LVOT};$$

and

$$EROA = RVol/VTI_{MR};$$

where *r* is the radius and SV is the stroke volume.

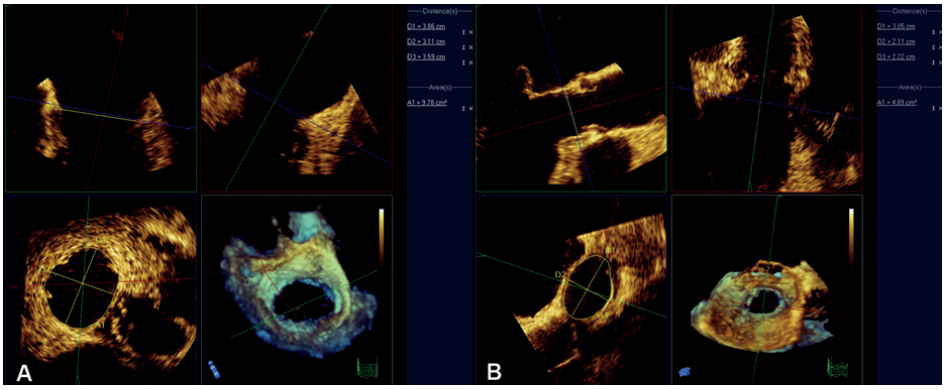

Figure 2.
Measurements of the 3D and 2D TEE PWDF methods. The 3D TEE data sets were displayed as three orthogonal images of the MA (A) and LVOT (B), and the visualization of the entire structures was optimized by adjusting the reference planes (the *green, red,* and *blue planes*). The blue planes showed the en face views of the MA and LVOT, in which the inner border of the CSAs of the MA and LVOT were traced manually and the CSAs and major and minor diameters were measured directly. The green plane (A) was adjusted to the four-chamber view and the mitral annular diameter was measured; the green plane (B) was adjusted to the long-axis view and the LVOT diameter was measured. All measurements were performed at the level at which the sample volume of pulsed-wave Doppler had been placed in the 2D TTE examinations.

Flow Convergence Method

The flow convergence of MR was shown in a zoomed view of color flow Doppler aliasing at the Nyquist velocity limit (30–40 cm/sec) in the apical four-chamber and three-chamber views. The selected cine loop was reviewed stepwise, and a clearly defined mid to late systolic maximal flow convergence zone was measured from the zenith to the regurgitant orifice. The averaged values measured in both views were used to calculate the RVol and EROA using the following formulas:

$$\text{EROA} = 2\pi r^2 \, x \, V_a / PkV_{\text{Regurg}}$$

and

$$\text{RVol} = \text{EROA} \, x \, \text{VTI}_{\text{MR}};$$

where r is the radius of the flow convergence, V_a is the aliasing velocity, and PkV_{Regurg} is the peak velocity of MR.

Vena Contracta Width

The vena contracta width of the MR jet was measured at the narrowest portion of the regurgitant jet in zoom mode with an adapted Nyquist limit (59.3 cm/sec) and averaged from the measurements in the four-chamber and three-chamber views.

Statistical analysis

All values are expressed as median (range) or as mean ± SD. One- factorial repeated-measures analysis of variance or Friedman's analysis of variance was used to compare the diameters, CSAs, SVs, RVols, and EROAs calculated using the different methods. When differences were found, any two methods were compared using the paired *t* test or Wilcoxon's signed-rank test with Bonferroni's correction. Linear regression analysis was used to assess the correlation of variables of interest. Agreement between methods was assessed using Bland- Altman method, in which differences were plotted against the means of measurements. Interobserver and intraobserver variabilities were tested by analyzing 2D and 3D images by two blinded observers (B.R., L.G.L.) and by the same observer (B.R.) at two difference times. The results were analyzed by the relative difference (expressed as the absolute difference divided by the mean) and Bland-Altman method.

RESULTS

Baseline Characteristics of the Patient Population in the Echocardiographic Studies

All patients included underwent MV repair. The baseline TTE examination was performed to ascertain the severity of MR, and the TEE examination performed on the same day was performed to determine the exact mechanism of MR and guide the selection of the cardiac surgeon. However, the preoperative TEE examination was declined or unsuccessful in eight patients, and in one patient, image quality was inferior because of poor general image quality and 3D stitching artifacts. For these nine patients, intraoperative TEE imaging under general anesthesia was chosen as the baseline TEE study. The intraoperative TEE examination was performed within 24 hours of the baseline TTE examination in three patients and 6 to 35 days after the baseline TTE examination in six patients. Of the 13 patients who underwent both baseline TTE and TEE imaging in the outpatient clinic, nine also underwent intraoperative TEE imaging. The time period between the preoperative TEE study and the intraoperative TEE study was 1 to 32 days. Although the hemodynamic characteristics of these nine patients changed significantly, the shapes and sizes of the MA and LVOT remained relatively constant (Table 1).

Table 1. Comparisons of the patients' hemodynamic characteristics and mitral annular and LVOT morphologies in the preoperative and intraoperative TEE examinations ($n = 9$)

Variable	Preoperative TEE imaging	Intraoperative TEE imaging
Heart rate (beats/min)	97 (71-123)	68 (48-99)
Bloodpressure (mmHg)		
Systolic	140 (110-163)	105 (80-125)
Diastolic	80 (60-88)	50 (40-75)
MA		
Major-axis/minor-axis diameter ratio	1.3 (1.0-1.6)	1.4 (1.1-1.5)
CSA (mm^2)	1,058 (840-1,542)	1,105 (747-1,788)
LVOT		
Major-axis/minor-axis diameter ratio	1.4 (1.2-1.7)	1.4 (1.1-1.5)
CSA (mm^2)	497 (443-723)	548 (424-630)

Data are expressed as median (range)

Comparison of the 2D and 3D Dimensions and CSAs of the MA and LVOT

The frame rate of the 2D data sets and volume rate of the 3D data sets were not different (49 6 ± frames/sec vs 46 ± 8 volumes/sec). As shown in Table 2, the 2D TTE and 2D TEE diameters of the MA and LVOT were not significant different from each other. Both the MA and LVOT were oval in the 3D en face views, with a significant difference between the major-axis and minor-axis diameters ($P < .001$ for both). The major-axis/minor-axis diameter ratio of the MA was 1.3 ± 0.2, and that of the LVOT was 1.4 ± 0.2. The 2D diameters

of the MA and LVOT were significantly different from both the major- axis and minor-axis diameters ($P < .05$ for all). The CSAs of the MA and LVOT calculated from 2D TTE and 2D TEE diameters were similar. For the CSA of the MA, the 2D TTE measurements were significantly different from the 3D TEE direct measurement ($P < .001$) and overestimated the CSA by 13 ± 12%; although the 2D TEE measurements were not significantly different from the 3D TEE measurements, the CSA was still overestimated by 7 ± 14%. For the CSA of the LVOT, both 2D TTE and 2D TEE measurements were significantly different from the 3D TEE direct measurements ($P < .001$ for both), and the CSAs were underestimated by 23 ± 10% by the 2D TTE measurements and 17 ± 10% by the 2D TEE measurements.

Table 2. The diameters and CSAs of the MA and LVOT in degenerative MR obtained with the 2D and 3D measurements

	Diameter (mm)				CSA (mm^2)		
	2D measurements		3D TEE measurements		2D measurements		3D TEE measurements
Structure	TTE imaging	TEE imaging	Major axis	Minor axis	TTE imaging	TEE imaging	
MA	39 ± 5[*,†]	38 ± 5[‡]	41 ± 4[§]	31 ± 4	1,185 ± 304[*,#]	1,117 ± 254[¶]	1,050 ± 247
LVOT	22 ± 2[*,†]	23 ± 2[‡]	29 ± 4[§]	21 ± 2	391 ± 73[*,#]	426 ± 80[‡]	517 ± 110

[*] P = NS for 2D TTE versus 2D TEE measurements.
[†] $P < .05$ for 2D TTE versus 3D TEE measurements.
[‡] $P < .001$ for 2D TEE versus 3D TEE measurements.
[§] $P < .001$ for 3D TEE major versus minor axis measurements.
[#] $P < .001$ for 2D TTE versus 3D TEE measurements.
[¶] P = NS for 2D TEE versus 3D TEE measurements.

Comparison of Mitral RVol and EROA by the 2D and 3D PWDF and Flow Convergence Methods

As a result of the differences in CSAs obtained by 2D and 3D measurements, the SV at the mitral annular level was overestimated by 13 ± 12% by the 2D TTE measurements and by 7 ± 14% by the 2D TEE measurements, while the SV at the LVOT level was underestimated by 23 ± 10% by the 2D TTE measurements and by 17 ± 10% by the 2D TEE measurements. The RVol and EROA obtained by the 3D TEE PWDF method were significantly smaller than those calculated by the 2D PWDF methods ($P < .001$ for all; Table 3). Compared with the 3D TEE measurements, RVol and EROA were overestimated by 54 ± 39% by the 2D TTE PWDF method and by 39 ± 40% by the 2D TEE PWDF method.

Compared with the flow convergence method, the RVols obtained by the 3D PWDF methods correlated better with the RVols obtained using the flow convergence method than the 2D PWDF methods did (2D TTE PWDF vs flow convergence, $r = 0.91$; 2D TEE PWDF vs flow convergence, $r = 0.72$; 3D PWDF vs flow convergence, $r = 0.94$; Figure 3). Com-

Table 3. SVs at the level of the MA and LVOT and mitral RVol and EROA obtained by the flow convergence and 2D and 3D PWDF methods

Variable	Flow convergence method	PWDF method		
		2D TTE imaging	2D TEE imaging	3D TEE imaging
SV (mL)		198 ± 55[*,†]	186 ± 44[‡]	175 ± 42
MA	-	61 ± 21[*,†]	66 ± 20[§]	80 ± 23
LVOT	-			
RVol (mL)	111 ± 49	137 ± 56[†,ǂ,¶]	120 ± 45[§,#]	95 ± 43[**]
EROA (mm^2)	79 ± 36	98 ± 45[*,†,¶]	880 ± 42[§,#]	69 ± 34[**]

[*] P = NS for 2D TTE versus 2D TEE PWDF method.
[†] $P < .001$ for 2D TTE versus 3D TEE PWDF method.
[‡] P = NS for 2D TEE versus 3D TEE PWDF method.
[§] $P < .001$ for 2D TEE versus 3D TEE PWDF method.
[ǂ] $P < .05$ for 2D TTE versus 2D TEE PWDF method.
[¶] $P < .001$ for 2D TTE PWDF versus flow convergence method.
[#] P = NS for 2D TEE PWDF versus flow convergence method.
[**] $P < .05$ for 3D TEE PWDF versus flow convergence method.

parisons with the flow convergence method revealed that RVol was overestimated by 24 ± 23% by the 2D TTE PWDF method (137 ± 56 vs 111 ± 49 mL, $P < .001$) and by 14 ± 40% by the 2D TEE PWDF method (120 ± 45 vs 111 ± 49 mL) but underestimated by 17 ± 17% by the 3D TEE PWDF method (95 ± 43 vs 111 ± 49 mL, $P < .05$). A very similar pattern was found for EROA. Here too, the EROAs obtained by the 3D PWDF method correlated better with those obtained using the flow convergence method than the 2D PWDF methods did (2D TTE PWDF vs flow convergence, $r = 0.92$; 2D TEE PWDF vs flow convergence, $r = 0.76$; 3D PWDF vs flow convergence, $r = 0.95$; Figure 3). The magnitude of the overestimation and underestimation by comparison with the flow convergence method was the same as for RVol: the EROA was overestimated by 24 ± 23% by the 2D TTE PWDF method (98 ± 45 vs 79 ± 36 mm^2, $P < .001$) and by 14 ± 40% by the 2D TEE PWDF method (88 ± 42 vs 79 ± 36 mm^2) but underestimated by 17 ± 17% by the 3D PWDF method (69 ± 34 vs 79 ± 36 mm^2, $P < .05$).

Bland-Altman analysis plots for agreement of the RVol and EROA between the PWDF methods and flow convergence method are also depicted in Figure 3. For RVol, the bias ± 2 standard deviations was 26 ± 48 mL (2D TTE PWDF vs flow convergence), 9 ± 71 mL (2D TEE PWDF vs flow convergence), and 16 ± 34 mL (3D TEE PWDF vs flow

convergence). For EROA, the bias ± 2 standard deviations was 20 ± 38 mm^2 (2D TTE PWDF vs flow convergence), 9 ± 56 mm^2 (2D TEE PWDF vs flow convergence), and 10 ± 23 mm^2 (3D TEE PWDF vs flow convergence). There was smaller bias and tighter limits of agreement between the 3D TEE PWDF and flow convergence methods than between the 2D PWDF and flow convergence methods.

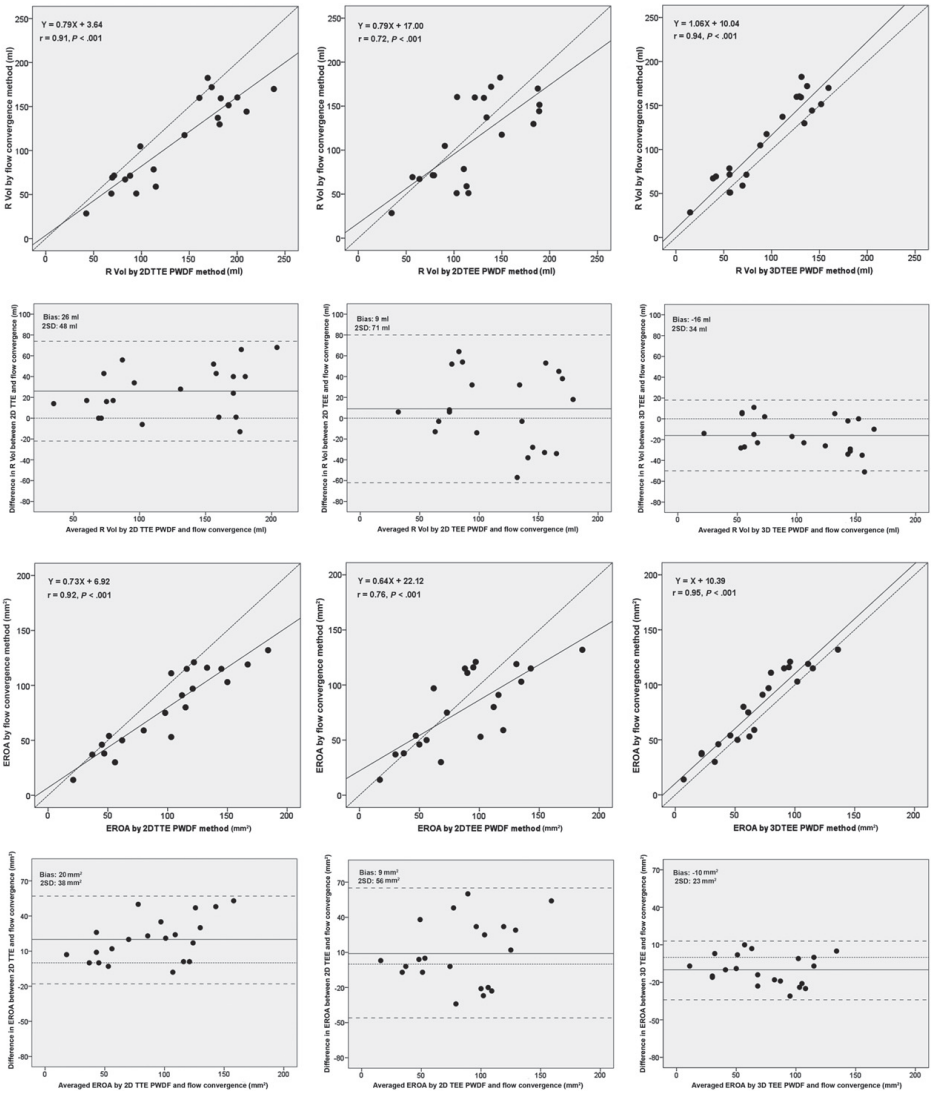

Figure 3.

Linear regression and Bland-Altman analysis comparing the mitral RVol and EROA by the 2D TTE (*left column*), 2D TEE (*mid- dle column*), and 3D TEE (*right column*) PWDF methods, with respective values by the flow convergence method.

Categorizations of MR Severity according to Different Methods

The MR severity of the patients included was categorized according to the RVol and EROA calculated by the 2D TTE, 2D TEE, 3D TEE PWDF, and flow convergence methods and vena contracta width on the basis of the American Society of Echocardiography's recommendations for evaluation of the severity of native valvular regurgitation using 2D and

Doppler echocardiography [1]. The severity of MR was different in five patients (Table 4) and the same for the other 17 patients.

Table 4. Categorization of MR severity in patients with discrepancies in MR severity using different methods (n = 5)

Patient	2D TTE PWDF	2D TEE PWDF	3D TEE PWDF	Flow convergence	Vena contracta
1	Severe	Severe	Moderate	Severe	Moderate
2	Severe	Severe	Moderate to severe	Moderate to severe	Moderate
3	Severe	Severe	Moderate to severe	Severe	Severe
4	Severe	Severe	Moderate to severe	Moderate to severe	Moderate
5	Severe	Severe	Moderate to severe	Severe	Severe

Intraobserver and Interobserver Variabilites of 2D and 3D Measurements

For all measurements, intraobserver and interobserver variabilities of the 3D TEE PWDF method was better in terms of the relative difference and limits of agreement (Table 5).

Table 5. Intraobserver and interobserver variabilities of the 2D and 3D PWDF methods in measurements of the diameters and CSAs of the MA and LVOT and mitral RVol and EROA

Variable	Intraobserver variability			Interobserver variability		
	2D TTE imaging	2D TEE imaging	3D TEE imaging	2D TTE imaging	2D TEE imaging	3D TEE imaging
Relative difference (%)						
Mitral annular diameter	6 ± 8	3 ± 2	-	13 ± 12	7 ± 8	-
Mitral annular CSA	12 ± 16	6 ± 4	10 ± 9	21 ± 20	14 ± 16	16 ± 11
LVOT diameter	6 ± 6	4 ± 3	-	8 ± 7	8 ± 6	-
LVOT CSA	11 ± 11	8 ± 6	6 ± 4	16 ± 13	16 ± 12	15 ± 9
RVol	24 ± 31	19 ± 18	22 ± 21	46 ± 61	27 ± 31	33 ± 26
EROA	24 ± 31	19 ± 18	22 ± 21	46 ± 61	27 ± 31	33 ± 26
Bias ± limits of agreement						
Mitral annular diameter (mm)	-1 ± 6	0 ± 3	-	-3 ± 8	1 ± 7	-
Mitral annular CSA (mm^2)	-21 ± 306	3 ± 174	-39 ± 271	-112 ± 325	55 ± 401	93 ± 228
LVOT diameter (mm)	-1 ± 3	0 ± 2	-	-1 ± 4	1 ± 4	-
LVOT CSA (mm^2)	-24 ± 106	7 ± 90	-13 ± 68	-37 ± 117	52 ± 122	-60 ± 114
RVol (mL)	1 ± 57	0 ± 30	-4 ± 49	-13 ± 91	12 ± 78	27 ± 73
EROA (mm^2)	1 ± 43	1 ± 23	-1 ± 36	-11 ± 69	10 ± 57	18 ± 50

Relative difference = absolute difference/mean × 100%; bias = mean of differences; limits of agreement = 2 standard deviations.

DISCUSSION

The main finding of this study is that compared with the 3D TEE PWDF method, the traditional 2D TTE PWDF method overestimated mitral RVol and EROA significantly. The overestimates were caused by the oversimplified 2D measurements and the geometric assumption of the CSAs of the MA and LVOT, which led to the CSA and SV being overestimated at the mitral annular level and underestimated at the LVOT level.

Measurements of the CSAs of the MA and LVOT Using the PWDF Method

In the 2D TTE PWDF method, the preferred sites to calculate the SVs are the MA and LVOT, so precise measurements of the MA and LVOT dimensions are crucial. Conventionally, the mitral annular dimension is measured in the apical four-chamber view and the LVOT dimension in the parasternal long-axis view [1,3,13]. These measurements have important limitations and lead to errors in calculating CSAs, because variable and unpredictable monoplanar cross-sections are made and circular geometry of the orifices is assumed. In reality, the CSAs of both the MA and LVOT are oval, with the major and minor diameters [14-18]. In this study, the 2D mitral annular diameters approached the 3D major-axis diameters, and the 2D LVOT diameters were close to the 3D minor-axis diameters (Figure 4), which is consistent with previous findings [16-19]. The monoplanar measurements and false geometric assumption are important sources of error in measuring the mitral annular and LVOT dimensions using the 2D PWDF method. The error is further magnified because the diameter (radius) values are squared in the geometric assumption formula. Due to the important geometric errors, the CSA of the MA and corresponding SV were overestimated by 13 ± 12% and the CSA of the LVOT and corresponding SV were underestimated by 23 ± 10% by the 2D TTE measurements, compared with the 3D CSAs measured directly in the en face views of the MA and LVOT at the level at which the velocity profiles had been recorded.

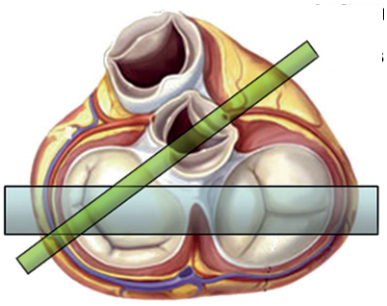

Figure 4.
Orientations of the traditional 2D echocardiographic imaging planes of the MA (apical four-chamber view) and LVOT (parasternal long-axis view).

The spatial resolution of the TEE images is better than that of the TTE images, thus allowing a clearer identification of anatomic landmarks (e.g., the hinge points of the mitral leaflets). The difference in CSAs between 2D TEE and 3D TEE measurements was smaller (2D TEE imaging overestimated mitral annular CSA by 7 ± 14% and underestimated LVOT CSA by 17 ± 10%). The errors, however, especially for the CSA of the LVOT, were still considerable. Moreover, the errors of both 2D TTE and TEE measurements in calculating the SVs were in different directions (i.e., overestimation at the mitral annular level and underestimation at the LVOT level), so the consequent impact in calculating RVol and EROA was even more significant, with an overestimate of 54 ± 39% by the 2D TTE PWDF method and 39 ± 40% by the 2D TEE PWDF method.

To measure the cardiac structures using the echocardiographic approaches, especially the CSAs of the MA and LVOT, we believe that 3D echocardiography improves the accuracy of measurements greatly because the structures of interest can be revealed in the en face views and measured directly without the geometric assumption used in the 2D echocardiographic method. Additionally, the transesophageal imaging approach contributes to improved accuracy because the cardiac structures (e.g., the MA) lie in the near field of the ultrasound field, resulting in better spatial resolution. We assume that the observer variability of 3D TTE measurements would be higher than those of 3D TEE measurements because of insufficient spatial resolution of the 3D TTE data sets.

The 2D and 3D PWDF Methods in Calculating Mitral RVol and EROA Compared with the Flow Convergence Method

The flow convergence method is one of the methods recommended for quantifying degenerative MR, because the isovelocity surface is usually hemispheric [10,20-22]. The RVol and EROA calculated by the 3D TEE PWDF method had better correlations and agreement with the flow convergence method than the 2D PWDF methods did. The 2D PWDF methods overestimated the RVol and EROA compared with both the 3D TEE PWDF and flow convergence methods. Surprisingly, the RVol and EROA calculated by the 3D TEE PWDF method were smaller than those obtained by the flow convergence method. The probable reason is that the flow convergence method overestimates the true RVol and EROA, as it estimates regurgitant flow from the ‘‘maximal’’ flow rate and thus overestimates the mean flow rate, especially in the situation of a dynamic orifice area change during systole seen in degenerative MR [23,24]. In our study, the flow convergence was measured in late systole in six cases because of the late systolic enhancement of MR due to prolapsed leaflets (Figure 5A). This overestimates the mean EROA because the timing of the flow convergence measurement and the peak velocity of the regurgitation is not synchronized. Additionally, the density of the continuous-wave Doppler profile of MR in these cases was faint in early systole and became denser in late systole (Figure 5B), probably causing overestimation of the VTI of MR and thus further overestimation of RVol. Other physiologic and technical

factors can also substantially influence flow quantification by this approach; they include the regurgitant orifice motion, aliasing velocity, and ratio of the aliasing velocity to peak orifice velocity[3,24].

It is crucial to understand the etiology and mechanism of MR and underlying principles and limitations of the flow convergence method when using this method to quantify MR. The pitfalls of applying the flow convergence method to the situations of a nonhemispheric flow convergence zone and a dynamically changing regurgitant orifice have been highlighted by extensive in vitro and clinical studies[4-11,23,25]. The major advantage of the PWDF method is the volumetric measures, whereby SV at the mitral annular level is measured in diastole and is thus not affected by the spatial or temporal homogeneity of MR in systole.

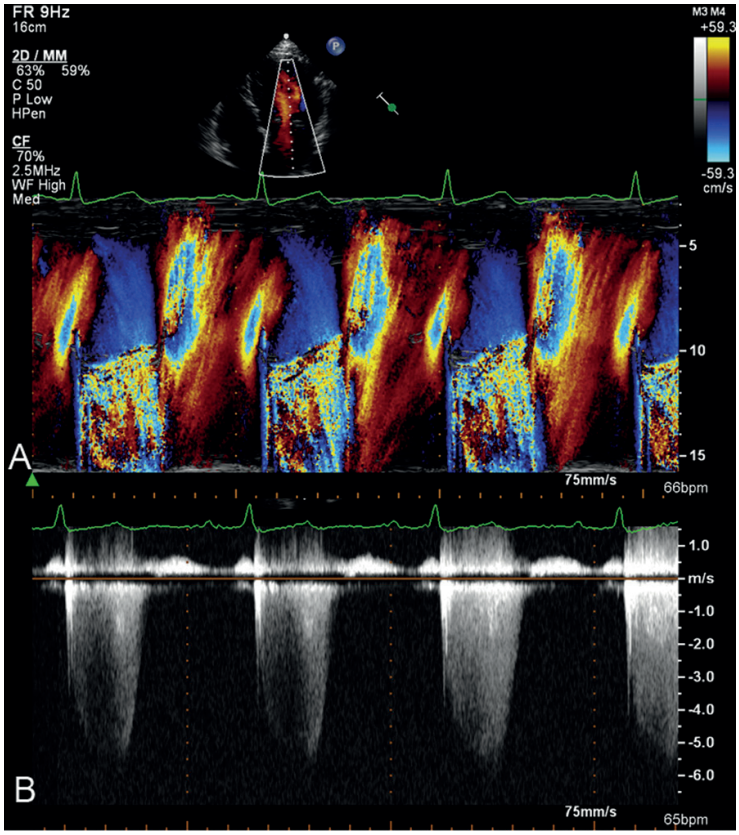

Figure 5.
The ‘‘late systolic enhancement’’ of MR due to a prolapsed P2 scallop. (A) Color M-mode echocardiography shows that the regurgitation increased progressively, with a maximum in late systole. (B) Continuous-wave Doppler echocardiography shows that the density of the profile was faint in early systole and became denser in late systole.

Discrepancies in Grading the Severity of MR according to Different Methods

In five patients, the categorization of MR severity was different according to different quantitative methods; more specifically, it was less severe according to the 3D TEE PWDF method. For patients 2 and 4 (Table 4), MR severity was probably overestimated by the 2D TTE PWDF method, which was confirmed by the 3D TEE PWDF method, flow convergence method, and vena contracta width. For patients 1 and 3, there was a late systolic enhancement of MR, so the severity was likely to be overestimated by the flow convergence method and vena contracta width as well. In only one patient, patient 5, there were mismatches of MR severity according to different methods. Because all five patients had been symptomatic, although MR severity was ''less than severe'' according to the 3D TEE PWDF method, clinical management was not changed, and all patients underwent MV repair. There is no clinical evidence that the five patients benefited less from MV repair.

Intraobserver and Interobserver Variabilities

The TEE PWDF methods were generally more reproducible than 2D TTE PWDF method, mainly because of the better spatial resolution of TEE imaging. Additionally, when the 3D TEE PWDF method was used, the relative differences and limits of agreement of the intraobserver and interobserver measurements for RVol and EROA were smaller than those in the 2D PWDF methods. As expected, the major cause of variability in PWDF methods was the measurements of the CSAs of the MA and LVOT. For the 2D and 3D PWDF methods, the variability resulted from the differences in choosing image frames and locating sampling planes for measurements. Although the intraobserver and interobserver variabilities of the 2D diameters of the MA and LVOT was relatively small, corresponding variability of the CSAs of the MA and LVOT was significantly higher because the 2D diameters (radii) are squared in the geometric assumption formula for CSA.

Limitations

A true gold standard for calculating RVol and EROA was absent in the present study. The flow convergence method was used as the reference method, but underlying assumptions of this method are not entirely valid in the situations of an eccentric regurgitant jet and a dynamic regurgitant orifice change during systole, as discussed previously. We believe that a nonechocardiographic imaging modality (e.g., cardiac magnetic resonance imaging) would be much more helpful in validating our findings.

Mitral regurgitant jets due to prolapsed leaflets usually direct eccentrically, and the flow convergence method is less accurate. In this study, most patients had isolated P2 scallop prolapse, and the flow convergence zones were visually smooth and measurable.

The sample size in this study was relatively small because only patients who had optimal available echocardiographic assessments of CSAs of the MA and LVOT by 3D TEE imag-

ing were included. Nevertheless, in all patients included, a consistent trend of overestimating mitral RVol and EROA using the 2D TTE PWDF method was obvious and therefore meaningful for clinical practice.

Because the MA and LVOT are dynamic structures, differences in timing of the measurements may produce different values. In this study, the 2D frame rate and 3D volume rate were comparable, and the time points of measurements were set approximately equal in the cardiac cycle. We assume that the acquisition depth during 3D TEE imaging, which was half that of the 2D acquisition, contributed most to the high volume rate of the 3D data sets.

Finally, in some cases, the Doppler sound beam was not perfectly parallel to the blood flow. However, small deviations ($<20^0$) in angle produce mild (<10%) errors in velocity measurements, and these errors may be acceptable for low-velocity flows [13].

CONCLUSION

The traditional 2D TTE PWDF method tends to overestimates mitral RVol and EROA because the 2D measurements are monoplanar, and it is assumed that the CSAs of the MA and LVOT are circular, which results in the SV being overestimated at the mitral annular level and underestimated at the LVOT level.

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Chapter 7

Real-World Echocardiography in Patients Referred for Mitral Valve Surgery: The Gap Between Guidelines and Clinical Practice

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ABSTRACT

Aim

Mitral regurgitation (MR) is a common disorder for which mitral valve surgery is an established therapy. Although surgical indications are clearly defined for the management of valvular heart disease, a gap exists between current guidelines and their effective application. The study aim was to provide an insight into the diagnostic information provided for cardiac surgeons before performing mitral valve surgery.

Methods

The source documents and echocardiographic studies of 100 patients, referred by nine hospitals, were screened for arguments for MR severity justifying referral for surgery. Details of the documented MR mechanism, mitral annulus (MA) size, tricuspid regurgitation (TR) severity and annulus size were also noted.

Results

According to the referring physician, MR was severe in 83% and moderate-to-severe in 17%. In the great majority of patients (98%) the MR mechanism was mentioned, although specific information on the prolapsing scallops was available in only 17% of cases. The recommended primary determinants of MR severity, vena contracta and proximal isovelocity surface area (PISA) were measured in only 22% and 31% of patients, respectively. In 94% of patients with available PISA information this was described only qualitatively. Correct image expansion using the zoom mode was performed in only 25% of these patients, and a correct adaptation of the Nyquist limit in only 6%. Tricuspid annulus measurements guiding the need for concomitant tricuspid valvuloplasty in patients with less than severe TR were reported in only 6% of patients.

Conclusion

These data demonstrate a clear and important gap between current guidelines and real-world practice with regards to the echocardiographic diagnostic information provided to the surgeon before performing mitral valve surgery.

INTRODUCTION

Mitral regurgitation (MR) is a common disorder [1] for which mitral valve surgery is an established therapy [2]. In both Europe and the United States [3,4], the guidelines clearly state that a surgical class I indication only exists when MR is severe, unless patients primarily undergo coronary artery bypass surgery. Although the definition of MR severity requires the integration of blood flow data from Doppler with morphological information as well as careful cross-checking on the validity of such data against the consequences on left atrial dimension, left ventricular dimension and function and systolic pulmonary artery pressure, the primary determinants are the vena contracta (VC) and the proximal isovelocity surface area (PISA) [5,6].

As with many fields of cardiovascular medicine, the management of valvular heart disease includes a gap between existing guidelines and their effective application [7,8]. Unfortunately, to the best of the present authors' knowledge, there is no information available on the establishment of an echocardiographic diagnosis of severe MR in the real-world in patientsreferred for mitral valve surgery. Also, little is known about the information provided on associated tricuspid regurgitation (TR) and tricuspid annulus size, defining the need for additional tricuspid valvuloplasty [3].

Hence, the aim of the present study was to provide an insight into the information provided to cardiac surgeons before performing mitral valve surgery.

CLINICAL MATERIAL AND METHODS

Patients

A total of 107 consecutive patients who had been referred, by nine different hospitals, to the authors' institution for primary mitral valve repair or replacement between November 2009 and January 2012 was included in the study. Source documents were defined as the referral letter from the treating cardiologist, the echocardiography repor,t and the report of the heart team's decision.

Seven patients were excluded from the analysis because one of these reports could not be obtained; thus the final study population included 100 patients (the nine hospitals referred 1, 1, 2, 5, 8, 11, 13, 18, and 41 patients, respectively).

All source documents and echocardiographic studies were screened for arguments for MR severity, justifying referral for surgery according to existing guidelines [5,6]. Specific signs for severe MR included: VC ³ 7mm, PISA ³ 9mm with lower thresholds in ischemic MR according to Grigioni et al [9], and systolic reversal in pulmonary veins. Supportive signs included a dense, triangular continuous-wave Doppler jet and E-wave dominance mitral inflow (E > 1.2 m/s) or an enlarged left ventricular (LV) and/or left atrial (LA)

size, in absence of LV dysfunction or (paroxysmal) atrial fibrillation. Also noted were the documented MR mechanism, mitral annulus (MA) size, TR severity and tricuspid valve annulus size; if different gradings were scored at transthoracic echocardiography (TTE) and transesophageal echocardiography (TEE), the most severe TR grade or largest annulus size was noted.

Approval to conduct the study was granted by the Institutional Review Board at the authors' hospital.

Statistical analysis

All statistical analyses were performed using SPSS version 17.0 (SPSS, Inc, Chicago, Illinois). Categorical data were presented as numbers and percentages, whereas continuous data were summarized as mean ± standard deviation (SD) or median value (range). The body surface area (BSA) of patients was calculated using the DuBois and DuBois formula [10].

RESULTS

Population characteristics

At study inclusion, all patients (56 males, 44 females; mean age 64 ± 11 years) were primarily referred for mitral valve surgery and operated on. Among the patients, 12, 42, 34 and 12 were in NYHA classes I, II, III, and IV, respectively. Concomitant coronary artery disease, hypertension and diabetes were present in 30, 49, and 17 patients, respectively.

Echocardiographic procedures

All patients underwent TTE, and 91 underwent TEE (the latter procedure was not performed in eight patients because the MR mechanism was known, and one patient refused due to fear of the procedure).

Mitral regurgitation mechanism

Information on the MR mechanism was provided for all patients but two. The most common mechanism was prolapse (58%), followed by restriction due to cardiomyopathy (11%), MA dilatation (16%) and endocarditis (3%); the remaining patients had a combination of mechanisms.

In 42 of the 58 patients with prolapse (72%), the involved leaflet was mentioned; specific information on the prolapsing scallops was available in 10 of these patients (17%). Among all patients, no information about the MA was available for 67%, in 20% a qualitative description was present, and in only 13% was MA quantitatively described.

Mitral regurgitation severity

According to the referring physician, the MR severity was moderate-to-severe in 17% and severe in 83%. The recommended [5,6] primary determinants of MR severity, VC and PISA were mentioned in only 22% and 31% of patients, respectively. In five of the 22 patients with available VC information, the condition was described only qualitatively ('present' or 'wide'); likewise, in 29 of the 31 patients with available PISA information, the condition was described only qualitatively ('present' or 'large'). No information was provided for any of the patients on effective regurgitant orifice area (EROA) or regurgitant volume (RV). Even when the presence of any (qualitative or quantitative) description of VC or PISA was considered evidence for significant MR (justifying surgery), it was present in only 45% of patients (quantitative information in 18 patients, qualitative information in 27 patients; see Fig. 1). In 14 of the remaining 55 patients (25%), reversal in one or more pulmonary veins was seen (left upper pulmonary vein at TEE in two patients, right upper pulmonary vein during TTE in nine patients, and both the left and right upper pulmonary veins in three patients). In the remaining 41 patients, significant MR according to the referring physician was based on supportive signs such as dense, triangular continuous-wave Doppler jet (n = 1), E-wave dominant (E > 1.2 m/s) mitral inflow (n = 1) or an enlarged LV and/or LA size, an absence of LV dysfunction or atrial fibrillation (n = 1). Hence, in 38% of patients it was unclear which criteria had been used for the diagnosis of significant MR justifying referral for surgery.

Quality of the VC and PISA recordings

As noted above, a PISA was described in 31 patients. Correct image expansion using the zoom mode was performed in only eight (25%) of these patients, and a correct adaptation of the aliasing velocity (by reducing the Nyquist limit to 15-40 cm/s) in only two (6%). When measuring the VC, correct image expansion using the zoom mode was performed in eight patients (36%).

Measurements in NYHA class 1 patients

Among 12 patients in NYHA class I, the primary determinants of MR severity, VC and PISA were measured in only four (33%) and two (17%) patients, respectively. In two of the four patients with available VC information, the condition was described only qualitatively ('present' or 'wide'); likewise, in all patients with available PISA information the condition was described only qualitatively ('present' or 'large'). When the presence of any (qualitative or quantitative) description of VC or PISA was considered evidence for significant MR (justifying surgery), it was present in only four of 12 (33%) patients. In one of the remaining eight patients (13%), a reversal in one or more pulmonary veins was seen, but in the remaining seven patients it was not clear on what bases significant MR was defined. Consequently, among 58% of patients in NYHA class I it was unclear which criteria had been applied for the diagnosis of MR justifying referral for surgery.

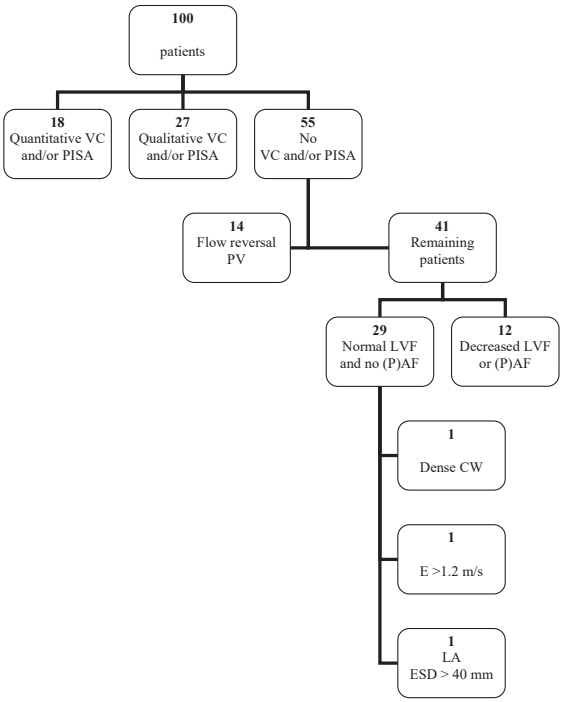

Figure 1. The criteria used by referring physicians for the diagnosis of MR severity. CW: Continuous-wave; ESD: End-systolic diameter; LA: Left atrium; LVF: Left ventricular function; (P)AF: (Paroxysmal) atrial fibrillation; PISA: Proximal isovelocity surface area, PV: Pulmonary vein; VC: Vena contracta. Patient numbers are shown in bold text.

Tricuspid regurgitation and tricuspid annulus size

TR severity was none or trace in 17% of patients, mild in 52%, moderate in 18%, and severe in 5%. The tricuspid annulus was measured in only 6% of patients (in two with severe TR, in one patient with moderate TR, and in three with mild TR). Tricuspid valvuloplasty was performed in all patients with known severe TR, in seven of 18 (39%) with moderate TR, and in four of 52 (8%) with mild TR according to preoperative assessments of the tricuspid annulus at the surgical center. In all patients but two with non- severe TR, the reason for tricuspid valvuloplasty was a dilated annulus (>40 mm or >21 mm/m2); in one patient with mild TR the reason for tricuspid valvuloplasty was unknown, and in one patient with moderate TR valvuloplasty was performed for 'surgical inspection'. Among the 11 patients with moderate TR but without tricuspid valvuloplasty, a dilated tricuspid annulus was not present in any case.

DISCUSSION

The main findings of the present study were that, in patients referred for MV surgery: (i) the severity of MR is often not based on VC and PISA parameters, as advised in current guidelines; (ii) the technical quality of VC and PISA recordings is questionable; and (iii) data on tricuspid annulus size, defining the need for additional tricuspid valvuloplasty, are virtually absent. These data clearly show an important gap between guidelines and real-world practice.

In the Euro Heart Survey on valvular heart disease, the characteristics of 499 patients with severe MR from 92 centers from 25 countries were described in detail [8,11]. Valvular interventions were advised in about halve of symptomatic patients and one-third of asymptomatic patients. Unfortunately, in this survey no diagnostic information was available other than the etiology of the MR. To the authors' knowledge the present study is the first real-world investigation describing the diagnostic process in terms of the details of patients with MR referred for MV surgery.

Echocardiographic diagnostic procedures

TTE was performed in all patients, and TEE in 91%. In the Euro Heart Survey on valvular heart disease, additional TEE was performed in only 103 of the 227 patients (45%) in whom the decision had been taken to operate for MR [11]. In a 2011 report on "Appropriate Use Criteria for Echocardiography", the evaluation of valvular structure and function by TEE to assess suitability for, and assist in planning of, an intervention was given the highest possible appropriateness score [12]. How often TEE is really necessary to establish the mechanism (or occasionally the severity) of MR is not clear, and highly dependent on sonographer and physician expertise [13].

Diagnostic information on the mitral valve

The presumed mechanism of MR was mentioned in the great majority of patients, although detailed information on, for example, the specifically involved prolapsing scallop (defining the difficulty of surgery) was available in only a small minority of patients. Of note, no attempt was made to verify the mechanistic findings. Data on MR severity were in many cases incomplete. According to current guidelines, the primary determinants of MR severity are the VC and PISA. Despite the intensive echocardiographic study of patients (i.e., including TEE in the vast majority), these parameters were assessed in only a minority of patients (22% and 31%, respectively).

No investigation was undertaken to determine why, in specific patients, specific measurements were not made. In general, the VC is more difficult to measure than is claimed in guidelines, in particular in non- degenerative MV disease. This issue was noted recently by Biner et al. who found that the interobserver agreement for VC and PISA measure-

ments between clinically experienced, practicing echocardiologists (even within the same institution) was disappointing, with kappa values ranging from 0.28 to 0.37 [14]. For PISA measurements it should be recognized that, even in the most simplified ways, the calculations may be time-consuming, especially for the inexperienced. Measurements also assume a perfectly symmetric spherical unconstrained flow acceleration, whereas the geometry in the real world is often irregular and asymmetric, or there is non-hemispherical flow convergence with flattening. In addition, PISA measurements vary substantially during the cardiac cycle, since the PISA is usually dynamic throughout systole and some physicians may not believe in the concept of defining the maximal flow representative for the overall MR. The VC is also dynamic, and it may be difficult to visualize the essential components that define the VC: the proximal flow convergence, the VC, and the downstream jet expansion[15]. Finally, it is unknown how to deal with multiple regurgitant jets.

The even more disappointing technical quality of the recordings (optimal PISA recordings were achieved in only two patients) show that there is a long way to go in the education and training of sonographers and cardiologists. In this respect it is also noteworthy that, in a substantial number of patients, the diagnosis of severe MR was made because of systolic flow reversal in one pulmonary vein. In none of the echocardiographic studies was more than one pulmonary vein visualized, and in only three patients was a reversal in more than one pulmonary vein shown by combining TTE and TEE data, visualizing the right and left upper pulmonary veins, respectively. As the MR jet may selectively enter one or the other pulmonary veins, sampling through all pulmonary veins is recommended, especially during TEE [5]. In the real-world, as represented by the present study, only two pulmonary veins were studied: the right upper during TTE and the left upper during TEE. All of these data raise serious concerns, in particular in a world in which patients may be treated even before they develop symptoms, when the indication for surgery is based solely on an assessment of MR severity (and its consequences).

Diagnostic information on the tricuspid valve

The treatment of TR in mitral valve disease is an unresolved issue. The recommendations in patients undergoing MV surgery during the time-frame of the present study (2009-2011) were, according to the 2006 AHA/ACC guidelines [4]: Class I “severe TR” and Class IIb “…may be considered for less than severe TR when there is pulmonary hypertension or tricuspid annular dilatation”; and according to the 2007 ESC guideline [16]: Class I “severe TR” and Class IIa “moderate secondary TR with dilated annulus (>40mm)”.

Since the time-frame of the present study (2009-2011), a 2012 ESC update [3] has been implemented that now includes Class I ‘severe TR’ and Class IIA ‘mild or moderate secondary TR with dilated annulus (>40 mm or 21 mm/m2)’. It is disappointing to note that tricuspid annular measurements were almost never provided by the referring center to the surgeon. Patients with severe or moderate TR in the present study were treated in

compliance with the 2006/2007 guidelines on the basis of intraoperative assessments of the tricuspid annulus at the surgical center. In addition - and in compliance with the 2012 guidelines - some patients with less than moderate TR were also treated in the presence of a large tricuspid annulus.

Study limitations

The main study limitations were that: (i) the sample size was relatively limited; and (ii) the results were based only on patients referred to a single surgical center in one country, and should not be generalized because the degree of expertise in managing valvular heart disease may vary widely between regions and countries. The present study may also plead for a more pronounced role of cardiologists specialized in the management of valvular heart disease, in order to better implement and apply accepted valvular guidelines, especially for asymptomatic patient with MR. Notably, in September 2014, the present study results were discussed with the cardiologists from the referring centers and, as a consequence, a new, prospective observational study will shortly commence, hopefully to demonstrate an improvement in adherence to guidelines.

CONCLUSION

Among patients referred for MV surgery the severity of MR is not based on solid recommended criteria in a substantial number of patients. Also, when data on VC and PISA were suggested as being indicative of severe MR, the technical quality of these measurements was questionable. TV annulus measurements guiding the need for concomitant tricuspid valvuloplasty in patients with less than severe TR were reported in only a very small minority of patients. Taken together, these data demonstrate a clear and important gap between current guidelines and real-world practice.

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Chapter 8

Evolution of Mitral Regurgitation in Patients with Heart Failure Referred to a Tertiary Heart Failure Clinic

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ABSTRACT

Aim

Significant mitral regurgitation (MR) is an important predictor for all-cause mortality and heart failure (HF) hospitalizations independent of left ventricular ejection fraction (LVEF). The aims of this study were to investigate (i) in how many patients referred to a tertiary outpatient HF clinic HF therapy could be optimized, (ii) the effect of optimized treatment on MR severity and (iii) whether a reduction in MR resulted in improvement of symptoms.

Methods

Forty-seven referred patients with therapy -resistant symptomatic chronic HF with a LVEF <40% and at least moderate MR were analysed on admission and after optimization of HF treatment after 6-18 months. The patients were classified as a volume responder when LV end-systolic volume (LVESV) decreased ≥15%, as LVEF responder when LVEF increased by ≥5% points, as clinical responder when New York Heart Association (NYHA) class improved at least one category, and as MR responder when MR severity improved at least one category to maximally moderate.

Results

After 14 ± 4 months of treatment optimization, optimal doses of angiotensin-converting enzyme inhibitors /angiotensin receptor blocker were seen in 18 (38%) patients compared with 3 (6%) at baseline (P <0.001), and optimal doses of beta-blockers were seen in 14 (30%) patients compared with four (9%) at baseline (P <0.001). In total, 68% of the patients were clinical responders, 57% MR responders, 34% volumetric responders, and 49% LVEF responders. NYHA class improved from 2.9 ± 0.6 to 2.0 ± 0.9 (P <0.001), MR class from 5.2 ± 0.8 to 3.6 ± 1.5 (P <0.001), LVEF from 24% ± 9% to 31% ± 12% (P <0.01) and LVESV non-significantly improved. The positive predictive value of MR response to NYHA response was 88%, the negative predictive value was 53%, agreement 69%, kappa 0.39. The positive predictive value of LVEF response to NYHA response was 76%, the negative predictive value was 44%, agreement 60%, kappa 0.21. The positive predictive value of LVESV volume response to NYHA response was 75%, the negative predictive value was 39%, agreement 51%, kappa 0.12.

Conclusion

Although this study was limited by a small number of patients, initiation and up-titration of recommended HF therapy in patients referred to our tertiary HF outpatient clinic resulted in significant MR reduction in over half of the patients, emphasizing the importance of optimal medical treatment in these very sick cardiac patients with otherwise grave prognosis. MR reduction was best correlated to NYHA improvement.

INTRODUCTION

Both in ischemic and non-ischemic cardiomyopathy, the presence of significant mitral regurgitation (MR) is an important predictor for all-cause mortality and heart failure (HF) hospitalizations independent of left ventricular ejection fraction (LVEF) [1]. To date, the most effective therapies for secondary MR are aimed at the underlying LV dysfunction. Given the main pathophysiological mechanism, that is, LV and annular dilatation, these include optimal medical HF therapy and cardiac resynchronization therapy (CRT) when appropriate. In particular, beta-blockers and angiotensin-converting enzyme inhibitors (ACE-Is) are recommended for all patients with LV dysfunction and secondary MR [2]. By reversing LV unloading and LV remodeling, optimal HF therapy may reduce MR. Surprisingly, however, few studies have examined the effect of beta-blockers [3-6] or ACE-Is [7] therapies on secondary MR. Secondary MR may also dramatically improve after optimization of fluid status by diuretics thorough lowering of the LV filling pressures [8]. More robust data are available on the LV remodeling and synchronizing effects of CRT on secondary MR [9-14].

In this study, we report our results in patients with chronic HF and at least moderate MR referred to our tertiary HF outpatient clinic for a second opinion, specific referral for MR intervention, and/or heart transplantation. The aims of this study were to investigate (i) in how many real-world referred patients HF therapy could be optimized, (ii) the effect of optimized treatment on MR severity, and (iii) whether a reduction in MR resulted in an improvement of symptoms.

METHODS

Study patient definition

All patients included in the study fulfilled the following inclusion criteria: (i) referred by a cardiologist to our tertiary HF outpatient clinic between 2005 and 2015 for a second opinion with (ii) therapy-resistant symptomatic chronic HF New York Heart Association (NYHA) class 2 to 4, (iii) LVEF <40%, and (iv) at least moderate MR. In addition, all included patients were required to have a baseline transthoracic echocardiogram before change in HF treatment at our tertiary HF outpatient clinic and a follow-up transthoracic echocardiogram between 6 to 18 months. Exclusion criteria were prior valvular surgery and concomitant congenital heart disease.

Clinical data

The following variables were noted: gender, age, heart rate, systolic blood pressure, aetiology of HF, prior HF hospitalization in the last 12 months, NYHA class, and renal dysfunction [defined as estimated glomerular filtration rate (eGFR) < 45 ml/min/1.73m^2].

Transthoracic echocardiography

Echocardiography was performed with a Sonos or iE33 system (Philips, Best, The Netherlands), equipped with a S5-1 transducer according to a standard HF protocol. The following variables were measured both at baseline and follow-up according to standard guidelines [15-17]: LV end-diastolic diameter and volumes, LV end-systolic diameter and volumes (LVESV), LVEF, left atrial (LA) diameter and volume, transmitral E-wave, transmitral deceleration time, diastolic early septal wall velocity as assessed with tissue Doppler imaging (e'), tricuspid valve regurgitation velocity, caval vein diameter, MR severity [according to seven scales (from 0 to 6): none, trivial, mild, mild to moderate, moderate, moderate to severe, severe] [17], and MR jet morphology in the LA (central or eccentric). LV volumes and LVEF were measured with TomTec triplane analysis in Imaging Arena (TomTec Imaging systems, Imaging Arena, version 4.6, Unterschleissheim, Germany). All measurement were performed by blinded observers: MR by MLG, LV volumes and ejection fraction by ES and all others by LdGdL.

Definition of responders

A patient was considered a volume responder when LVESV decreased ≥15%, a LVEF responder when LVEF increased by ≥5% points, a clinical responder when NYHA class improved at least one category, and a MR responder when MR severity improved at least one category to maximally moderate.

Medication and devices

In all patients, the following drugs (including dosage) were noted at baseline and at the time of follow-up echocardiography: ACE- I or angiotensin receptor blocker (ARB), beta-blocker, loop diuretic, mineralocorticoid receptor antagonist (MRA), and digoxin. Optimal treatment dosages were defined according to the guideline [2]. Also, other interventions like thyroid hormone or Vitamin-D supplementation were noted. Finally, it was noted whether the patient had an implanted cardiac defibrillator (ICD) or had undergone (upgrade to) cardiac resynchronization therapy (CRT).

Statistical analysis

Statistical analysis was performed using SPSS version 21.0.0.1 (SPSS, IBM, Armonk, NY). Categorical data are presented as numbers and percentages, whereas continuous data are summarized as mean ± standard deviation or median value with range. Comparisons of proportions were done with a two-sided Z test. P-values <0.05 were considered significant.

The agreement between MR response, EF response and LVESV volume response to the NYHA response was assessed by calculating the Kappa coefficient (a value 0.21 to 0.40 indicating a fair agreement, a value 0.41 to 0.80 indicating a moderate agreement, and a value >0.80 indicating an excellent agreement)

RESULTS

Baseline clinical and echocardiographic characteristics

Forty-seven patients (mean age 52 ± 13 years, 68% male patients) were included in the study, see Figure 1. As seen in Table 1, heart rate was 81 ± 19 beats per minute, and systolic blood pressure 102 ± 15 mmHg. HF aetiologies were ischemic in 14 (30%) patients, 25

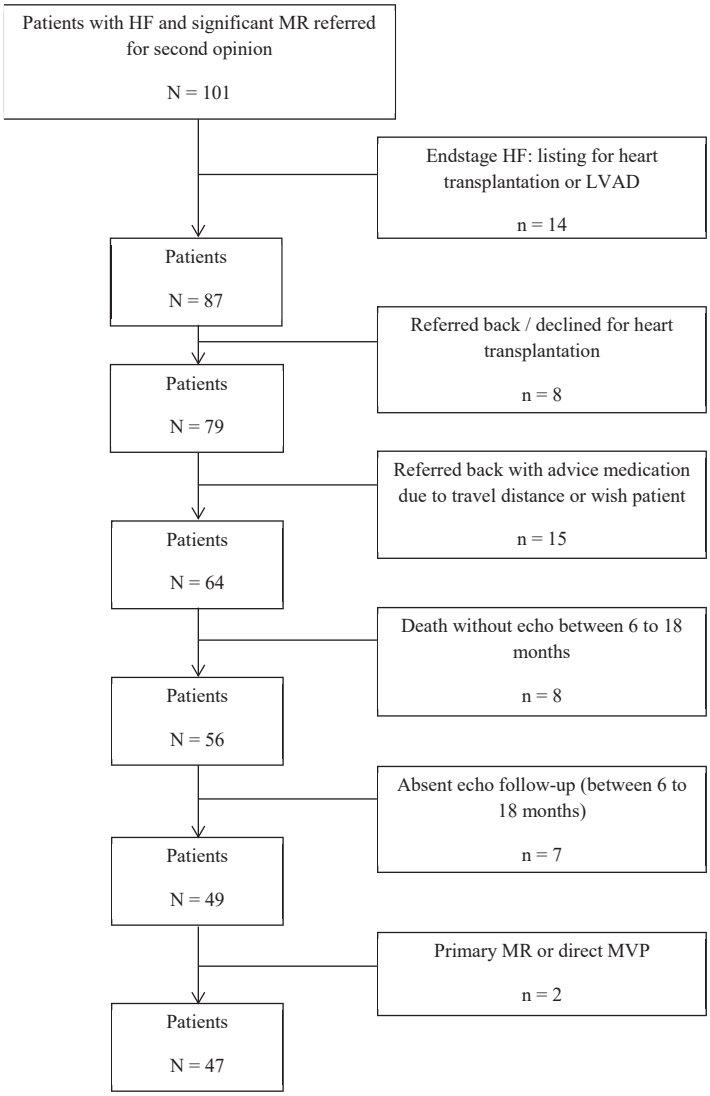

Figure 1. Inclusion patients
HF = Heart failure, LVAD = Left ventricular assist device, MR = mitral regurgitation, MVP = mitral valve plasty

Table 1. Clinical and echocardiographic data.

	All patients baseline N = 47	All patients follow-up N = 47	MR responder N = 27	MR non-responder N = 20
Clinical data				
Male gender	32 (68%)		17 (63%)	15 (75%)
Age, years	52 ± 13		56 ± 12	49 ± 13
Heart rate (bpm)	81 ± 19	66 ± 12	85 ± 20	77 ± 16
Systolic blood pressure	102 ± 15		101 ± 13	103 ± 18
Ischemic etiology	14 (30%)		8 (30%)	6 (30%
Prior HF hospitalization	25 (53%)		15 (56%)	10 (50%)
NYHA class III or IV	36 (77%)	12 (26%)	21 (78%)	15 (75%)
Glomerular filtration rate	61 ± 20	58 ± 21	64 ± 22	56 ± 14
Renal dysfunction[a]	12 (26%)	10 (21%)	7 (26%)	5 (25%)
Echocardiographic data[b]				
LVEDD	68,4 ± 13,2	66,8 ± 11,9	68,3 ± 12,8	68,4 ± 13,8
LVEDD delta		-1,6 ± 11,2	-4,8 ± 13,5	1,1 ± 8,2
LVESD	61,3 ± 13,8	56,4 ± 13,1	60,8 ± 13,4	61,6 ± 14,5
LVESD delta		-4,9 ± 11,1*	-8,0 ± 13,4*	-2,3 ± 8,1
LVEDV	264,6 ± 102,6	246,5 ± 100,3	272,7 ± 119,6	257,8 ± 88,6
LVEDV delta		-18,1 ± 86,6	-48,0 ± 112,6	6,9 ± 46,1
LVESV	204,8 ± 97,0	179,5 ± 99,1	210,4 ± 113,5	200,0 ± 83,6
LVESV delta		-25,3 ± 89,9	-54,2 ± 120,5	-0,9 ± 42,7
LVEF	24,5 ± 9,3	30,7 ± 11,7	25,3 ± 9,4	24,0 ± 9,4
LVEF delta		6,1 ± 12,2*	9,0 ± 16,2*	3,7 ± 7,0*
LA diameter	49,5 ±7,8	46,4 ± 9,0	47,9 ± 7,1	50,9 ± 8,3
LA diameter delta		-3,1 ± 8,1[#]	-6,7 ± 8,3[#]	-0,1 ± 6,8
LA volume	117,1 ± 37,7	102,6 ± 49,6	115,1 ± 36,0	118,8 ± 39,9
LA volume delta		-14,5 ± 52,1	-41,8 ± 37,4[#]	8,5 ± 52,4
e'	4,7 ± 1,7	5,2 ± 2,0	4,4 ± 1,8	4,9 ± 1,7
e' delta		0,5 ± 1,9	0,5 ± 1,9	0,5 ± 1,9
E/e'	22,5 ± 9,1	17,6 ± 12,1	24,0 ± 10,6	21,2 ± 7,7
E/e' delta		-4,9 ± 13,2*	-8,6 ± 13,9*	-1,8 ± 12,2
TR velocity	2,9 ± 0,6	2,6 ± 0,8	2,9 ± 0,6	3,0 ± 0,6
TR velocity delta		-0,3 ± 0,8*	-0,6 ± 0,7[#]	-0,1 ± 0,7
IVC diameter	20,9 ± 5,2	16,3 ± 4,9	20,1 ± 5,5	21,5 ± 5,0
IVC diameter delta		-4,6 ± 5,6[#]	-5,3 ± 6,1[#]	-3,9 ± 5,2[#]
MR central jet	26 (55%)	26 (55%)	16 (59%)	10 (50%)
MR severe	21 (45%)	6 (13%)	13 (48%)	8 (40%)

[a]Glomerular filtration rate <45 ml/min/1,73m^2

[b]In the MR responder columns only baseline and delta values are displayed. Limited to the 35 patients with complete echo data available.

HF = Heart Failure, EDD = End Diastolic Diameter, EDV = End Diastolic Volume, EF = Ejection Fraction, ESD = End Systolic Diameter, ESV = End Systolic Volume, IVC = Inferior Vena Cava, LA = Left Atrium, LV = Left Ventricular, MR = Mitral regurgitation, NYHA = New York Heart Association, TR = Tricupid regurgitation

*P < 0.05

[#] P < 0.01

(53%) patients were hospitalized because of HF in the previous 12 months, and NYHA class was 2.9 ± 0.6 [NYHA 2 in 11 (23%), NYHA 3 in 30 (64%), and NYHA 4 in 6 (13%)]. Significant renal dysfunction was present in 12 (26%) patients. Mean volumes were 265 ± 103 ml for LV end-diastolic volume and 205 ± 97 ml for LVESV, and LVEF was 25% ± 9%. Moderate, moderate-to-severe, and severe MR was present in 11 (23%), 15 (32%) and 21 (45%) patients. As seen in Table 2, ACE-I/ARBs were present in 45 (96%) patients, beta-blockers in 37 (79%), diuretics in 42 (89%), MRAs in 32 (68%) and digoxin in 12 (26%). However, optimal doses of ACE-I/ARBs were present in three (6%) patients, and optimal doses of beta-blockers in four (9%). CRT was present in 10 (21%) patients (CRT-D in nine and CRT-P in one), and an isolated ICD was present in 13 (28%) patients.

Table 2. Baseline heart failure therapy and changes in the study population (n = 47)

	Baseline		Follow-up			
	At referral	**Optimal dose**	**Up-titration**	**Initiation**	**Finally**	**Optimal dose**
ACE-inhibitors / ARBs	45 (96%)	3 (6%)	22 (47%)	2 (4%)	47 (100%)	18 (38%)*
Beta-blocker	37 (79%)	4 (9%)	20 (43%)	9 (19%)	46 (98%)	14 (30%)*
Diuretics	42 (89%)		22 (47%)	3 (6%)	45 (96%)	
MRAs	32 (68%)		3 (6%)	7 (15%)	39 (83%)	
Digoxin	12 (26%)		0 (0%)	25 (53%)	37 (76%)	
CRT-P	1 (2%)			0 (0%)	1 (2%)	
CRT-D	9 (19%)			8 (17%)[a]	17 (36%)	
ICD only	13 (28%)			5 (11%)	15 (32%)	

[a]including three upgrades from ICD only

* P < 0.001 compared with baseline

ACE = angiotensin-converting enzyme, ARB = angiotensin receptor blocker, CRT-D = *cardiac resynchronization therapy defibrillator, CRT-P = cardiac resynchronization therapy pacemaker,* ICD = Implantable Cardioverter Defibrillator, MRA = mineralocorticoid receptor antagonist

Medical interventions

Ten patients (21%) were immediately after first outpatient assessment hospitalized to optimize HF. As seen in Table 2 and Figure 2, in the total group of patients, ACE-I/ARBs were initiated in two (4%) patients and up-titrated in 22 (47%) patients, beta-blockers were initiated in nine (19%) patients and up-titrated in 20 (43%) patients, diuretics were initiated in three (6%) patients and up-titrated in 22 (47%) patients, MRAs were initiated in seven (15%) patients and up-titrated in three (6%) patients, and digoxin was initiated in 25 (52%) patients and up-titrated in none. At follow-up optimal doses of ACE-I/ARBs were present in 18 (38%) patients compared with three (6%) at baseline (P <0.001), and optimal doses of beta-blockers were present in 14 (30%) patients compared with four (9%) at baseline (P <0.001). Six (13%) patients were on the evidence-based dose of both beta-blockers and

ACE-inhibitors / ARBs at the time of follow-up echocardiography vs. 0 (0%) at baseline. Heart rate decreased from 81 ± 19 to 66 ± 12 beats per minute (P <0.001).

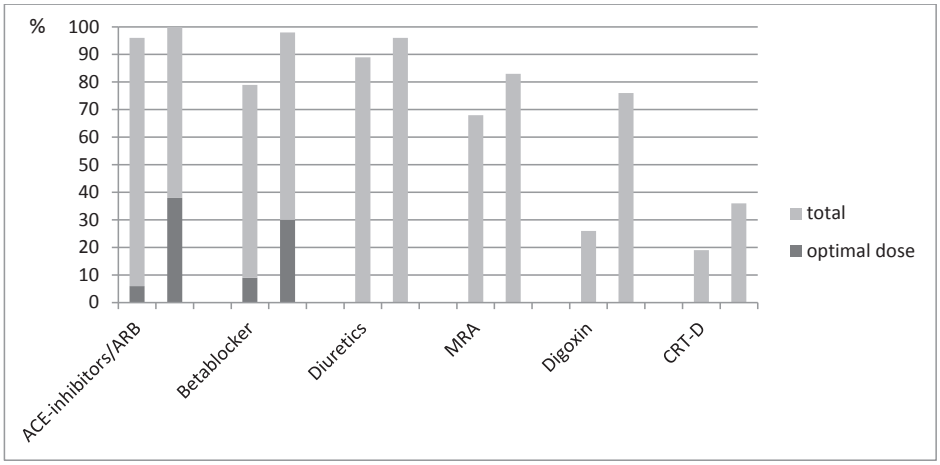

Figure 2. Baseline (left) and change (right) in heart failure therapy.
ACE = angiotensin-converting enzyme, ARB = angiotensin receptor blocker, CRT-D = *cardiac-resynchronization-therapy-defibrillator,* MRA = mineralocorticoid receptor antagonist

Device interventions

As seen in Table 2, CRT was initiated in eight (17%) patients, of whom in three patients, existing ICD therapy was upgraded to a CRT-D system. An additional five patients received an isolated ICD.

Clinical and echocardiographic improvement

After a mean of 14 ± 4 months NYHA class improved from 2.9 ± 0.6 to 2.0 ± 0.9 (P <0.001), and 32 patients (68%) were clinical responders. MR class improved from 5.2 ± 0.8 to 3.6 ± 1.5 (P <0.001), and 27 patients (57%) were MR responders (Figure 3). In these latter patients, vena contracta width improved from 7.0 ± 1.4 mm to 2.7 ± 1.2 mm (P < 0.001), whereas in the non-responders, no significant improvement was seen in vena contracta width (7.3 ± 1.5 versus 6.9 ± 1.6 mm, P =not significant).

Left ventricular end-systolic volume non-significantly improved from 205 ± 97 to 180 ± 99 mL (P = not significant), and 12 patients (34%) were volumetric responders. LVEF improved from 24% ± 9% to 31% ± 12% (P <0.01), and 17 patients (49%) were LVEF responders.

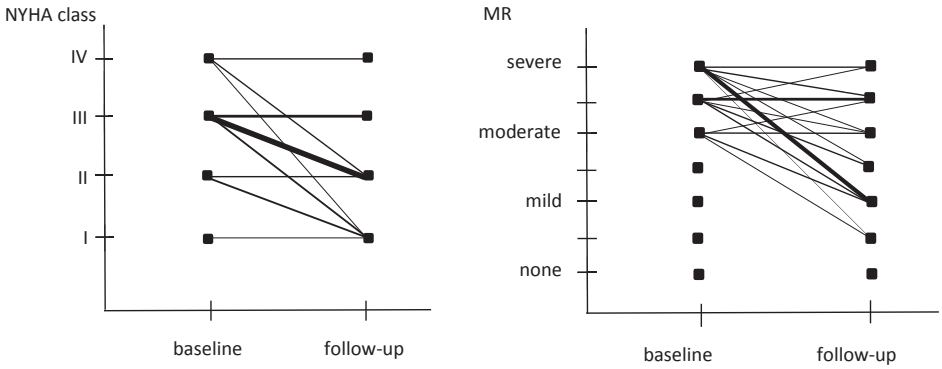

Figure 3. New York Heart Association **(**NYHA) class (left) and mitral regurgitation (right) response to optimize treatment. Thickness of the line corresponds to the number of patients.

Predictors for MR improvement

As seen in Table 1, none of the baseline variables predicted improvement (responders) in MR. Associated with MR improvement were a decrease in LV end systolic diameter, LA diameter and volume, E/e', tricuspid regurgitation velocity and inferior vena cava dimension, and an increase in LVEF.

Relation between mitral regurgitation and ejection fraction improvement vs. New York Heart Association response

The positive predictive value of MR response to NYHA response was 88%; the negative predictive value was 53%, agreement 69%, kappa 0.39. The positive predictive value of LVEF response to NYHA response was 76%; the negative predictive value was 44%, agreement 60%, kappa 0.21. The positive predictive value of LVESV volume response to NYHA response was 75%; the negative predictive value was 39%, agreement 51%, kappa 0.12.

Relation between MR improvement and renal dysfunction

Estimated glomerular filtration rate non-significantly decreased from 61 ± 20 to 58 ± 21 mL/min/1.73m^2. In MR responders, eGFR remained stable (0 ± 13), whereas in MR non-responders, eGFR deteriorated with 8 ± 12 mL/min/1.73m^2 ($P<0.05$). In both EF responders and non-responders, eGFR remained stable.

DISCUSSION

The main findings of this study in patients referred by cardiologists to our tertiary HF clinic with therapy-resistant HF and at least moderate MR are (i) although the vast majority of

the referred patients received recommended medication, optimal dosages were seen in only a very small minority, (ii) initiation of therapy resulted in presence of the recommended medication in virtually all patients, (iii) despite up-titration of recommended medication in almost half of the patients, still approximately only one-third of patients could tolerate the maximum recommended drug dosages, (iv) MR reduced significantly in over half of the patients, and (v) MR reduction best correlated to NYHA improvement.

Medical therapy

Medical therapy for HF consists of vasodilators (ACE-Is), beta-blockers, MRAs, and diuretics. The main effects of these drugs include reversal or delay of LV remodeling and reduction of MR thorough lowering filling pressures. The use of afterload-reducing agents, including ACE-Is, might reduce MR volume and improve LV forward stroke volume by decreasing the pressure gradient between the LV and the left atrium through systolic unloading. A similar effect of reduction in MR is obtained with preload reduction through the use of diuretics that decrease LV size and tethering with a consequent decrease in MR volume [8]. It is well known that ACE-Is and beta-blockers reduce mortality and morbidity in symptomatic patients with HF with reduced LVEF [18-20] and are complementary. According to the guideline, these drugs should be gradually up-titrated to the maximum tolerated dose [2]. In this study, it is shown that although referred patients often were on ACE-Is and beta-blockers, optimal doses were rarely seen. In a significant number of patients, beta-blockers could be initialized by the HF specialist, and drugs could be up-titrated. Still, at the last moment of assessment (between 6 and 18 months) optimal doses of ACE-Is and beta-blockers were only seen in one-third of our patients. Hypotension, bradycardia, and renal failure are well-known causes of failure to up-titrate HF drugs, in particular in patients with advanced HF. Patients referred to our outpatient HF clinic represent the sickest of the sick: the majority were hospitalized because of HF in the previous 12 months, and outpatient NYHA class was in the vast majority NYHA class 3 or 4. Further evidence for the severity of HF disease is seen in the hemodynamic characteristics. The mean heart rate of 81 is quite comparable with patients included in the major HF landmark trials [18-20], but the systolic blood pressure of 102 mmHg is significantly lower than the 120-130 mmHg range reported in the major HF landmark trials [18-20] that included also mainly patients in NYHA class 3 or 4.

Despite these issues, the subscription of ACE-Is and beta-blockers in 100% and 98% of patients is a remarkable achievement. For example, in a Spanish prospective cohort of patients hospitalized for HF from 2008 to 2011, beta-blockers were after 12 months only present in 68% of patients [21], and numbers also seen in other registries like the Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients With Heart Failure (OPTIMIZE-HF) registry [22]. In this latter trial, target doses of metoprolol and carvedilol were seen in only 8% and 18% of patients 3 months after discharge.

In the recently published European Society of Cardiology Heart Failure Long-Term Registry, patients with chronic HF had 1 year follow-up ACE-Is/ARBs, beta-blockers and MRAs in 87%, 89% and 59% of patients, respectively [23]. In these trials, baseline values of systolic blood pressure and heart rate were 124 ± 21 mmHg and 73 ± 15 b.p.m., and 25% of patients were in NYHA class III or IV. So, our patients referred because of refractory HF were also compared to this contemporary registry clearly the sickest of the sick.

Device therapy

According to the baseline LVEF, 63% of patients who had a primary prophylactic ICD indication had an ICD (with or without CRT) implanted before referral. At the end of the follow-up period, this percentage was 94%; in addition, all patients with left bundle branch block had CRT. These numbers seem also much better than the low numbers reported in the European Society of Cardiology Heart Failure Long-Term Registry, although it cannot be clearly distillated from this registry how many patients actually had a clear indication for CRT and/or ICD [23].

Mitral regurgitation

In HF patients, the presence of significant MR is a significant predictor for mortality [1,24,25] and exercise capacity [26]. By inclusion, all our patients had at least moderate MR. The described therapeutic interventions resulted in a significant reduction of MR in over half of the patients, consistent with findings recently published by Stolfo et al. [27]. The relation between clinical effects and MR reduction by medical therapy is not well described in the literature. In contrast, it is well known that improvement of significant MR by CRT is sustained and patients with less residual MR 6 months after CRT have a better survival [28]. In this study, it is clearly shown that MR reduction is best related to NYHA class improvement. The potential improvement in MR by HF therapy optimization by a dedicated HF cardiologist may prevent in a large number of HF patients the need for surgical or percutaneous mitral valve interventions.

Limitations

The major limitations of this study are the retrospective character and the limited number of patients. The latter was mainly caused by our stringent study inclusion criteria, excluding patients in whom adjustment of therapy was started before the first echo in our center. Also, approximately 20% of patients were deemed to have irreversible HF and referred for heart transplantation. Considering the total cohort of patients, a significant MR reduction in over half of the patients may therefore be an overestimation. On the other hand, approximately 10% of patients was referred back with medical advices thought to be easily implemented by the referring physician, and it may be expected that in these patients, even a larger proportion of patients would have shown improvement in MR. Finally, sacubitril/valsartan

was not available at the time of our study. Sacubitril/valsartan has been not only shown to reduce the rate of HF hospitalization and cardiovascular mortality in selected symptomatic patients with HF with an LVEF <35% [29] but also to reduce MR severity in patients initially on optimal medical therapy with an ACE-I/ARB and beta-blocker and significant secondary MR [30].

CONCLUSIONS

Initiation and up-titration of recommended HF therapy in patients referred to our tertiary HF outpatient clinic resulted in significant MR reduction in over half of the patients, emphasizing the importance of optimal medical treatment in these very sick cardiac patients with otherwise grave prognosis. MR reduction was best correlated to NYHA improvement.

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Chapter 9

Single-centre Experience with Mitral Valve Repair in Asymptomatic Patients with Severe Mitral Valve Regurgitation

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ABSTRACT

Aim

Guidelines recommend surgical mitral valve repair in selected patients with asymptomatic severe mitral valve regurgitation (MR), but the role of repair remains a matter of debate. Survival analyses of operated asymptomatic patients have been reported, but long-term haemodynamics and quality of life are not well defined. The aim of this study was to report the long-term follow-up focusing on these aspects.

Methods

Our database identified patients who underwent primary isolated mitral valve repair for severe MR and were asymptomatic by New York Heart Association Class I and in sinus rhythm. To obtain sufficient length of follow-up, only patients operated on before 2006 returned for an echocardiogram and quality-of-life assessment (SF-36).

Results

Between May 1991 and December 2005, 46 asymptomatic patients with severe MR and a normal left ventricular function (ejection fraction >60%) were operated on. Mean age was 50.2 ± 13.2 years and 89% of patients were male. There were no operative deaths. Mean follow-up was 8.4 ± 3.9 years with 386 patient-years, survival was 93.3% at 12 years and comparable with the general age-matched Dutch population. Follow-up echocardiography showed that 92% had no to mild MR, and 3 patients had moderate MR. Left ventricular function was good/impaired/moderate in 66/29/5% of patients. Quality-of-life SF-36 assessment showed that mean physical and mental health components were 83 ± 17 and 79 ± 17, which was comparable with that of the general age- and gender- matched Dutch population.

Conclusion

Our experience shows that mitral valve repair for severe MR in asymptomatic patients is safe, and has satisfactory long-term survival with a low recurrence rate of MR, good left ventricular function, and excellent quality of life that is comparable with the general Dutch population.

INTRODUCTION

Mitral valve regurgitation (MR) is the most common regurgitant heart valve lesion and is most commonly caused by degenerative valve disease [1]. Cardiologists and surgeons often hesitate to recommend surgery in patients with no or minimal symptoms. In this regard, the usefulness of mitral valve surgery in asymptomatic patients with MR remains controversial, even though guidelines do recommend it for selected indications [1].

Previous studies have reported long-term survival analyses, which led to a worldwide consensus and acceptance of surgical repair of the native valve for preventing left ventricular dysfunction and myocardial damage [2]. Through preservation of the normal valvular tissue and subvalvular apparatus, valve repair optimizes postoperative ventricular function and is preferred over valve replacement. Compared with valve replacement, mitral valve repair has a lower surgical mortality risk and provides better survival [3]. The decision to proceed with surgical repair, especially in asymptomatic patients, is easier if a repair seems feasible. However, with nothing to gain in symptomatic improvement, surgery exposes the patient to perioperative morbidity and mortality, the risk of failed repair with subsequent hazards of prosthetic valve complications [3].

It has been suggested that surgery should not be delayed until severe symptoms develop, because irreversible left ventricular dysfunction could develop while waiting for the onset of symptoms [4]. However, the concept of mitral valve repair was developed in a limited number of patients from a few selected experienced centres and supporting evidence from other institutes is poor [2,5]. The rationale for preventive, reconstructive mitral valve repair in asymptomatic patients therefore deserves a critical examination. No analyses have yet explored long-term valvular haemodynamics, quality of life, or a comparison with the general population, while these aspects could potentially create a strong recommendation for surgery in asymptomatic patients. This study aims to describe these out- comes after mitral valve repair for asymptomatic MR (i.e. New York Heart Association [NYHA] Class I for dyspnoea) in a large tertiary centre.

METHODS

Study design and patient population

The medical records of 46 consecutive patients with asymptomatic severe MR who underwent primary isolated mitral valve repair at the Department of Cardiothoracic Surgery of the Erasmus MC Rotterdam were reviewed. A heart murmur was found during a work-related medical examination, coincidental identification by the general practitioner, or coincidental identification during a work-up for other general surgery. Severe MR was measured and quantified according to the existing valvular guidelines. A truly asymptomatic status of

patients was defined by a NYHA Class I and sinus rhythm. To allow for a sufficient length of follow-up, only those patients operated on between May 1991 and December 2005 were included. The total number of mitral valve repairs during these years was 1099 (Figure 1). The study protocol was approved by the institutional review board of the Erasmus MC Rotterdam (MEC 07-416). Individual patient consent for the study was waived.

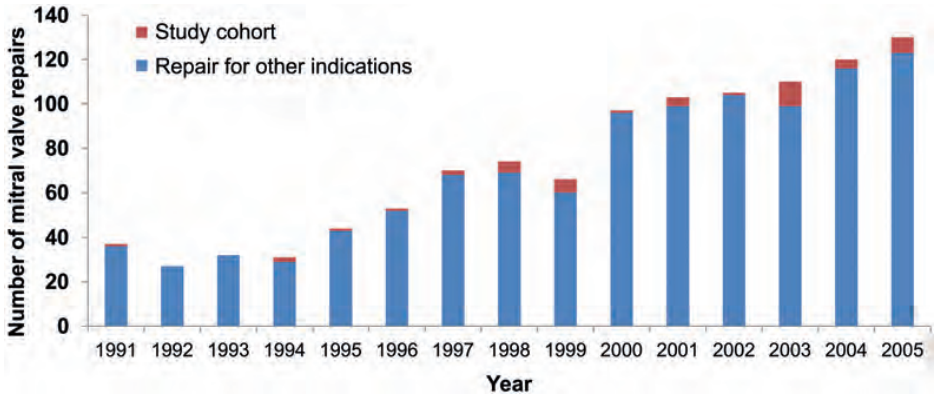

Figure 1. Number of mitral valve repairs during the study period.

Patients were followed with regular visits to the outpatient clinic. The civil registry was consulted and, subsequently, patients were invited through a telephone call to come for an outpatient visit with echocardiogram, electrocardiogram, and quality-of-life assessment. Five patients declined participation. Data were collected from hospital records, operative reports, and correspondence with the patients and treating physicians.

Perioperative details and follow-up were reported in accordance with the 2008 guidelines for reporting morbidity and mortality after cardiac-valve interventions [6]. Operative events were defined as those occurring within 30 days after surgery or any event later during the same postoperative hospital stay.

Surgical techniques

Intraoperative transoesophageal echocardiography was carried out routinely before and after repair. The majority of patients (>90%) were operated on by the same surgeon. The techniques of mitral valve repair used in this series were basically those described by Carpentier, but certain modifications were introduced over the years, for instance, the use of expanded polytetrafluoroethylene sutures to reinforce or replace chordae tendinae. All patients received warfarin during the first 3 months post-surgery, if in sinus rhythm.

Clinical follow-up

All patients had a comprehensive examination, including M-mode and 2-dimensional echocardiography, as well as conventional and Doppler examinations in our centre. All tests were conducted by experienced echocardiographers. Since the vena contracta width and the regurgitant orifice area have not been validated after mitral valve repair, the severity of residual MR was graded by expert consensus based on a score that considered (i) jet penetration, (ii) continuous-wave Doppler jet intensity and character, (iii) pulmonary artery pressure, (iv) pulmonary venous flow pattern, and (v) left atrial size [7]. Left ventricular function was scored as good, impaired, moderate or poor.

Quality of life

The quality-of-life assessment was performed using the SF-36 questionnaires. According to the guidelines, this questionnaire was sent to the patient and completed at home before each study visit [8]. The questionnaire consists of 36 scale-rated health-related questions, grouped into eight multi-item domains that are not disease-specific and that measure functioning in different aspects of daily life: 'physical functioning (PF)'; physical health related to age- and role-specific activities: 'role-physical (RP)', 'bodily pain (BP)', 'general health (GH)', 'vitality (VT)', 'social functioning (SF)'; personal feelings of performance in age- and role-specific activities: 'role-emotional (RE)' and 'mental health (MH)'. The eight domains form two physical and mental health composite scores. The PF, RP, BP and GH domains contribute to the scoring of the 'physical component summary(PCS)' measure, whereas the VT, MH, RE and SF domains contribute to the 'mental component summary (MCS)'. To compare these outcomes to the general age-matched Dutch population, we used Dutch norms that were previously published by Aaronson et al. [9].

Statistical analysis

Continuous data are presented as mean ± 1 standard deviation; categorical data are presented as proportions. Cumulative survival and freedom from reoperation were analyzed using the Kaplan–Meier method. Age- and gender-matched survival in the general population were calculated using the Dutch population life tables (http://statline.cbs.nl/). Quality of life comparison of the study population with the general age-matched Dutch population was performed using the paired *t*-test (observed paired with age-matched norm). All tests were two-sided; a *P*-value of <0.05 was considered statistically significant. Statistical analyses were performed using SPSS 17 for windows (SPSS, Chicago, IL, USA) and GraphPad PRISM version 5 (GraphPad Prism Software, Inc., San Diego, CA, USA).

RESULTS

Baseline and procedural characteristics

The baseline characteristics are presented in Table 1. Mean age was 50.2 ± 13.2 and 89% of patients were male. All patients had a normal left ventricular function as defined by a preoperative ejection fraction of >60% measured on echocardiography. Posterior leaflet prolapse was diagnosed in 76% and in 52% of patients, the annulus was severely dilated. In 45 (98%) patients, a mitral ring was implanted, which was a Carpentier-Edwards Physioring in 40 patients. Quadrangular resection was performed in 78% of patients and posterior leaflet sliding in 65%. Other techniques are listed in Table 2.

Table 1. Baseline characteristics

Characteristic	N = 46
Age (mean ± standard deviation [SD])	50.2 ± 13.2
Range	(25.2-78.2)
Male gender	41 (89%)
Aetiology	
Degenerative	2 (4%)
Myxomatous	39 (85%)
History of endocarditis	5 (11%)
Valvular characteristics	
Anterior mitral valve leaflet prolapse	8 (17%)
Posterior mitral valve leaflet prolapse	35 (76%)
Cusp perforation	5 (11%)
Annulus dilatation	45/46
None	1 (2%)
Moderate	20 (43%)
Severe	24 (52%)
Annulus calcification	2 (4%)

Operative (early) outcomes

In our centre, mitral valve repair is the routine procedure for asymptomatic patients. In all patients (n = 46), the procedure was performed as preoperatively planned with echocardiography. There were no cases in whom repair was doubtful; there were no conversions to mitral valve replacement. Intraoperative echocardiography after repair revealed a direct significant reduction in the degree of MR in all patients to ≤1+. The mean length of stay was 9.7 ± 5.7 days, during which 2 patients had a transient ischaemic attach (TIA). Four (8.7%) patients required a re-exploration for bleeding/tamponade. There were no cases of 30-day mortality.

Table 2. Procedural characteristics

Operative technique	**N = 46**
Ring implantation	45 (98%)
Cosgrove-Edwards ring	5 (11%)
Carpentier-Edwards Physio ring	40 (89%)
Size	
28	1 (2%)
30	6 (13%)
32	12 (26%)
34	12 (26%)
36	8 (17%)
38	4 (9%)
40	1 (2%)
Quadrangular resection	36 (78%)
Papillary muscle shortening	4 (9%)
Chordal shortening	3 (7%)
Artificial chords	4 (9%)
Chordal transfer	5 (11%)
Posterior mitral valve leaflet sliding	30 (65%)
Annulus decalcification	2 (4%)
Flipover	5 (11%)
Patch	5 (11%)

Long-term outcomes

The mean follow-up was 8.4 ± 3.9 years and comprised 385.5 patient-years. During follow-up, 3 patients died (0.78%/patient- year); the cause of death was cardiac (at 1.9 years), and non-cardiac as a result of stroke (at 3.4 years) and pulmonary embolism after kidney transplantation (at 2.8 years). Cumulative survival at 12 years was 93.3% and comparable with the age- and gender-matched survival in the general Dutch population (Figure 2). One patient required a reoperation at 1.7 years for severe MR during which the patient received a prosthetic valve (0.26%/patient-year). Valve-related complications during follow-up included three cerebrovascular accidents (0.78%/patient-year) and one transient ischaemic attack (0.26%/patient-year).

Long-term echocardiographic examination during follow-up was available in 38 patients at a mean of 9.2 ± 3.5 years. Of these, 92% (n = 35) had no to mild MR grade at follow-up and 3 patients had moderate MR (Figure 3A). Left ventricular function was good or mildly impaired in 95% of the patients (Figure 3B). There were only 2 patients with moderate LV function and none with poor function.

At the time of the last follow-up, 74% (n = 29) of patients were asymptomatic (NYHA Class I), 21% (n = 8) were in NYHA Class II, 5% (n = 2) in NYHA Class III, and none in NYHA Class IV. Data on cardiac rhythm were available from 41 patients, of whom there

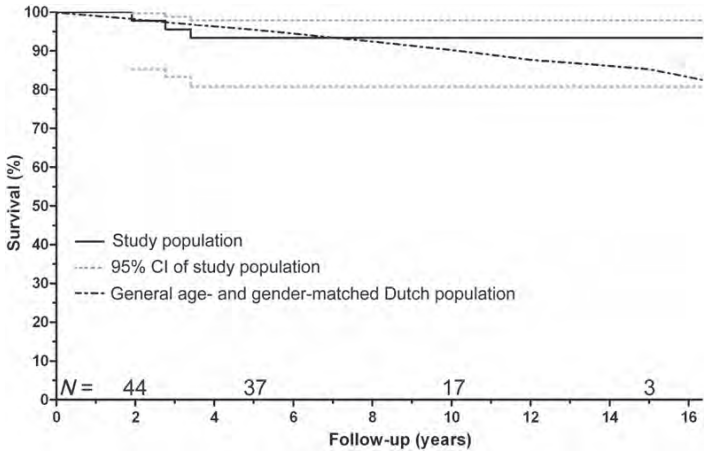

Figure 2. Long-term survival of patients with asymptomatic severe mitral valve regurgitation compared with the general age- and gender-matched Dutch population.

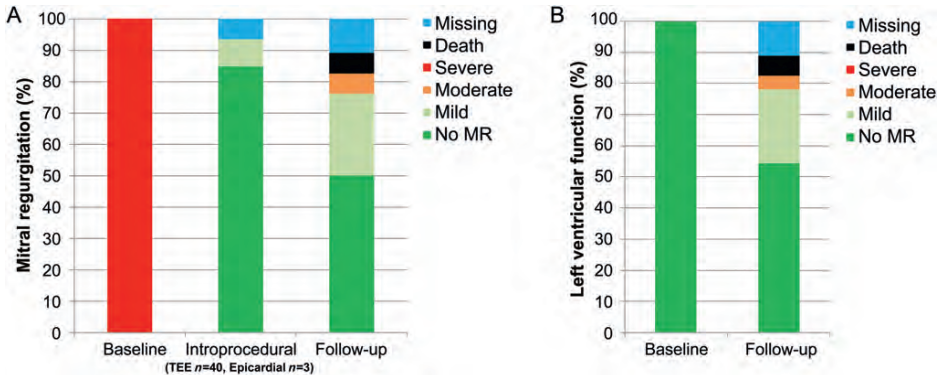

Figure 3. : Long-term echocardiographic outcomes of patients with asymptomatic severe mitral valve regurgitation who underwent repair. There was an early reduction in the severity of mitral regurgitation in all patients that was maintained during the follow-up (A), and good left ventricular function (B).

were 4 (10%) with episodes of atrial fibrillation during follow-up. The remaining patients were in sinus rhythm.

The SF-36 questionnaire was completed by 36 patients and showed that quality of life was good and comparable with that of the general age-matched Dutch population (Figure 4 and Table 3). Remarkably, the individual physical domains and the composite PCS showed an even better quality of life than that of the general population.

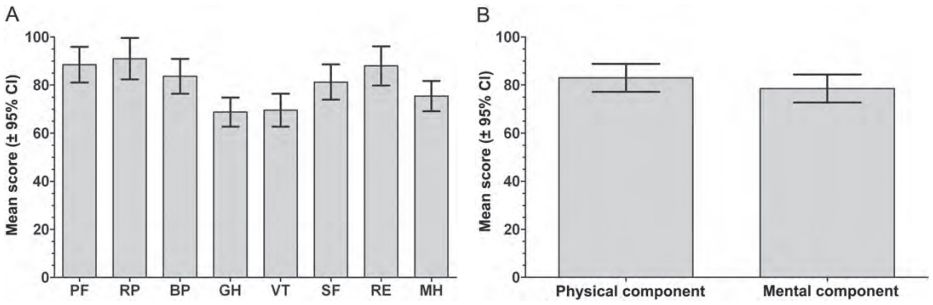

Figure 4. Long-term quality of life of patients with asymptomatic severe mitral valve regurgitation compared with the general age-matched Dutch population.

Table 3. Quality-of-life comparison with the general age-matched Dutch population

	Study population N = 36 (mean ± SD)	General Dutch population (mean ± SD)	*P*-value
PF	88.5 ± 21.9	76.2 ± 10.6	0.001
RP	91.0 ± 25.4	69.7 ± 7.8	<0.001
BP	83.7 ± 21.5	71.2 ± 2.8	0.002
GH	68.8 ± 17.8	66.4 ± 5.4	.044
VT	69.6 ± 20.3	67.1 ± 2.7	0.49
SF	81.3 ± 21.7	81.8 ± 3.3	0.88
RE	88.0 ± 24.1	80.3 ± 3.0	0.057
MH	75.4 ± 18.6	75.6 ± 1.5	0.95
PCS	83.0 ± 17.3	70.9 ± 6.5	<0.001
MCS	78.6 ± 17.2	76.2 ± 2.6	0.42

PF: physical functioning; RP: role-physical; BP bodily pain; GH: general health; VT: vitality; SF: social functioning; RE: role-emotional; MH: mental health; PCS: physical component score; MCS mental component score; SD: standard deviation

DISCUSSION

In asymptomatic patients with a normal left ventricular function undergoing surgical repair of severe MR, long-term outcomes were excellent. Survival at 12 years was 93.3% and comparable with the general age- and gender-matched Dutch population. Furthermore, 92% of surviving patients had none to mild MR grade and 95% had a good or mildly impaired left ventricular function at 9-year follow-up. Lastly, quality of life as measured by SF-36 questionnaires was not impaired and is comparable with the general age-matched Dutch population.

Current valvular guidelines indicate that mitral valve surgery, preferably mitral valve repair, might be beneficial in asymptomatic patients with severe MR and LV dysfunction, atrial fibrillation, and/or pulmonary hypertension [1]. However, the role and timing of surgery

remain controversial. Observational studies comparing these two treatment options have shown promising results for surgical patients. A propensity-matched analysis reported significantly better event-free survival at 7 years for those patients who underwent surgery (99 vs 85%, $P = 0.001$) [10]. This was confirmed by Montant et al. [4] who reported a 86% survival rate at 10 years compared with only 50% for patients who were treated conservatively.

The American guidelines specifically recommend referring patients to centres of excellence who have much experience with mitral valve repair. The rationale is that, in this relatively young patient population (the mean age in our series was 50 years), mitral valve repair is much preferred over mitral valve replacement [11]. Surgery is indicated if the chance of repair is > 90%, however, inexperienced surgeons/centres might not always succeed in valve repair, resulting in the need for mechanical valve replacement [12]. It has been confirmed that annual hospital volume of mitral operations is a significant predictor of improved in-hospital rates of major adverse cardiac or cerebrovascular events, and a higher valve-repair rate [12, 13]. Therefore, experience may partly explain the large variation in the rate of valve repair among cardiac centres [14].

These recommendations imply that surgery should be performed in high-volume, experienced centres. In our series, of 46 patients, 3 deaths occurred in 385 patient-years, and survival was 93% at 12-years of follow-up. These rates correspond well to those of the general Dutch population.

In conventionally treated asymptomatic patients, indications for surgery arise in about 25–30% within 5 years [10,15]. With regard to the risk-benefit ratio, the benefit of surgery is still unclear and whether it is justified depends on the surgical risks and chance of successful repair. Therefore, asymptomatic patients may mostly benefit from repair if they have low comorbidity and/or if there is a low risk associated with surgery [1]. In our series, we are able to safely perform valve repair in 100% of the cases where there were no conversions to valve replacement and no procedural mortality or stroke. These outcomes are similar to other series of asymptomatic patients [2,10,16,17] and reflect strict patient-selection policy [18].

Most asymptomatic MR studies have predominantly reported survival and reoperation analyses. Medium-term echocardiographic follow-up has also been reported [17], but long-term follow-up echocardiographic results are limited. David et al. found that freedom from MR ≥2+ was 96% at 10 years [16]. However, only 11 of the initial 199 patients (5.5%) actually had a 10-year echocardiographic follow-up. In addition, Gillinov et al. showed that 71% at 10-year follow-up had grade ≤1+ MR irrespective of preoperative NYHA Class, but the mean follow-up was only 6.9 years, and the authors did not specify how many patients were at risk [2]. In our current series, mean echocardiographic follow-up was at 9.2 years and 34.5% (16/46) completed >10-year echocardiography. A remarkable 92% of patients had less-than moderate MR, suggesting that longevity of valve repair is not an issue in asymptomatic patients. Furthermore, 95% of patients had normal or mildly impaired LV function.

Moreover, quality-of-life analyses are an important aspect of follow-up in these asymptomatic patients, since repair is performed to prevent the onset of symptoms due to congestive heart failure [19]. Most patients are in NYHA Class I at medium- or long-term follow-up [16,17], such analysis, however, might not be a valid measure of quality of life [20]. We found that quality of life—as measured with SF-36 questionnaires—was comparable with the general age-matched population. This provides additional arguments to perform surgery, since it seems to prevent progression of the disease. Further data on quality of life in conservatively treated patients are necessary to put these results into perspective, although the higher rate of mortality and heart failure in conservatively treated patients may already be evidence that quality of life is impaired.

One of the major concerns remains the incidence of cerebrovascular events, as highlighted in previous studies [4,16]. In our series, the risk of (non)fatal stroke was similar at 0.78% per patient-year. Compared with the overall Dutch population, in which the incidence of developing stroke is 0.23% per patient- year in 55–64 year olds [21], patients after mitral valve repair may be at higher risk. This is likely related to the higher incidence of atrial fibrillation and consequently, the risk of stroke [22–24].

In our series, atrial fibrillation during follow-up occurred in nearly 10% of the patients, but none of them had a stroke or TIA. However, the limited number of patients may have prevented us from finding a correlation. It is highly recommended to perform regular echocardiography and electrophysiological follow-up assessments in which early diagnosis of atrial fibrillation and ad- ministration of appropriate therapy may prevent stroke.

Limitations

This was a small single-centre analysis, with its inherent limitations. Due to its retrospective nature, there were no data available on preoperative quality of life. Unfortunately, quality-of-life norms of the Dutch population only allow age-matching, but not age- and gender-matching [9]. The occurrence of atrial fibrillation during follow-up may have been underestimated since some patients may not have been detected at the time of electrocardiography.

Ideally, a control group of patients with asymptomatic MR who did not undergo surgery would have been included. Unfortunately, our database did not include these patients, and retrospective identification of such a group could not be performed.

CONCLUSION

Our experience shows that mitral valve repair for severe MR in asymptomatic patients is safe, and has satisfactory long-term survival with a low recurrence rate of MR, good LV functioning, and excellent quality of life that is comparable with the general Dutch

population. However, this was a retrospective single-centre study with a small number of patients and, therefore, we encourage further exploration and acceptance of this indication for mitral valve repair.

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Chapter 10

Echocardiographic and Clinical Outcome after Mitral Valve Plasty with a Minimal Access or Conventional Sternotomy Approach

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ABSTRACT

Aim

To evaluate the effects of minimal access mitral valve surgery (MAMVS) versus conventional surgery with or without concomitant tricuspid valve plasty (TVP) in consecutive patients with mitral regurgitation (MR) on clinical and echocardiographic outcome.

Methods

One-hundred-and-twenty patients operated for MR (91 conventional and 29 MAMVS) were followed by echocardiography and quality-of-life assessment before and 6 months after surgery.

Results

Patients in the MAMVS group were younger, more often in NYHA functional class I-II and had lower NT-proBNP levels. Only four patients (all in the conventional group) underwent mitral valve replacement. There were no significant differences in complications between MAMVS and conventional surgery. At 6-months comparable MR reduction and left ventricular remodeling data were seen, left atrial remodeling was most prominent in the MAMVS group, 71[55-90] to 43[35-58] versus 69[53-89] to 49[41-70] ml/m^2 in the conventional group ($P < 0.05$). Significant improvement for all quality of life domains were seen, except for pain, with no intergroup differences. Twenty-seven (23%) patients underwent concomitant TVP, all in the conventional group. Tricuspid regurgitation decreased after concomitant TVP ($P < 0.001$), whereas in patients with no TVP no significant changes occurred. At 6 months tricuspid regurgitation grade was comparable in patients with TVP versus patients without need for TVP.

Conclusion

MR severity reduced significantly, with no difference between conventional surgery and MAMVS in reducing MR, with superior left atrial remodeling in the MAMVS group. In-hospital complications and NYHA class and quality of life assessment were not different between conventional surgery and MAMVS.

INTRODUCTION

Mitral regurgitation (MR) is the second most frequent operated form of valve disease [1]. The conventional approach is a full sternotomy, but the last decades a minimal access approach, with a set of small chest wall incisions, has become an alternative. Low mortality and morbidity rates, high rates of mitral valve (MV) repair and excellent late results have been reported [2]. Still, papers in which detailed and complete echocardiographic and clinical outcome are provided are sparse. Therefore, the current study was undertaken to evaluate the effects of MV surgery with or without concomitant tricuspid valve (TV) repair in consecutive patients on clinical and echocardiographic outcome in our hospital.

METHODS

Patients population

Approval to conduct the study was granted by the Institutional Review Board at the authors' hospital. Informed consent was waived. A total of 120 consecutive patients who had been operated for MR between November 2009 and February 2013 with complete echo and laboratory results were included in the study (13 patients were excluded because of a missing baseline echocardiogram and 10 patients were excluded because of a missing follow-up echocardiogram). Ninety-one patients were operated according to the conventional approach with a full sternotomy and 29 patients with minimal access mitral valve surgery (MAMVS) by right thoracotomy. Absolute exclusion criteria for MAMVS were: 1) coronary artery disease (CAD) necessitating revascularization, 2) significant calcification of the MV apparatus or ascending aorta, 3) significant sclerosis/calcification or tortuosity of the iliac artery, and 4) adhesions or pathology of the pleural space notified by a computed tomography scan.

All patients underwent transthoracic echocardiography (TTE), electrocardiography (ECG) and blood testing (renal function, NT-proBNP) following on their visit at the outpatient clinic two weeks before and six months after MV surgery. A quality-of-life assessment was performed in 68 patients (16 in the MAMVS and 52 in the conventional group) using the SF-36 questionnaires, consisting of not disease-specific scale-rated questions that measure functioning in different aspects of daily life. According to the guidelines, this questionnaire was given or sent to the patient and completed at home before operation and before visit to the outpatient clinic at 6 months [3].

Image acquisition and analysis

All TTE studies were performed by expert sonographers using a Philips iE 33 ultrasound system (Philips Medical Systems, Best, the Netherlands), equipped with a S5-1 transducer

according to the recommendations published by Monin et al. [4]. Left atrial (LA) volumes (LAV), left ventricular (LV) volumes and ejection fraction (EF) were measured with TomTec triplane analysis (TomTec Imaging systems, Unterschleissheim, Germany). Left atrial volume index (LAVI) was determined by dividing LAV by body surface area. The mechanism of the MR was scored according to a modified echocardiographic classification proposed by Shah and Raney [5]. MR and tricuspid regurgitation (TR) pre-operative and 6 months postoperative were scored categorically according to 7 scales (from 0 to 6): none, trace, mild, mild-to-moderate, moderate, moderate-to-severe and severe. For MR also the MR index was determined. This index is derived from 6 echocardiographic variables and includes jet penetration, proximal isovelocity surface area, continuous-wave Doppler jet intensity and character, pulmonary artery pressure, pulmonary venous flow pattern and LA size [6]. Surgical complications were noted according to the guidelines published by Akins et al. [7].

Surgical techniques

A right lateral mini-thoracotomy incision is made of approximately 5 cm in the 3rd or 4th intercostal space. After the thoracotomy is made, two auxiliary working ports are established to allow positioning of a CO2 insufflator, camera device, ventricular vent and pericardial stay sutures. A cut down technique is used to expose the femoral vein and artery, which are cannulated. Femoral vein cannulation is done under echographic guidance. The ascending aorta is cross clamped and antegrade St. Thomas cardioplegia is administered via the aortic root. The mitral valve is exposed via left atriotomy along the groove of Waterston. Depending on the mechanism of MR various standard mitral valve repair techniques were used and, usually, a Physio II ring annuloplasty is performed. Valve competence is confirmed with hydrostatic saline test and the left atrium is closed. If significant tricuspid valve regurgitation or annulus dilation is present, an annuloplasty using a Phsyio ring is performed. The pericardium is approximated in all cases.

In the conventional subgroup a full sternotomy is performed with standard bicaval cannulation. The mitral valve is exposed via left atriotomy, or, in case of concomitant tricuspid valve surgery, a trans-septal approach.

Statistical analyses

Statistical analysis was performed using R (R Development Core Team, Vienna, Austria, version 3.3.4). Normality of continuous variables was evaluated by Shapiro-Wilk tests Continuous data were then presented as median and interquartile range (IQR) (non-Gaussian) or mean ± standard deviation (SD) (Gaussian) and differences were tested with student t-test or Mann-Whitney U test, as appropriate. Categorical data were presented as percentages and tested with chi-square test or Fisher's exact test, as appropriate. Paired tests were used for within subject comparison at different follow-up moments. For the

ordinal echocardiographic outcomes, within subject differences were tested with the paired Wilcoxon signed rank test. A p-value <0.05 was considered statistically significant.

RESULTS

Baseline clinical and echocardiographic characteristics

Table 1 shows the baseline clinical characteristics of the total cohort and the 29 patients with MAMVS compared with the 91 who underwent the conventional or "open" approach. Patients in the MAMVS group were younger (60 [50-63] vs. 66 [60-74] years, P <0.001), more often in New York Heart Association (NYHA) functional class I and II (86% vs. 49%, P <0.001) and had a lower NT-proBNP level (21 [13-51] vs 111 [34-259] pmol/L, P <0.001). Because of the exclusion criteria none of the patients in the MAMVS group had significant CAD, whereas in the conventional group 35 patients (38%) had significant CAD. Patients in the MAMVS group were less often preoperatively treated with oral anticoagulation (14% v. 39%, P <0.05), beta-blockers (38% vs. 65%, P <0.05) and diuretics (24% vs. 71%, P <0.001). There were no significant differences between the groups in terms of gender, atrial fibrillation, heart rate, blood pressure, cardiovascular risk factors and chronic renal failure.

Table 1. Baseline clinical characteristics of the study population.

	Total cohort N = 120	**MAMVS N = 29**	**Conventional N = 91**	**P-value**
Age (years)	64 [59-71]	60 [50-63]	66 [60-74]	**<0.001**
Males	65 (54%)	18 (62%)	47 (52%)	0.443
NYHA class I II III - IV	13 (11%) 56 (47%) 51 (42%)	7 (24%) 18 (62%) 4 (14%)	6 (7%) 38 (42%) 47 (52%)	**0.001**
Rhythm Sinus rhythm Atrial fibrillation Other	 95 (79%) 20 (17%) 5 (4%)	 26 (90%) 2 (7%) 1 (3%)	 69 (76%) 18 (20%) 4 (4%)	0.250
Heart rate (beats per minute)	70 [63-81]	67 [60-76]	71 [64-84]	0.051
Blood pressure, systolic (mmHg)	135 [120-145]	135 [125-155]	130 [120-145]	0.169
Blood pressure, diastolic (mmHg)	80 [70-85]	85 [75-90]	80 [70-85]	0.096
Coronary artery disease Absent 1 vessel disease 2 vessel disease 3 vessel disease	 85 (71%) 13 (11%) 9 (7%) 13 (11%)	 29 (100%) 0 0 0	 56 (62%) 13 (14%) 9 (10%) 13 (14%)	**0.001**
Previous cardiac surgery	1 (1%)	0	1 (1%)	--

Table 1. Baseline clinical characteristics of the study population. (*continued*)

	Total cohort N = 120	MAMVS N = 29	Conventional N = 91	P-value
Percutaneous coronary intervention	7 (6%)	1 (3%)	6 (7%)	0.862
Cerebro-vascular disease	13 (11%)	2 (7%)	11 (12%)	0.660
Smoker	18 (15%)	3 (10%)	15 (17%)	0.612
Chronic renal failure				0.117
GFR < 30	4 (3%)	0 (0%)	4 (4%)	
GFR 30-59	20 (17%)	2 (7%)	18 (20%)	
GFR > 60	96 (80%)	27 (93%)	69 (76%)	
Diabetes Mellitus	14 (12%)	1 (3%)	13 (14%)	0.211
Hypertension	58 (48%)	14 (48%)	44 (48%)	0.999
COPD	11 (9%)	2 (7%)	9 (10%)	0.907
Medication				
Antiplatelet	36 (30%)	3 (10%)	33 (36%)	**0.016**
Oral anticoagulation	39 (33%)	4 (14%)	35 (39%)	**0.025**
Beta-blocker	70 (58%)	11 (38%)	59 (65%)	**0.019**
ACE-inhibitor / ARB	88 (73%)	18 (62%)	70 (77%)	0.277
Diuretics	72 (60%)	7 (24%)	65 (71%)	**<0.001**
Calcium-antagonist	10 (8%)	2 (7%)	8 (9%)	0.999
NT-proBNP (pmol/L)	63 [22-191]	21 [13-51]	111 [34-259]	**<0.001**

ACE = angiotensin-converting enzyme, ARB = angiotensin receptor blocker, COPD = chronic obstructive pulmonary disease , GFR = glomerular filtration rate, NT-pro-BNP = N-terminal pro b-type natriuretic peptide, NYHA = New York heart association

Baseline echocardiographic measurements, mechanism of MR and grading of MR and TR are shown in Table 2. LV-EF was significantly higher in the MAMVS group (56 [51-61] vs. 52 [43-57] %, P <0.005) and also the mechanisms of MR were different (P <0.005) with more leaflet restriction in the conventional group. TR severity differed also, although not significant.

The only difference at baseline in quality-of-life assessment was the physical health related to age- and role-specific activities (role limitations/physical), being better in the MAMVS group.

Surgical results

Four patients in the conventional group underwent MV replacement: one because of extensive endocarditis, one because of substantial calcification of the mitral annulus, and two patients because of unsuccessful repair. Twenty-seven (23%) patients underwent concomitant TV repair, all in the conventional group. None of the MAMVS patients crossed-over to the conventional group. There were no significant differences in complications between the MAMVS and the conventional group (Table 3).

Table 2. Baseline echocardiographic characteristics of the study population.

	Total cohort N = 120	MAMVS N = 29	Conventional N = 91	P-value
LV end-diastolic volume (ml)	177 [140-211]	181 [152-220]	173 [135-207]	0.192
LV ejection fraction (%)	53 [47-58]	56 [51-61]	52 [43-57]	**0.003**
LAVI (ml/m^2)	69 [53-89]	71 [54-90]	69 [53-89]	0.818
Mechanism*				**0.002**
1 Annulus dilatation				
1A	1 (1%)	0 (0%)	1 (1%)	
1B	2 (2%)	1 (3%)	1 (1%)	
1C	7 (6%)	0 (0%)	7 (8%)	
2 Leaflet prolapse				
2A	51 (42%)	17 (59%)	34 (37%)	
2B	12 (10%)	7 (24%)	5 (6%)	
2C	7 (6%)	2 (7%)	5(6%)	
3 Leaflet restriction				
3A	3 (2%)	0 (0%)	3 (3%)	
3B	25 (21%)	1 (3%)	24 (26%)	
3C	8 (7%)	0 (0%)	8 (9%)	
5	4 (3%)	1 (3%)	3 (3%)	
MR severity#				0.154
Moderate	21 (17%)	4 (14%)	17 (19%)	
Moderate-severe	27 (23%)	4 (14%)	23 (25%)	
Severe	72 (60%)	21 (72%)	51 (56%)	
TR Vmax (m/s)	2.6 [2.3-2.9]	2.5 [2.3-2.8]	2.6 [2.4-3.0]	0.270
TR severity#				0.098
None	6 (5%)	3 (10%)	3 (3%)	
Trace	50 (42%)	13 (45%)	37 (41%)	
Mild	34 (28%)	8 (28%)	26 (29%)	
Mild-moderate	11 (9%)	4 (14%)	7 (8%)	
Moderate	8 (7%)	1 (3%)	7 (8%)	
Moderate-severe	5 (4%)	0	5 (5%)	
Severe	6 (5%)	0	6 (7%)	

LAVI = left atrial volume index; LV = left ventricle; MR = mitral regurgitation; TR = tricuspid regurgitation
* = see methods for explanation in detail
# = judged 2 weeks before operation

Follow-up at 6 months

In the post-operative evaluation at 6 months 8 patients had died in the conventional group (Table 4), including the 1 patient with MV replacement, resulting in 11 patients excluded from echocardiographic repair analysis (8 patients died and 3 patients underwent MVR at the time of surgery, all in the conventional group).

Table 3. In-hospital complications after surgery.

	Total cohort N = 120	MAMVS N = 29	Conventional N = 91	P-value
Hospital stay median (IQR)	7 (6-9)	7 (6-8)	8 (6-10)	0.095
Intensive care stay median (IQR)	1 (1-1)	1 (1-1)	1 (1-1)	0.329
Hospital mortality n (%)	4	0 (0.0)	4	0.572
Re-thoracotomy n (%)	10 (8.3)	2 (6.9)	8 (8.8)	0.999
Acute Kidney Injury stage n(%)				0.689
0	97 (80.8)	26 (89.7)	71 (78.0)	
1	10 (8.3)	1 (3.4)	9 (9.9)	
2	10 (8.3)	2 (6.9)	8 (8.8)	
3	3 (2.5)	0 (0.0)	3 (3.3)	
New permanent PM implantation n (%)	2 (1.7)	0 (0.0)	2 (2.2)	0.999
Intra-aortic balloon pump n (%)	3 (2.5)	1 (3.4)	2 (2.2)	0.567
Infection with focus n (%)	9 (7.5)	3 (10.3)	6 (6.6)	0.450
Fever unkown origin n (%)	2 (1.7)	0 (0.0)	2 (2.2)	0.999
Delirium n(%)	6 (5.0)	1 (3.4)	5 (5.5)	0.999
Discharge atrial fibrillation n (%)	4 (3.3)	1 (3.4)	3 (3.3)	0.999
Valve thrombosis n (%)	0 (0.0)	0 (0.0)	0 (0.0)	-
Endocarditis n (%)	1 (0.8)	0 (0.0)	1 (1.1)	0.999
Thrombo-embolic cerebral n (%)	3 (2.5)	1 (3.4)	2 (2.2)	0.567
Thrombo-embolic noncerebral n (%)	0 (0.0)	0 (0.0)	0 (0.0)	-
Bleeding event n (%)	3 (2.5)	0 (0.0)	3 (3.3)	0.999

PM = pacemaker

Table 4. Mortality before and after discharge

Cause of death	Age	MR mechanism	Pre-operative ejection fraction	Latest known MR severity after surgery
Before discharge				
Mediastinitis	66	Prolaps	68%	moderate-to-severe
Sepsis	78	Restriction	56%	none
LV failure / assist device	68	Prolaps	55%	not known
Cerebro-vascular accident	81	prolaps	64%	mild-to-moderate
After discharge				
Suicide	52	Restriction	40%	moderate
Sudden cardiac death	77	Restriction	34%	none
Late tamponade	78	Annulus dilatation	48%	mild
Cerebro-vascular accident	72	Restriction	24%	mild

MR = mitral regurgitation

As seen in Figure 1 MR decreased significantly after 6 months for both groups with no significant difference between the groups (P = 0.960). Other echocardiographic parameters as LV end-diastolic volume, LV-EF and LAVI also improved significantly after surgery as well as NYHA class (Table 5). Comparison of the echocardiographic parameters at 6 months for the two groups shows a significant difference for LAVI with more remodeling in the MAMVS group, 71 [55-90] to 43 [35-58] (ml/m^2) versus 69 [53-89] to 49 [41-70] (ml/m^2) in the conventional group (P < 0.05). For the total cohort NYHA class improved from II [II-III] pre-operatively to I [I-II] post-operatively at 6 months, respectively. NT-proBNP 6 months after surgery shows in the MAMVS group no significant improvement, but in the conventional group this value decreased significantly from 110 [33-242] to 59 [35-123] pmol/L (P <0.05).

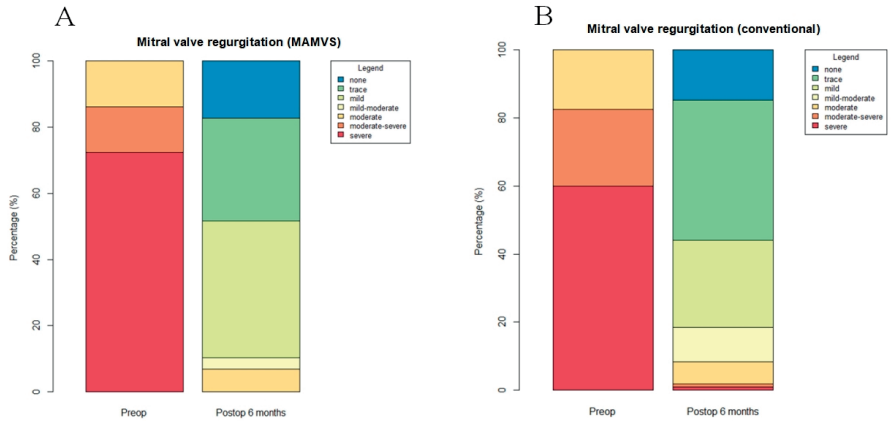

Figure 1: Severity of mitral regurgitation at baseline and 6 months after mitral valve surgery for the MAMVS (A) and conventional (B) group.

Table 5. Echocardiographic and clinical parameters at baseline and 6 months follow-up

	MAMVS N = 29		**p-value**	**Conventional N = 80**		**p-value**
	Pre	**6m**		**Pre**	**6m**	
Mitral regurgitation			< 0.001			< 0.001
None	0	5 (17%)		0	11 (14%)	
Trace	0	9 (31%)		0	36 (45%)	
Mild	0	12 (41%)		0	16 (20%)	
Mild-moderate	0	1 (3%)		0	10 (13%)	
Moderate	4 (14 %)	2 (7%)		14 (18%)	5 (6%)	
Moderate-severe	4 (14%)	0		21 (26%)	1 (1%)	
Severe	21 (72%)	0		45 (56%)	1 (1%)	
LV end-diastolic volume (ml)	181 [152-220]	138 [110-170]	< 0.001	173 [135-207]	136 [117.5-170]	< 0.001

Table 5. Echocardiographic and clinical parameters at baseline and 6 months follow-up (*continued*)

	MAMVS N = 29		p-value	Conventional N = 80		p-value
LV ejection fraction (%)	56 [51-61]	51 [48-55]	0.001	52 [43-57]	49 [37-53]	< 0.001
LAVI (ml/m^2)	71 [55-90]	43 [35-58]	< 0.001	69 [53-89]	49 [41-70]	< 0.001
TR Vmax (m/s)	2.6 ± 0.5	2.4 ± 0.3	0.03	2.7 ± 0.5	2.5 ± 0.5	0.001
Tricuspid regurgitation						
None	3 (10%)	1 (3%)		3 (4%)	6 (8%)	
Trace	13 (45%)	13 (45%)		33 (41%)	40 (50%)	
Mild	8 (28%)	11 (38%)		23 (29%)	26 (32%)	
Mild-moderate	4 (14%)	3 (10%)		6 (8%)	5 (6%)	
Moderate	1 (3%)	1 (3%)		7 (9%)	3 (4%)	
Moderate-severe	0	0		4 (5%)	0	
Severe	0	0		4 (5%)	0	
Death		0			8	
NYHA class			< 0.001			<0.001
I	7 (24%)	24 (83%)		5 (6%)	52 (65%)	
II	18 (62%)	3 (10%)		37 (46%)	25 (31%)	
III - IV	4 (14%)	2 (7%)		38 (48%)	3 (4%)	
NT-proBNP (pmol/L)	21 [13-51]	31 [20-51]	0.127	110 [33-242]	59 [35-123]	0.018

LAVI = left atrial volume index; LV = left ventricle; NYHA = New York Heart Association; TR = tricuspid regurgitation

TR decreased after concomitant TVP (P < 0.001), whereas in patients without TV repair no significant change occurred (P = 0.831). Final results of TR after TV repair were comparable to patients without a need for TV repair at 6 months (P = 0.408) (Figure 2).

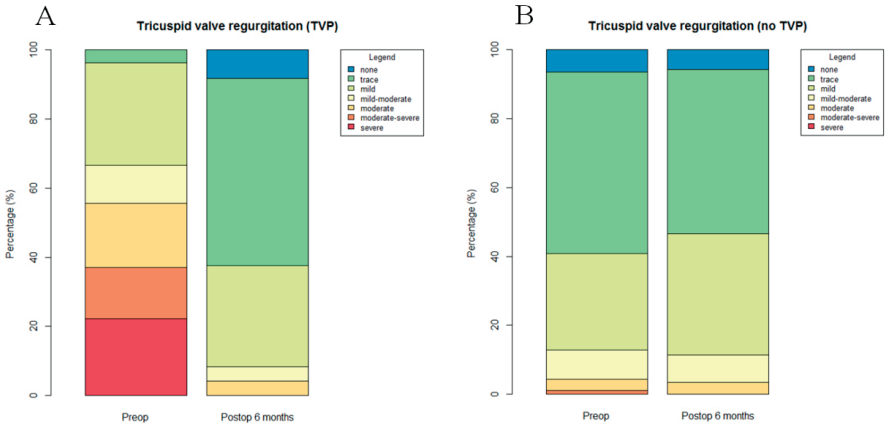

Figure 2: Severity of tricuspid regurgitation at baseline and 6 months after mitral valve surgery in patients with (A) and without (B) tricuspid valve plasty.

Analyses of the quality of life questionnaires showed a significant improvement at all domains after 6 months, except for pain (Figure 3). Comparing the improvements of both groups demonstrated no significant differences with P-values between 0.220 and 0.934 for 8 domains.

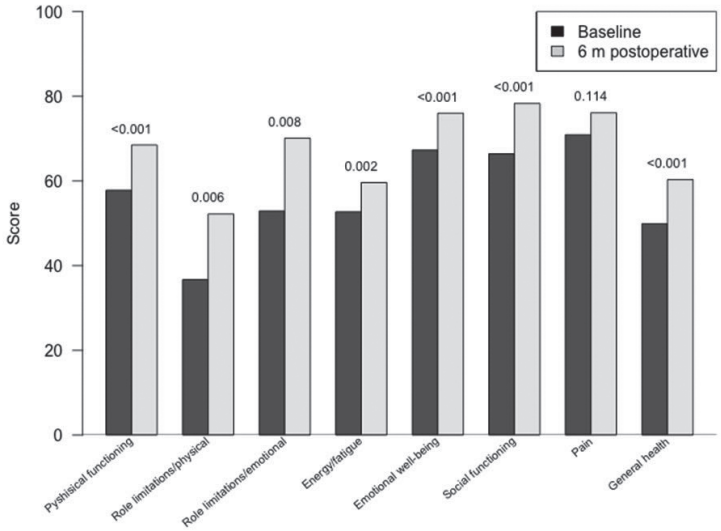

Figure 3: Quality of life at baseline and 6 months after mitral valve surgery.

DISCUSSION

This study investigated the clinical and echocardiographic outcome after MV surgery and concomitant tricuspid valve surgery in our hospital. The main findings are

1) MR severity was significantly reduced, with no difference between conventional surgery and MAMVS in reducing MR
2) LA remodeling was superior in the MAMVS group
3) In-hospital complications were not different between conventional surgery and MAMVS
4) NYHA class and quality of life as measured by SF-36 questionnaires improved after surgery, except for pain with no significant differences between the conventional surgery or MAMVS
5) TV repair was done in a quarter of all patients, usually based on an enlarged tricuspid annular diameter, and only a very small minority of patients (3%) had at short-term (6-months) follow-up moderate TR and none had more than moderate TR

Reduction in MR severity

Echocardiography is the principal technique to assess the severity and mechanism of the MR, as well the suitability for repair and residual MR after surgery [8,9]. The mechanism of

MR was different in the MAMVS and conventional groups, with more leaflet restriction and moderate to severe TR in the conventional cohort, most likely because these parameters are part of the decision for suitability for MAMVS. MR decreased significantly after 6 months for both groups with no significant difference between the groups. In the MAMVS group only 2 patients (7%) had moderate MR at follow-up and in the conventional group 5 (6%) patients had moderate MR and 2 (2%) had more than moderate MR. So, the overall success of MV repair was greater than 90% (4 patients converted to MV replacement and 9 patients had at least moderate MR at follow-up). Of note, in the 8 patients who died before the 6-month assessment also 2 had at least moderate MR after conventional surgery, so ultimately 11 patients had at least moderate MR at follow-up, still resulting in a successful MV repair rate of >90%.

LV and LA remodeling

Whereas there were no changes between conventional surgery and MAMVS in LV reverse remodeling, reverse LA remodeling was more pronounced in the MAMVS group. This may be important because LA size may be a predictor of outcome [10-12]. However, the more pronounced reduction in LA volume is most likely explained because of greater pre-operative MR severity at baseline in the conventional surgery group. It should also be noted that patients in the conventional group tended to have a higher incidence of atrial fibrillation, probably limiting LA reverse remodeling. Alternatively, Machdo et al. reported an association of LA reverse remodeling after MV surgery with higher LV-EFs [13]. In our study the preoperative LV-EF was significant higher in the MAMVS group providing an alternative explanation for more LA reverse remodeling in this group.

In-hospital complications

MAMVS has been shown to have excellent results, compared with the conventional approach, in terms of mortality, morbidities and pain, providing shorter hospital stay, faster recovery and return to normal activities with outstanding long-term results [2,14]. Our results are in line with the current literature with an in-hospital mortality of 0.8% (total cohort) and no significant differences in complications between MAMVS and the conventional approach.

Clinical follow-up results

The quality of life assessment is, besides the NYHA classification, an essential component in evaluating the efficacy of the benefits obtained after surgery. Only, few studies investigated quality of life after MV surgery for MR, especially in asymptomatic patients [15,16]. In their prospective study Bayer-Topilsky and co-authors report a psycho-emotional status alteration to normal 6 month after MV surgery for organic MR, suggesting that severe MR in patients with NYHA class I and II for symptoms of heart failure has a negative impact

on mental health and that surgical procedures improve their mental outcomes [16]. Our study confirms these data for a more heterogeneous group with 58% of patients in NYHA class I or II and not only organic MR.

Reduction in TR severity

TR in MV disease may result from 1) pulmonary hypertension and subsequent right ventricular enlargement and dysfunction with an increasing tricuspid valve diameter, leaflet tethering or papillary muscle displacement, 2) atrial fibrillation with subsequent increasing tricuspid valve diameter, and 3) a similar disease process. For MR surgery, concomitant TV repair is recommended in patients with a tricuspid annular dilatation ≥ 40 mm since this is a risk factor for developing late functional TR after left sided valve surgery [8,17]. In our study 27 (23%) of patients underwent TV repair. In 6 patients this was based on severe TR, in the remaining patients it was based on tricuspid annular dilatation, with the notice that the sensitivity of transthoracic echocardiography was less than transesophageal echocardiography. Whereas at baseline 19 (16%) of patients had at least moderate TR, at short-term (6-months) follow-up only 4 (3%) of patients had moderate TR and none had more than moderate TR. In the MAMVS group no patient had undergone TV repair and only 1 patient had progression from pre-operatively mild to moderate TR at follow-up. In the conventional group 3 patients had moderate TR at follow-up; 2 patients without annulus dilatation and without TV repair with pre-operatively respectively mild-to-moderate and moderate TR and 1 patient showed regression of pre-operative severe to moderate TR after TV repair. So, actually in total only 2 patients showed mild progression of untreated TR [18,19].

Limitations

This was a single center experience and in particular the number of patients that underwent MAMVS was relatively small. Therefore we opted for univariable comparisons. Approximately 15% of patients from the consecutive series could not be included in the study because of missing baseline or follow-up echocardiograms. At baseline, significant differences were seen between the two patient groups in age, NYHA class, CAD presence and LV-EF and this selection bias may obviously limit the comparison between the groups. However, the main goal of the study, the reduction of MR, will only to a small extent not be affected by these differences. Also, three-dimensional echocardiography was not used in this study although it may improve volumetric [20] and functional analysis [21]. Finally, in most studies for MAMVS, long-term successful repair was defined as absence of moderate or more MR >6 months after surgery [2,14,22]. Our 6-months data do therefore not provide true long-term outcome. However, in the 47 patients in whom 2 year echo follow-up data were available (14 in the MAMVS group and 33 in the conventional group) none of the patients showed progression from less than moderate to moderate or more MR. Also, in

three additional patients with restrictive MR who died in the 6 to 24 month period none had moderate or greater MR after surgery.

CONCLUSIONS

MR severity was significantly reduced, with no difference between conventional surgery and MAMVS in reducing MR, with greater LA remodeling in the MAMVS group. In-hospital complications and NYHA class and quality of life assessment were not different between conventional surgery and MAMVS. The overall successful MV repair rate was >90%.

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Chapter 11

Anatomy of the Mitral Valvular Complex and Its Implications for Transcatheter Interventions for Mitral Regurgitation

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ABSTRACT

Mitral regurgitation (MR) poses a significant clinical burden in the adult population, which is expected to increase even more with the ever prolonging life expectancies in developed countries. New technology has brought MR, once exclusively the arena of cardiac surgeons, to the attention of interventional cardiologists. A variety of device-oriented transcatheter strategies have evolved in recent years. A comprehensive understanding of mitral valvular anatomy is crucial for the selection of patients, the implementation of devices, and further refinements of these transcatheter techniques if they are eventually to produce procedural and clinical success. The aim of this review is to elucidate the morphology of the mitral valvular complex, integrating key anatomical features into the developing transcatheter options for the treatment of MR.

INTRODUCTION

Valvular heart disease frequently affects the adult population in developed countries [1]. Because age is the dominant risk factor and is uncontrollable, the incidence of such problems will rise. In the U.S., 0.7% of young adults below the age of 45 years have moderate to severe valvular heart disease, a proportion increasing to one-sixth of those over 75 years of age. In every age group, mitral regurgitation (MR) is the most common valvular disorder, with a global prevalence of 1.7%, increasing to 10% in those age >75 years.

The mitral valvular apparatus is a complex anatomical and functional entity [2]. One or more flaws in its components can result in MR. According to etiology and pathophysiology, MR can be divided somewhat artificially into primary or organic and secondary or functional categories [3,4]. In primary lesions, 1 or more of the components of the mitral valve (MV) itself is deranged, whereas in secondary lesions, geometric and/or functional changes of the left ventricle (LV) are the core of the problem.

Despite guidelines for the management of patients with severe MR, a recent European survey established that one-half of these patients are not referred for surgery, largely because of their advanced age, the presence of comorbidities, or impaired LV function [5–7]. Even more notably, repair as opposed to valvular replacement was performed in only one-half of those who underwent surgery, mostly because of a lack of institutional expertise in this particular technique. The surgical treatment of functional MR remains a subject of debate [8].

This underserved population of patients with severe MR opens the door for several innovative transcatheter concepts, which are comparable with various aspects of surgical repair [9]. To take full advantage of these new technologies, it is axiomatic that those attempting treatment should have comprehensive knowledge of the anatomy of the mitral valvular apparatus and its relationship to the LV. Our aim in this review, therefore, is to address the anatomy of the mitral valvular complex with catheter-based techniques for valvular repair in mind.

HISTORY

It was the Belgian anatomist and physician Andreas Vesalius, while working in Padua, Italy, who likened the bifoliate left atrioventricular valve to a bishop's mitre, hence the term "mitral valve" [10]. The physiology of the working components of the valve, its 2 leaflets, can be understood only when note is taken of their crucial relationships to the adjacent anatomical structures, namely, the left atrium (LA), the LV, the aortic valve, the papillary muscles, the tendinous cords, and the cardiac central fibrous body. In 1972, Perloff and Roberts put forward the concept of a mitral valvular complex to underscore this essential and harmonious structural relationship [2]. From a clinical perspective, the French surgeon Alain Carpentier introduced the paradigm of the pathophysiologic triad to better define

regurgitation across the valve, pointing out that the underlying disease, the first leg of the triad, creates structural or geometric changes in the valvular apparatus, this being the second leg, which may lead to valvular dysfunction as the third leg [3,4].

More recently, the extraordinary revolution in cardiac imaging has contributed to better understanding and integration of the anatomy, physiology, and pathophysiology of the MV, with 3-dimensional echocardiography, multislice computed tomography, and cardiac magnetic resonance imaging all proving invaluable in evaluating valvular regurgitation and playing a defining role in the development and execution of transcatheter valvular therapies [11–16].

THE MITRAL VALVULAR COMPLEX

For normal closure of the MV, both leaflets must align in the same plane as they coapt along their solitary zone of apposition. To achieve such apposition, it is necessary to have an optimal size of the so-called valvular annulus, a geometrically correct orientation of the papillary muscles giving rise to the tendinous cords, and appropriate closing forces generated by muscular contraction of the LV. Thus, it is necessary to take account not only of the mitral valvular apparatus when considering the salient anatomy but also of the relationship between its components and surrounding structures, such as the atrioventricular conduction axis, the aortic valve, the coronary sinus, and the circumflex coronary artery.

The left atrioventricular junction

From an anatomical perspective, the term “mitral annulus” is a misnomer. The essential structure supporting the valvular leaflets is the left atrioventricular junction, this being the D-shaped orifice formed at the confluence between the LA walls and the supporting LV structures [2,10,17,18]. On the ventricular aspect, these supporting structures are not exclusively myocardial, because there is an extensive area of fibrous continuity (the so-called aortic-mitral curtain) between the anterior leaflet of the MV and the aortic valve in the roof of the LV (Figure 1). When considered 3-dimensionally, the overall atrioventricular junction is nonplanar, with elevated septal and lateral segments at the ends of the solitary zone of apposition between the leaflets and complementary depressed medial segments along the central component of the zone of apposition, giving a characteristic saddle-shaped overall appearance (Figure 2) [19]. It is along the depressed anterior segment of the junction that 1 of the leaflets of the valve is in fibrous continuity with the noncoronary and left coronary leaflets of the aortic valve, this extensive area being well described as the aortic-mitral curtain (Figure 1). At either end, the central part of the fibrous curtain, which represents the annulus of the aortic or anterior leaflet of the valve, is attached by fibrous expansions, the left and right fibrous trigones, to the ventricular myocardium (Figures 3 and 4). The right trigone is itself continuous with the membranous septum, the combined entity forming the

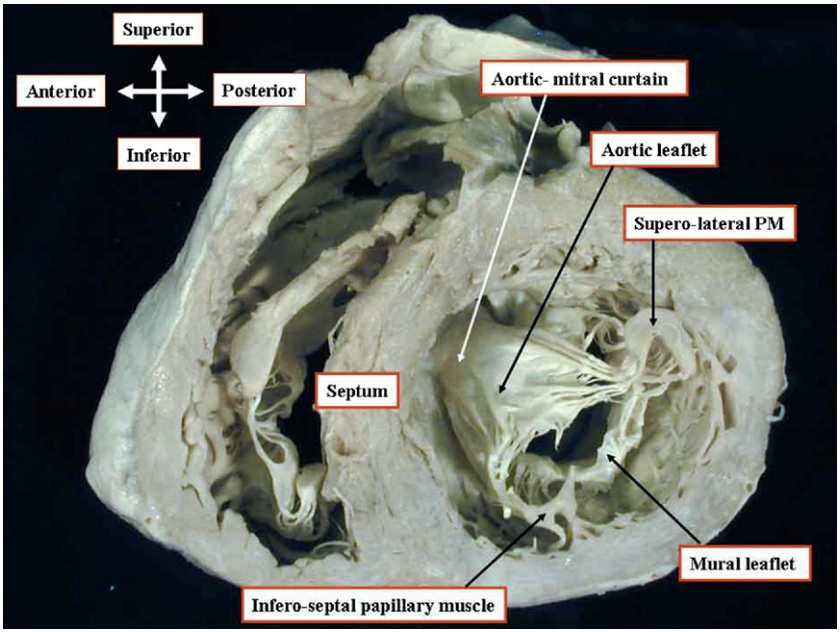

Figure 1. Anatomical Orientation of the Left Atrioventricular Junction. The ventricular mass has been sectioned along its short axis and photographed from the cardiac apex; the heart is presented in the location it occupies in the thorax. Note that the septum is anteriorly located, and the papillary muscles (PM) supporting the leaflets of the mitral valve, when assessed in attitudinally appropriate location, are positioned inferoseptally and superolaterally. Note also that 1 of the leaflets of the mitral valve is in fibrous continuity with the leaflets of the aortic valve, the fibrous aortic-mitral curtain formed by the area of their continuity creating the roof of the left ventricle.

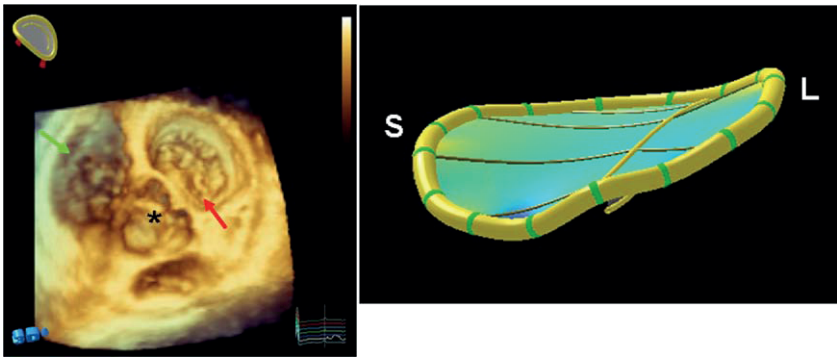

Figure 2. 3-Dimensional Echocardiographic Reconstruction of the Left Atrioventricular Junction. (Left) Three-dimensional echocardiographic reconstruction of the left atrioventricular junction, demonstrating the location of the mitral valve (red arrow) relative to the aortic valve (*). The green arrow indicates the right ventricle. (Right) Saddle-shaped appearance of the mitral atrioventricular junction or "annulus." Note the elevated septal (S) and lateral (L) segments and complementary depressed segments along the central zone of apposition.

central fibrous body, and with the penetrating part of the atrioventricular conduction axis passing through the atrioventricular component of the membranous septum [18]. Fibroelastic cords of various firmness and structure extend from the fibrous trigones through the mural part of the left atrioventricular junction. It is rare for the cords to form a complete ring to support the mural, or posterior, leaflet of the valve. The so-called annulus, therefore, is much more resistant to pathologic dilation along the aortic as opposed to the mural leaflet. Especially in its posterior aspects, several deficiencies in the annular structure are filled with adipose tissue. The absence of a well-formed fibrous cord in this particular position opposite the aortic-mitral curtain explains its predilection for annular dilation and calcification, which result in a disproportional increase in the aortic-to-mural, or septal-to-lateral, diameter of the valvular orifice, potentially precluding adequate leaflet coaptation.

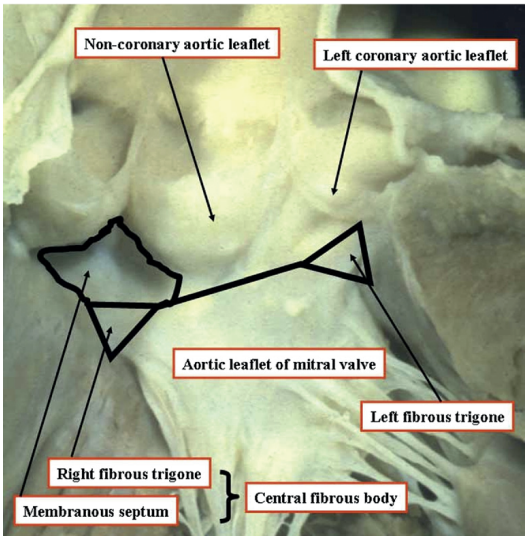

Figure 3. The Aortic-Mitral Curtain and Fibrous Continuity. The heart has been opened through the outflow tract of the left ventricle, showing the ventricular surface of the aortic leaflet of the mitral valve. Note how the ends of the area of fibrous continuity between the aortic leaflet of the mitral valve and the noncoronary and left coronary leaflets of the aortic valve anchor the aortic-mitral curtain in the roof of the left ventricle. The ends of the area of fibrous continuity are the left and right fibrous trigones. As can be seen, the right fibrous trigone is itself continuous with the membranous septum, the conjoined are being known as the central fibrous body.

The goal of surgical annuloplasty when the atrioventricular junction is dilated is to decrease the circumference of the valvular orifice, the aim being to reduce the septal-to-lateral diameter by at least 8 mm [20]. Transcatheter strategies now exist to achieve this same goal (Figures 5A and 5B). Key anatomical features for success are the patency of the coronary sinus and the anatomical relationship between the myocardial components of the mural junction, the sinus itself, and the circumflex coronary artery. The potential to produce damage to the atrioventricular conduction axis should also be remembered (Figure 4).

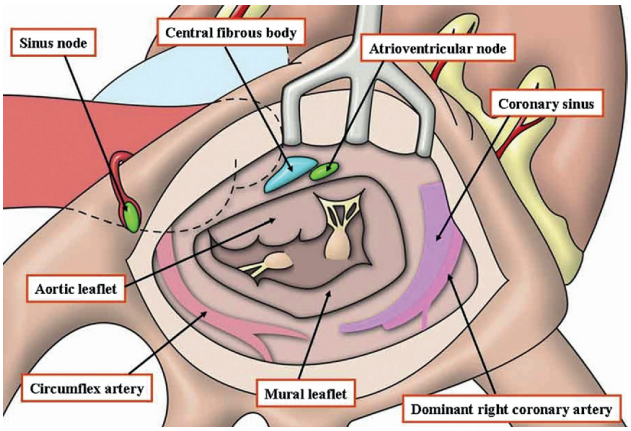

Figure 4. Anatomical Structures Surrounding the Left Atrioventricular Junction. Relationships of the mitral valve as seen by the surgeon operating through the roof of the left atrium.

Transcatheter annuloplasty can be performed indirectly by reshaping and restraining the valvular orifice via the coronary sinus (see the following discussion) or by approaching the junction directly via the LA or LV [9]. The Mitralign system (Mitralign, Inc., Tewksbury, Massachusetts) and Accucinch (Guided Delivery Systems, Inc., Santa Clara, California) are both direct annuloplasty devices. Dedicated catheters are advanced retrogradely into the LV to position anchors to the ventricular side of the posterior segment of the left atrioventricular junction. By pulling the anchors together with sutures, the circumference of the atrioventricular junction is reduced. Mitral cerclage annuloplasty is a circumferential suture-based concept that combines the indirect and direct techniques [21]. A guidewire is advanced through the coronary sinus into the first septal perforating branch of the great cardiac vein and subsequently directed across a short segment of myocardium to establish a right ventricular or right atrial re-entry. The guidewire is then ensnared and exchanged for a suture and tension fixation device. A rigid arch protects the suture at the site where the coronary sinus crosses the circumflex artery. Annuloplasty can also be achieved by applying thermal radiofrequency to the fibroadipose tissue of the left atrioventricular junction, producing shrinkage without jeopardizing the cardiac vessels or mitral valvular leaflets (QuantumCor system, QuantumCor, Inc., Bothell, Washington) [22].

The valvular leaflets

The MV is bifoliate. The leaflet classically described as being anterior is in fibrous continuity with 2 of the leaflets of the aortic valve, hence the alternative term “aortic leaflet.” The opposing posterior leaflet is also appropriately described as the mural leaflet [10,18]. The aortic leaflet has a wider surface with a shorter base and guards one-third of the left atrioventricular junction. It separates the LV inflow and outflow tracts. The mural leaflet is shallower but wider, guarding two-thirds of the junctional circumference. The surface area of both

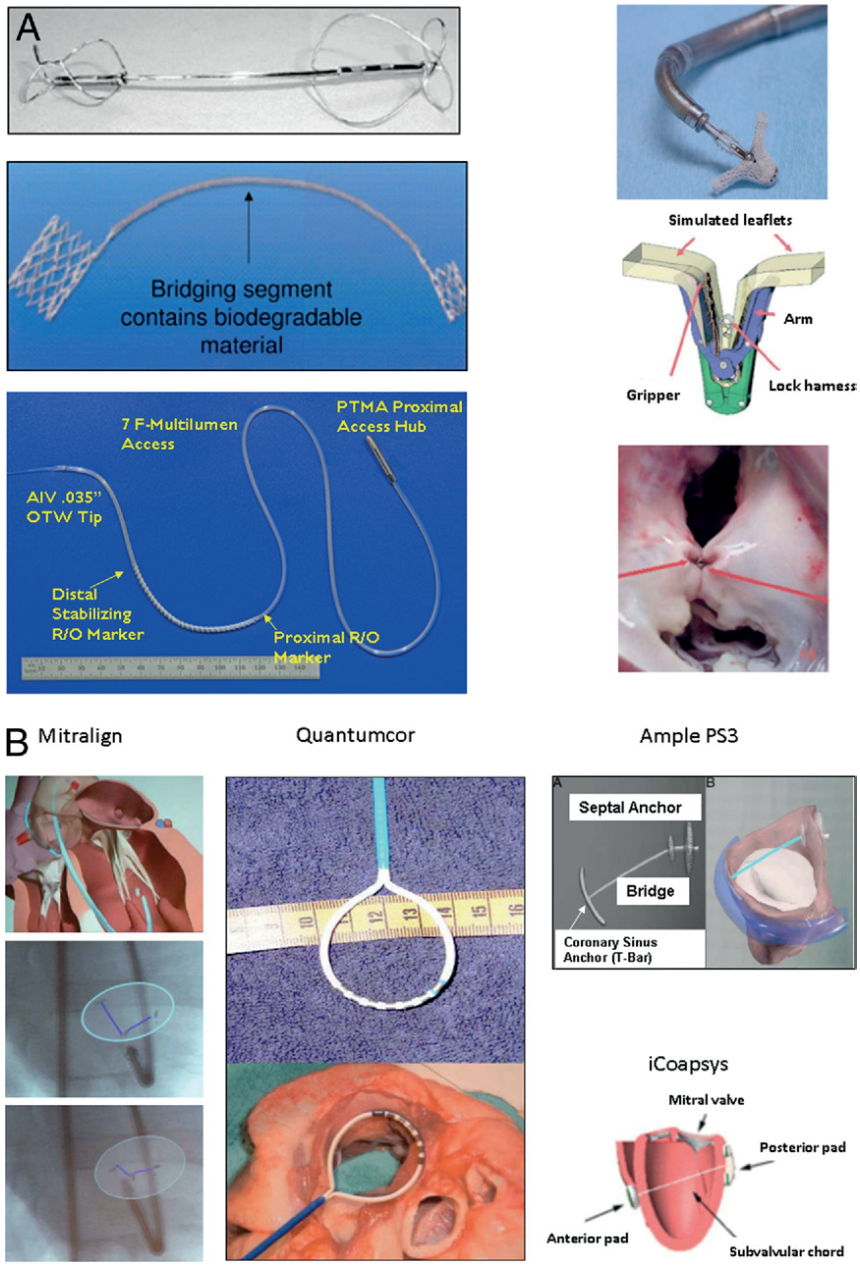

Figure 5. Devices for Indirect Transcatheter Mitral Annuloplasty and MitraClip and Devices to Reduce Mitral Regurgitation. (A) Devices available for indirect transcatheter mitral annuloplasty. (Left) From top to bottom, the Carillon (Cardiac Dimensions, Inc., Kirkland, Washington), Edwards MONARC (Edwards Lifesciences, Irvine, California), and Percutaneous Transvenous Mitral Annuloplasty (PTMA) (Viacor, Inc., Wilmington, Massachusetts) devices. (Right) The MitraClip (Evalve, Inc., Menlo Park, California). (B) Devices to reduce mitral regurgitation through transcatheter repair of the mitral valve. AIV = anterior interventricular vein; OTW = over-the-wire; R/O = radio-opaque.

leaflets taken together is 2.5 times the area of the valvular orifice. In systole, the leaflets coapt over a height of, on average, 8 mm, giving an "overlapping reserve" or "coaptation reserve" in case of annular dilation (Figure 6). The zone of apposition between the leaflets is obliquely oriented relative to the orthogonal planes of the body but is recognized as the "mitral smile" on short-axis echocardiography. Its 2 ends are positioned inferoseptally and superolaterally (Figure 1), although these positions are currently incorrectly described as being posteromedial and anterolateral [17]. Slits in the mural leaflet create 3 scallops, while further segments of leaflet tissue are found at the ends of the solitary zone of apposition, this zone representing the true valvular commissure. These various components of the mural leaflet produce a more flexible structure compared with the more rigid aortic leaflet and combine with the dynamic motions of the junction to produce the so-called sphincter mechanism.

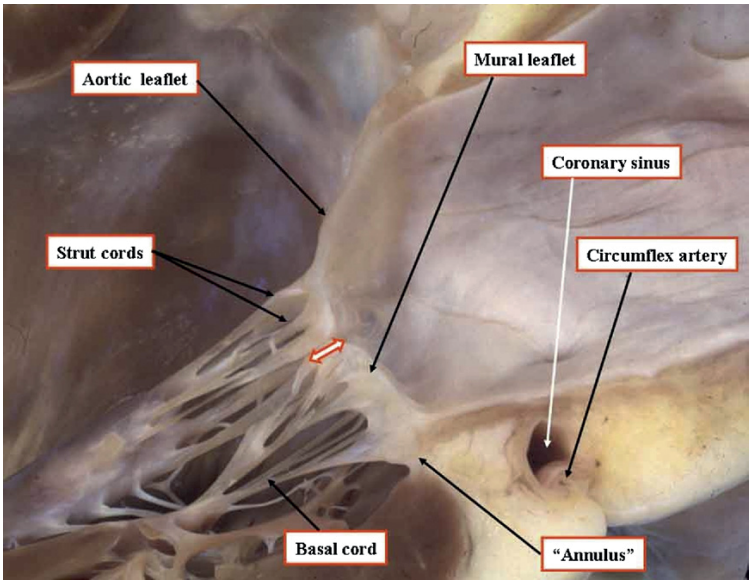

Figure 6. Mitral Leaflet Coaptation. The heart has been sectioned along the long axis of the left ventricle, having fixed the heart with the leaflets of the mitral valve in closed position. The double-headed arrow indicates the coapting surfaces of the leaflets. Note the strut cords supporting the ventricular aspect of the aortic leaflet of the valve and the basal cord supporting the ventricular aspect of the mural leaflet. Note also the relationships of the coronary sinus and the circumflex artery to the mural leaflet of the valve.

When regurgitation across the valve is the consequence of inappropriate coaptation of the leaflets, one approach to surgical treatment is to create a double orifice by suturing together the free edges of the middle segments of the anterior and posterior leaflets, the edge-to-edge or Alfieri stitch [23]. This technique has now been adapted for transcatheter use, and has received Conformité Européenne mark approval as the MitraClip (Evalve, Inc., Menlo Park, California). Unlike the surgical approach, however, the transcatheter technique does

not currently involve an annuloplasty, although the clinical value of a combined approach remains debatable [24].

The Alfieri stitch is used for organic as well as functional MR [25]. A transseptal puncture is required to advance the catheter to the LA. The MitraClip uses 1 or 2 clips to join the 2 leaflets at the level of the middle scallop of the mural leaflet. After implantation, a tissue bridge forms across the clip between the leaflets, providing additional support for the repair and preventing septal-to-lateral dilation. Importantly, the contractile function of the atrioventricular junction is preserved. For MitraClip trial inclusion, several anatomical premises must be fulfilled. First, the regurgitant jet must be centered at the level of the zone of coaptation in the central two-thirds of the line of coaptation. Second, coaptation length of at least 2 mm, and a depth below the mitral annular plane of no more than 11 mm, must be available for coaptation between the leaflets, although the coaptation depth may be less important. Should one of the leaflets be flail, the gap and the width of the flail segment can be no more than 10 and 15 mm, respectively (Figure 7).

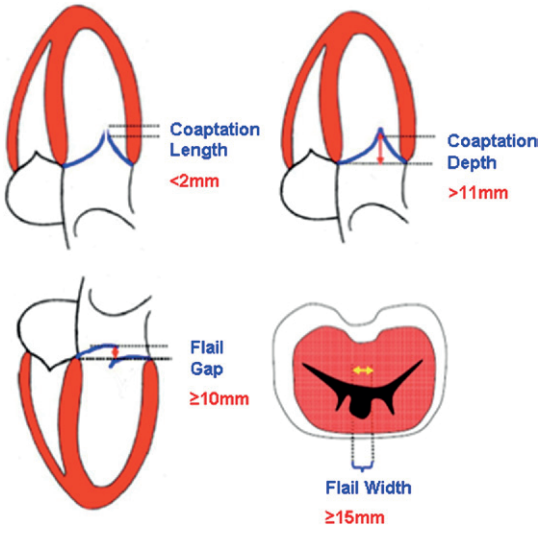

Figure 7. Key Anatomical Dimensions for the MitraClip. Anatomical measurements less favorable for the MitraClip device (Evalve, Inc., Menlo Park, California).

Tendinous cords and papillary muscles

The mitral valvular leaflets, via the tendinous cords and papillary muscles, are connected to the LV free wall like the shrouds of a parachute [2,10,18]. The fibrocollagenous tendinous cord, or chordae tendineae, take origin from the papillary muscles, bifurcate several times, and attach to the free edges and ventricular aspects of both leaflets. The cords are thinnest at their sites of insertion on the leaflets, and this is the site of predilection for chordal rupture.

Most of the cords insert uniformly along the free margins of the leaflets, thus preventing marginal prolapse and aligning the zone of coaptation. Strut cords attach to the ventricular aspect of the aortic mitral leaflet (Figure 1), precluding billowing and serving to distribute load throughout the leaflet. The basal cords originate directly from the ventricular wall and attach exclusively to the ventricular surface of the mural leaflet, contributing to ventricular geometry and fortifying the ventricular aspect of the atrioventricular junction.

The cords arise from the paired papillary muscles, which arise from the apical to middle thirds of the LV free wall, with each muscle made up of a variable number of heads. It is conventional wisdom to state that the superolateral muscle is supplied by 1 or more branches of the circumflex artery, or by diagonal branches, whereas the inferoseptal papillary muscle is supplied by a single branch of the circumflex or right coronary artery, depending on coronary artery dominance. Because of its single vascular supply, the inferoseptal muscle in particular is susceptible to coronary ischemia. Organic disease usually involves these components of the mitral valvular complex [26]. Myxomatous degeneration can render the cords inappropriately long and abolish their specific elastic properties, thus inducing prolapse. Fibroelastic deficiency produces the exact opposite phenomenon. There will be retraction of tissue, making the cords vulnerable to rupture and resulting in a partial or total flail leaflet. As already discussed, it is the MitraClip that represents the transcatheter approach targeting degenerative regurgitation.

Integration of the LA and LV

The myocardium of the LA and LV is intimately connected to support the mural leaflet of the MV. The term “disjunction” refers to the fact that the valvular tissue hinges directly from the myocardium rather than being supported by an anatomical cordlike structure [27]. The insertion of the LA myocardium follows the general contour of the junction, as opposed to the LV myocardium, which has no relationship with the aortic leaflet of the MV. Indeed, the LV outflow tract interposes between the aortic leaflet of the MV and the ventricular septum [10]. The posteroinferior wall of the LV, in contrast, supports directly the mural leaflet through the basal cords. Given the tight interdependence with the ventricular free wall and the unique arrangements of the different components, changes in ventricular geometry can have serious consequences for mitral valvular dynamics [28]. LV mural dyskinesia can change the orientation of the basal cords, producing a tethering effect on the mural leaflet. More global LV dilation can displace the papillary muscles in an apical direction, creating tenting of the leaflets with lack of coaptation and eventual regurgitation.

Catheter techniques have been developed to remodel the LV by introducing a transventricular bridge between anterior and posterior pads, placed through the pericardial space (iCoapsys, Edwards Lifesciences, Irvine, California). By drawing the pads together, it is possible to change the LV geometry, potentially narrowing the atrioventricular junction

and optimizing the orientation of the papillary muscles relative to the leaflets, although this technology is currently in abeyance [29].

Transcatheter replacement of the MV, via either a transapical or a transseptal approach, is a much anticipated technique. Several anatomical hurdles remain. The inherent radial force needed to anchor the stented valve might squeeze the LV outflow tract, while the tendinous cords might impede positioning, expansion, and anchoring of the prosthesis [30,31]. The asymmetry of the mitral orifice is also a technical challenge.

Coronary venous and arterial anatomy

In a venous system known to show marked variability, consistent entities are the great cardiac vein and the coronary sinus (Figure 8) [12,32,33]. In general, the great cardiac vein, also known as the anterior interventricular vein, originates at the lower or middle third of the anterior interventricular groove [32]. It follows the groove toward the base of the heart and then turns inferiorly at the atrioventricular junction, fusing with the oblique vein of the LA, a remnant of the embryonic left superior caval vein, to become the coronary sinus. The middle cardiac vein runs along the inferior interventricular groove to empty into the coronary sinus close to its orifice in the right atrium. At its orifice, the coronary sinus is guarded by a thin semicircular valve, the Thebesian valve. There is significant variability in the morphology and composition of this valve, such that it can become a notorious obstacle to cannulation of the sinus [33]. The location of the coronary sinus changes as it courses through the left atrioventricular junction. In over nine-tenths of cases, the body of the sinus is adjacent to the inferior LA wall, well above and cranial to the deeper atrioventricular junction (Figure 6) [12,16,34]. It is closest to the lateral segment of the atrioventricular junction at the midpoint of the mural leaflet and furthest away at the ends of the solitary zone of apposition. When there is significant regurgitation, particularly in the setting of ischemic cardiomyopathy,

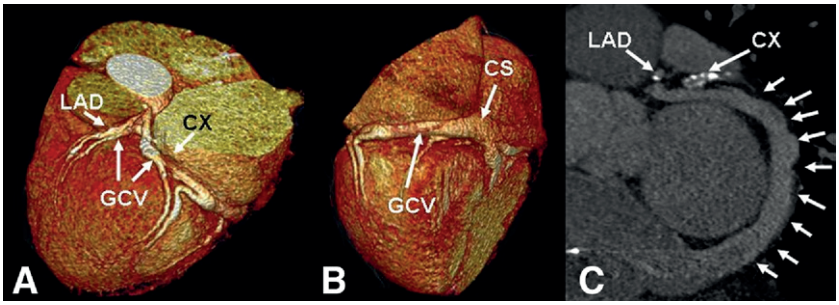

Figure 8. CS and Left CX by Multislice Computed Tomography. Electrocardiographically-gated dual-source 128-slice computed tomographic scan showing the morphology of the coronary sinus (CS). (A, B) 3-dimensional reconstructions showing the great cardiac vein (GCV) originating from the CS and extending into the left atrioventricular groove. (C) Cross-sectional plane taken parallel to the left atrioventricular groove showing the entire circumferential course and diameter of the great vein (arrows), demonstrating its relationship to the coronary arteries. CX = circumflex coronary artery; LAD = left anterior descending coronary artery

the sinus is lifted away from the posterior segment and conversely moves closer to the ends of the solitary zone of apposition between the leaflets [11,12]. This coincides with flattening of the saddle-shaped "annulus" and an increase in the septal-to-lateral annular diameter [35]. As the sinus approaches its right atrial termination and receives several tributaries, its caliber grows. The sinus is always a close neighbor of the circumflex artery, which crosses the venous structure in up to four- fifths of patients. The point of crossing, the length of the overlapping segment, the length of the parallel course, as well as the distance of the crossing point to the atrioventricular junction are all highly variable. The great cardiac vein crosses diagonal or intermediate arterial branches in one-sixth of individuals [33].

Several different devices are in development to provide indirect transcatheter annuloplasty [36–38]. Depending on the anatomical proximity of the coronary sinus to the left atrioventricular junction to accomplish an indirect annuloplasty, however, has obvious limitations. Coronary arteries can be pinched, and the location of the sinus relative to the annulus may be unfavorable, precluding procedural success. Various imaging techniques have been used to identify these spatial interrelationships. To date, however, none has been shown to accurately predict the suitability of the sinus for the purposes of transcatheter annuloplasty, nor could they predict whether the technique would jeopardize the circumflex artery. Cardiac failure, with at least moderate to severe MR, seems the tentative target indication. With this in mind, we briefly review the main devices under investigation.

Transcatheter indirect mitral annuloplasty devices

The Percutaneous Transvenous Mitral Annuloplasty device (Viacor, Inc., Wilmington, Massachusetts) consists of up to 3 straight and rigid nitinol rods seated in a dedicated multilumen polytetrafluoroethylene (Teflon, DuPont, Wilmington, Delaware) catheter, which is introduced in the coronary sinus with its distal atraumatic silicone tip in the great cardiac vein down the interventricular groove 38. The assembly will produce an outward force at its proximal and distal ends, resulting in anterior displacement of the middle scallop of the mural leaflet and a decrease in the septal-to-lateral diameter of the valve. After positioning, the titanium proximal Percutaneous Transvenous Mitral Annuloplasty hub is closed and sutured to the subclavian fascia, as would happen with a permanent pacemaker device.

The Carillon device (Cardiac Dimensions, Inc., Kirkland, Washington) consists of a curved nitinol arc connecting a proximal and a distal anchor [36]. A dedicated delivery catheter is used to position the distal anchor near the point at which the great vein enters the anterior interventricular groove. The device is then passively deployed by retracting the delivery catheter. During the implantation procedure, the functional efficacy on regurgitation, and potential coronary compromise, can be evaluated with ability to recapture the device if needed.

The Edwards MONARC system (Edwards Lifesciences) is a nitinol assembly with a small distal anchor, a larger proximal anchor, and a springlike bridging segment [37]. The

device is introduced through a delivery catheter. Both anchors are self-expandable. By retracting the delivery system, the device is deployed, and both anchors are drawn together, displacing the inferior part of the annulus more superiorly. The bridge contains biodegradable material, causing the system to shrink over the following weeks. Hence, the final result becomes evident only after 4 to 6 weeks. The downside of this system is 2-fold: the impact of the MONARC system on the dimensions of the valvular orifice and flow through the coronary arteries cannot be monitored during the implantation, and the device is not retrievable. The great cardiac vein must be at least 3 mm wide to receive the distal anchor, and the total length of the coronary venous system should be from 14 to 18 mm.

The various indirect coronary sinus annuloplasty devices have suffered fractures after implantation. The mechanical stresses in the coronary sinus are difficult to model and have not been fully appreciated. Also, not only the circumflex artery and its branches but also the diagonal and intermediate branches are at risk for impingement over time. All of these devices have been redesigned and require further study.

Indirect remodeling and concomitant reduction in the circumference of the valvular orifice through transatrial fixture is pursued with the Transcatheter Septal Sinus Shortening or PS3 device (Ample Medical, Inc., Foster City, California) [39]. This system creates a transatrial bridge using an atrial septal occluder and a T-bar element constricting the LA, thus reducing the septal-to-lateral dimension of the atrioventricular junction. Despite promising pre-clinical data and the first human experience, no further investigational efforts are currently scheduled.

CONCLUSION

The MV is a complex anatomical structure. Normal valvular mechanics require a sophisticated interaction of its components, along with the adjacent LV and atrial myocardium. Surgery is currently the standard of care for patients with severe MR [5,6,40,41]. In this respect, repair has a clear advantage over replacement, preserving as it does LV systolic function, obviating the need for oral anticoagulation, and improving survival [8,42]. Unfortunately, surgical repair is not always feasible, and at many cardiothoracic centers, the required surgical expertise is unavailable, and patients end up with MV replacement [43]. In addition, patients do not undergo surgical intervention because of age and comorbidities, while the indications for surgery in the setting of moderate to severe functional regurgitation are highly debated [7,8,44]. This confers a window of opportunity for the creation of new transcatheter technology. Knowledge of the anatomy of the mitral valvular complex is crucial for the clinical implementation and further refinement of these technologies. If their efficacy and safety can be demonstrated in relevant trials, the stage might be set for a paradigm shift whereby these transcatheter interventions could be added to the therapeutic

armamentarium in the heart failure arena and as a potential alternative for surgical valvular repair in selected cases.

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Chapter 12

Impact of the Learning Curve in Device Time, Echocardiographic Outcome and Clinical Outcome in Patients Treated with MitraClip®

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Submitted

ABSTRACT

Background

Contradictory findings are published with respect to a learning curve for echocardiographic and clinical outcome of mitral valve (MV) repair with the MitraClip® system.

Methods

The study included 39 patients with heart failure symptoms and at least moderate mitral regurgitation (MR) who underwent MitraClip® implantation. The learning curve was analyzed after creating three subgroups of 13 patients each according to the treatment period . A patient was defined as echocardiographic responder when MR severity decreased by at least 1 class considering the 6-scale MR classification to maximally moderate, and as clinical responder when the patient was alive and NYHA class improved to class 1 or 2 without a hospitalization for heart failure.

Results

Mean device time decreased continuously from 122±57 to 75±39 to 51±17 minutes in periods 1 to 3 ($P < 0.05$). There were no differences in number of patients with a complication between the different time periods. After 3 to 6 months the percentage of echocardiographic responders increased from 18% to 62% to 69% ($P < 0.05$). In the cardiomyopathy subgroup the percentage of echocardiographic responders also increased from 18% to 67% to 80% ($P < 0.05$). The number of clinical responders however did not significantly increase , in particular in the cardiomyopathic subgroup: 33% to 33% to 40%. Mortality in the cardiomyopathy cohort was 24% compared to 0% in the non-functional MR group.

Conclusion

Despite an increase in echocardiographic responders after MitraClip® in time the number of clinical responders did, in particular in patients with functional MR, not increase.

INTRODUCTION

Mitral regurgitation (MR) is a common disorder[1] and mitral valve (MV) surgery is worldwide an established therapy to cure the disease.[2] More recently, percutaneous edge-to-edge mitral valve repair using the MitraClip® (Abbott, Abbott Park, IL, USA) has been shown to be a reasonable alternative, in particular for older patients with multiple co-morbidities and high operative risk.[3,4] In fact, the number of MitraClip® implantations is currently exponentially increasing and numerous new centers will introduce this technique for MR treatment in the future. Being a rather complicated technique, experience of the treating team (in particular the imaging and interventional cardiologist) seems crucial and an important learning curve is expected. Unfortunately, only sparse data are available in the literature with conflicting results.[5,6] In the German Mitral Valve Registry it was claimed that the training and proctor system leads to already high initial procedure success and relatively short procedure time without a learning curve. However, in a study by Schillinger *et al.* procedural times steadily decreased and durability and completeness of MV repair increased as a function of the learning curve although mortality and hospitalization up to 6 months were not significantly influenced by the learning curve. The current study therefore assessed the echocardiographic and clinical outcome of MV repair with the MitraClip® according to our experience in time with the procedure.

METHODS

Study design and patients

The study included 39 patients with heart failure symptoms and at least moderate MR (Table 1). Patients were assigned to MitraClip® therapy following the decision of a Heart Team in consideration of current guidelines,[7] surgical risk, anatomical aspects, and eligibility for percutaneous treatment. Enrollment and treatments were performed from May 2012 until July 2015. The learning curve was analyzed after creating three subgroups of 13 patients each according to treatment period (period 1: patients 1–13; period 2: patients 14–26; period 3: patients 27–39). The study was approved by the institutional review board and consent was obtained in all patients for anonymised prospective data collection for research purposes.

Procedure

The MitraClip® and implantation procedure have been described in detail previously.[8] The MitraClip® system consists of a 24 F-guiding catheter and a cobalt chromium clip, which is mounted on the tip of a delivery system. Under fluoroscopy and echocardiography guidance, the device is introduced through the femoral vein into the right atrium. After trans-

septal puncture, the MitraClip® is advanced through the left atrium into the left ventricle to grasp the mitral leaflets. Finally, both arms of the clip are closed and the free edges of the leaflets are connected together creating a double orifice. All procedures were performed by the same interventional team. Device time was defined as time from insertion of the steerable MitraClip® guiding catheter until removal of the clip delivery system.

Echocardiographic measurements

Left ventricular ejection fraction (EF) was measured with a triplane method, with use of TomTec software (TomTec, Unterschleissheim, Germany). All other variables were measured at baseline and follow-up according to standard guidelines.[9-11] MR severity was scored according to 6 scales: none/trivial, mild, mild-to-moderate, moderate, moderate-to-severe, severe).[10]

Complications

All complications were reported according to the Mitral Valve Academic Research Consortium (MVARC) consensus document.[12]

Follow-up

Clinical and transthoracic echocardiographic examinations were performed at baseline, predischarge and after 3 to 6 months. The following major adverse events were documented: death (cardiac or non-cardiac), hospitalization due to congestive heart failure and New York Heart Association (NYHA) functional class. Echocardiography was performed according to current recommendations.[11] A patient was defined as echocardiographic responder when MR severity was moderate or less. In case a patient died before 6 months the latest available echo before death but after MitraClip® was considered as echocardiographic end-point. A patient was defined as clinical responder when the patient was alive and NYHA class improved to class 1 or 2 without a hospitalization for heart failure.

Statistical analyses

Categorical data are presented as numbers and percentages. Normality of continuous variables was evaluated by Shapiro-Wilk tests and data were then presented as mean ± standard deviation (SD) or median and interquartile range (IQR). Differences in treatment periods were tested by one-way ANOVA followed by unpaired t-test with Bonferroni adjustment or by Kruskall–Wallis ANOVA followed by Dunn-Bonferroni test. Differences in the percentage, classes, or grades were tested by chi-square test or Fisher's exact test where appropriate. Mann-Whitney U test was used for testing within groups of echoresponders and nonresponders. A p-value <0.05 was considered statistically significant. Analyses were performed using SPSS version 21.0.0.1 (SPSS, IBM, Armonk, NY).

RESULTS

Baseline characteristics

Total cohort

Baseline characteristics are given in Table 1. The etiology of MR was functional due to ischemic (n = 21) or non-ischemic (n = 9) cardiomyopathy in 30 (77%), isolated annular dilatation in 5 (13%) and prolapse in 4 (10%) of patients. Mean age was 72.0 ± 9.9 years. All patients presented with relevant general or specific (e.g. porcelain aorta) co-morbidities, which is reflected by a high mean logistic EuroSCORE of 20.9 ± 15.9 %.

Patients stratified by treatment period

The number of patients with functional MR due to a cardiomyopathy decreases from 13 (100%) in period 1 to 12 (92%) in period 2 and 5 (38%) in period 3 ($P < 0.001$). Later included patients were older ($P < 0.05$) with smaller left ventricular end-diastolic dimensions ($P < 0.005$) and higher left ventricular ejection fractions ($P < 0.005$)

Procedural data

Mean device time was 85 ± 51 minutes and decreased continuously from 122 ± 57 to 75 ± 39 to 51 ± 17 minutes in periods 1 to 3 ($P < 0.05$). The mean numbers of implanted clips in periods 1, 2, and 3 were 1.33 ± 0.65, 1.38 ± 0.65, and 1.33 ± 0.49, respectively, with no significant differences between the periods (P = NS). Mean resultant transmitral gradients were 3.1 ± 1.3, 4.2 ± 2.1 , and 3.8 ± 2.2 in the respective periods (P = NS).

Complications

All major and minor complications are reported in Table 2. There were no differences in the number of patients with a complication between the different time periods.

Echocardiographic outcome

Total cohort

Six-months echocardiographic outcome was not available in 2 patients from period 1 because of lost to follow-up in one patients and death in one other patient. In 3 other patients who died during the first 6 months the latest available echo after MitraClip® was incorporated into analyses. One patient with failed clip insertion (period 1) and one with left atrial perforation (period 3) send for emergent surgery (without percutaneous or surgical repair of the MV done) were analysed according to an intention-to-treat approach. In none of the patients clip detachment occurred during follow-up. In total 19 patients of the 37 considered for analysis (51%) were echocardiographic responders. The number of

echocardiographic responders increased from period 1 to 3 from 2 (18%) to 8 (62%) to 9 (69%). (P <0.05). Left ventricular EF did not change significantly, both in responders (-4% ± 7%) and non-responders (+1% ± 9%). Indexed LA volumes did also not change significantly both in echocardiographic responders (-1 ± 18 ml/m^2) and non-responders (+7 ± 11 ml/m^2).

Temporal changes in MR response after Mitraclip implantation between pre-discharge and the follow-up

As can be seen in Figure 1, in the 37 patients available for analysis 9 were at discharge MR non-responders, all these patients remained non-MR responders at 3-6 months follow-up. Twenty-eight patients were at discharge MR responders, of whom 19 remained MR responders and 9 deteriorated to MR non-responders. The total number of MR non-responders thus increased from 9 (24%) to 18 (49%) during short-term follow-up.

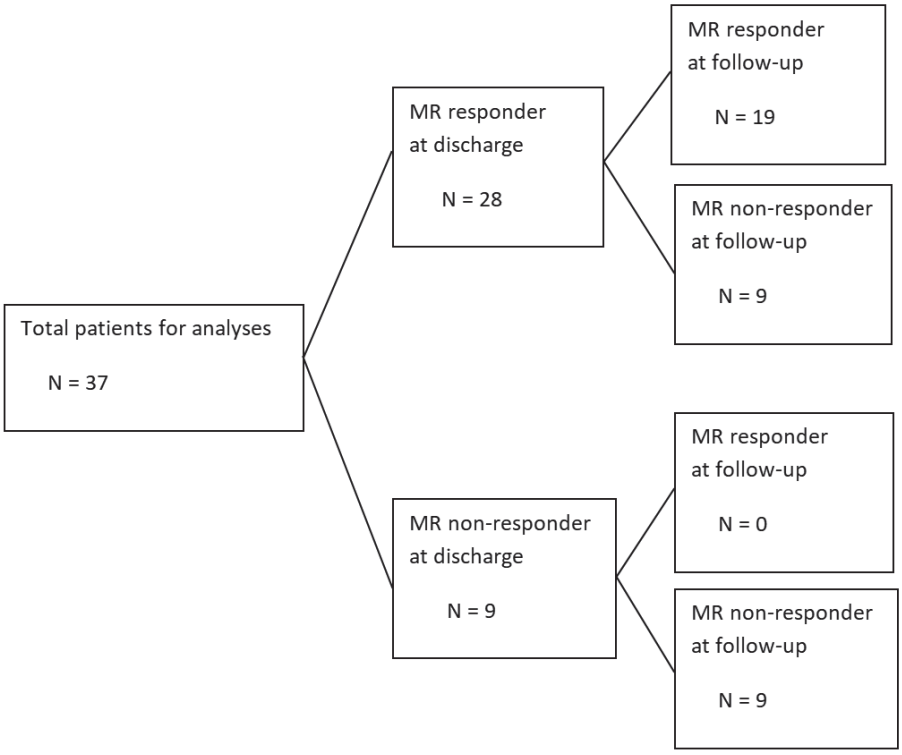

Figure 1
Temporal changes in MR response after Mitraclip implantation between predischarge and the follow-up.

Cardiomyopathy cohort

As mentioned before functional MR due to cardiomyopathy was present in 30 (77%) of patients and decreased significantly from period 1 to 3 (P <0.001). Echocardiographic outcome could be assessed in 28 from the 30 patients, due to the aforementioned reasons. Fourteen patients (50%) were echocardiographic responders (period 1: 18%; period 2: 67%; period 3: 80%, P <0.05). No differences were seen in echocardiographic responders in patients with functional MR versus non-functional MR (50% vs. 56%). In the patients with MR secondary to cardiomyopathy left ventricular EF did not change significantly in both responders and non-responders (respectively, -4% ± 7% and +1% ± 9%). Although overall LA volumes remained unchanged (0 ± 16 ml/m^2), LA volumes decreased non-significantly by 5 ± 17 ml/m^2 in responders compared to a non-significantly increase of 6 ± 13 ml/m^2 in non-responders.

Clinical outcome

Total cohort

The clinical end-point mortality was seen in seven out of 38 analysable patients (18%), five patients died because of heart failure, one patient died because of bleeding complications after MitraClip® implantation (period 2) and one patient had non-cardiac death. Mortality and/or hospitalization for heart failure was seen in 14 patients (37%) and mortality and/or hospitalization for heart failure and/or NYHA class ≥3 in 22 patients (58%).

Patients stratified by treatment period

The number of clinical responders did not significantly increase from period 1 (4 patients, 33%) to period 2 (4 patients, 31%) to period 3 (8 patients, 62%) (P= 0.22). Three patients died in period 1, 4 in period 2, and in period 3 there was no mortality in the first 6 months.

Cardiomyopathy cohort

In the subgroup of patients with secondary MR due to heart failure 10 patients (35%) were clinical responders. No differences were seen in the different periods (period 1: 4 out of 12 patients, 33%, period 2: 4 out of 12 patients, 33%, and period 3: 2 out of 5 patients, 40%). The number of clinical responders tended to be lower in the group of patients with functional MR compared to the non-functional MR group (35% vs. 67%, P <0.10). Mortality in the cardiomyopathy cohort was 24% (7/29). Mortality tended to be higher in the group of patients with functional MR compared to the non-functional MR group (24% vs. 0%, P =0.12).

DISCUSSION

This study investigated the learning curve of percutaneous MV repair with the MitraClip® in a single center. The main findings are that 1) procedural times steadily decreased, 2) indications shifted from functional MR to a mix of functional MR and non-functional MR, 3) echocardiographic responders steadily increased both in functional MR and non-functional MR and 4) the number of clinical responders in patients with functional MR was lower and did not increase in time.

The learning process in MitraClip® repair of the MV involves several factors, including patient selection by an interdisciplinary heart team discussing the risk of surgery and the probability of having a successful MitraClip® repair, experience of the interventional team (technical skills, defining the best strategy, and interaction with the echocardiographer during the procedure. Data on the impact of the learning curve are sparse and contradictory.[5,6]

Learning curve effects on device time

In most studies a reduction in device implantation or procedural time was reported in time[6,8,13,14] even despite a higher number of clips implanted per patient in later periods in some studies.[14] In the present study, mean procedural times steadily decreased from 122 ± 57 minutes to 51 ± 17 minutes, unrelated to the number of clips implanted in the different periods and despite inclusion of patients with degenerative MR in the later cohorts, by some reported associated with longer device time.[13,15]

Learning curve effects on MR outcome

Only sparse data on learning curve effects on MR outcome are available in the literature with conflicting results.[5,6] Schillinger *et al.* were the first to describe a rather quick learning curve in 3 consecutive cohorts of 25 patients that underwent MitraClip® implantation. Procedural times steadily decreased and durability and completeness of MV repair increased as a function of the learning curve. In contrast, in the large German mitral valve registry by Ledwoch *et al.* a learning curve in procedural time or MR reduction was absent in 2 consecutive cohorts of approximately 25 patients per center (totaling to 250 patients per cohort for the total of 10 centers). Explanations for the absent learning curve were 1) the learning curve may take more time to show, 2) guidance by the proctor of the operator through the procedure may be very effective, and 3) the learning curve may be masked by the inclusion of more complex cases over time (more difficult prolapse in terms of location or extent or gap of the prolapsing segment(s) or cardiomyopathic patients with greater coaptation depth). Unfortunately, these variables were not registered in the registry. With respect to the first explanation it should be noted that results were already excellent in the first cohort with 95% of patients having maximally moderate MR (under anesthesia). In the present study the number of echocardiographic responders significantly increased both

in the overall cohort as well as the functional MR subgroup in accordance to the study of Schillinger *et al.*.[6] It should be noticed that in our study included patients became progressively older and pathology shifted from MR secondary to cardiomyopathy (functional MR, in fact in the first period only such patients were included) to a more heterogeneous group of patients with different pathologies including also mitral annulus dilatation and MV prolapse (degenerative MR).[16] Because in most studies trends have been described in degenerative etiology towards less improvement and more deterioration in MR our results are remarkable.[13,15,17,18]

Learning curve effects on clinical outcome

Clinical outcome according to the learning curve was only reported by Schillinger *et al.*.[6] Despite the above described increased durability and completeness of MV repair as a function of the learning curve mortality and hospitalization up to 6 months were not significantly influenced by the learning curve. In particular in the functional MR group the number of clinical responders was low (31%) and clinical outcome was poor (mortality was 24%). Although it is clear that chronic secondary MR adds to the burden of HF by imposing volume overload on an already compromised LV and worsens prognosis, there is according to the present guidelines remarkably little evidence that correcting chronic severe secondary MR prolongs life or even improves symptoms for a prolonged period.[19] This paradox may result from the fact that mitral interventions in ischemic MR do not prevent coronary artery disease from progressing, nor does it prevent the continued idiopathic myocardial deterioration in non-ischemic chronic secondary MR. Importantly, the in our study included patients with functional MR were often end-stage disease patients with a median LV end-diastolic diameter of 73mm. In the randomized MITRA-FR trial percutaneous clipping of the mitral valve for severe secondary MR in symptomatic heart failure had also no impact on mortality and unplanned hospitalization.[20] In contrast, in the recently published randomized COAPT (Clinical Outcomes Assessment of the MitraClip® Therapy Percutaneous Therapy for High Surgical Risk Patients) trial an impressive reduction in mortality was seen. [21] The ongoing RESHAPE-HF (A Randomized Study of the MitraClip® Device in Heart Failure Patients With Clinically Significant Functional Mitral Regurgitation) in patients with functional MR associated with congestive heart failure (NYHA class III or IV and $15\% \geq EF \leq 40\%$) will certainly contribute further to better elucidation of the role of MitraClip® therapy in high surgical risk patients with functional MR.

CONCLUSIONS

Despite an increase in echocardiographic responders after MitraClip® in time the number of clinical responders did, in particular in patients with functional MR, not increase.

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Chapter 13

Summary and Conclusions

Samenvatting en Conclusies

Discussion and Future Perspectives

SUMMARY AND CONCLUSIONS

In this thesis the contemporary role of echocardiography in mitral regurgitation (MR) was investigated, in particular identification of the MR mechanism, quantification of MR and evaluation of MR outcome.

Identification of MR mechanism

The general introduction (**Chapter 1**) of this thesis gives a short summary of the etiology and pathophysiology of MR and the diagnostic tools and possible therapies. The anatomy of the mitral valve (MV) is described with causes of MR, as well as echocardiographic criteria for quantification of MR severity and invasive therapies such as MV surgery and percutaneous MV repair.

An overview of a new, updated echocardiographic classification of MR mechanisms is given in **Chapter 2** in order to provide a more comprehensive and detailed assessment of MV disorders which may be relevant to modern MV repair techniques. Special attention was made to the added value of three-dimensional (3D) echocardiography in each type of MV pathology.

Mitral annulus (MA) dilatation is an important cause of MR. In **Chapter** 3, we sought to assess in which transthoracic two-dimensional (2D) echocardiographic view and specific time point in the cardiac cycle the MA diameter should be best measured. Two-dimensional MA measurements were validated against 3D transoesophageal echocardiography (TOE) MV areas. It was concluded that MA measurements may be best done in the end-systolic parasternal long-axis view. The upper limit of the normal MA annulus in this view was 35 mm.

For accurate acquisition and interpretation of the 2D images of MV prolapse a high level of expertise is required. In **Chapter 4** we sought to assess the relative values of transthoracic 2D, 2D xPlane and 3D echocardiography for the definition of the site and extent of MV prolapse in patients who underwent MV surgery. Two-dimensional xPlane imaging proved to be an accurate imaging modality to correctly diagnose the site and extent of the MV prolapse. Three-dimensional echocardiography should be the more intuitive technique, in particular for non-experts.

In **Chapter 5** the value of standard 2D transthoracic echocardiography (TTE), 2D-TOE and 3D-TOE for the identification of posterior MV prolapse was assessed in three groups of readers with different echocardiographic experience. Differences between readers in determining the precise localization and extent of MV prolapse existed in particular in the 2D-TTE analysis with increased diagnostic accuracy from novice to trainees to cardiologists. Three-dimensional TOE showed the best diagnostic accuracy with identification of P1 and P3 prolapse with the same improvement between the readers. This analysis was also faster compared to the 2D analysis methods.

Quantification of MR severity

In **Chapter 6** the circular geometric assumption of the MA and left ventricular (LV) outflow tract (LVOT) was analyzed and the error made by the 2D-TTE pulsed-wave Doppler flow method in calculating MR volume was estimated. We compared this method with cross-sectional areas of the MA and LVOT measured directly in the "en face" views of 3D-TOE. The oval shaped MA and LVOT areas had significantly different major and minor axis diameters. In addition, it was shown that the MA cross-sectional area is overestimated by the 2D method in about 13% and the LVOT cross-sectional area is underestimated in about 23%. The error in calculating the MR volumes is even more significant because the errors are in different directions with an overestimate of about 54% by the 2D method.

In **Chapter 7** the information to the surgeon on MR, tricuspid annulus size and tricuspid regurgitation in patients referred for MV surgery was investigated in detail. Comparing these data with the guidelines showed an important gap between the guidelines and real-world practice. The severity of MR was often not based on vena contracta and the proximal isovelocity surface area (PISA) measurements, with questionable technical quality of these parameters. Data on tricuspid annulus size, in most patients essential to define the need for additional tricuspid valvuloplasty (TVP), were virtually absent.

Evaluation of MR outcome

In **Chapter 8** the results of optimization of medical therapy in patients with therapy resistant symptomatic chronic HF and significant MR referred to our tertiary heart failure (HF) outpatient clinic were described, in particular on MR severity, LV volumes, LV ejection fraction (LV-EF) and clinical outcome. Angiotensin-converting enzyme inhibitors / angiotensin receptor blockers and beta-blockers could be introduced or up-titrated in most patients. As a result significant improvements in MR severity, LV-EF, LV volumes and New York Heart Association (NYHA) class were seen. NYHA class improvement was best correlated to MR reduction.

In **Chapter 9** valvular and clinical outcomes were studied in asymptomatic (NYHA class I and in sinus rhythm) patients with severe MR and normal LV-EF who underwent MV repair. MV repair in these patients is safe and has satisfactory long-term survival (93% at 12 years, comparable with the general age-matched Dutch population). There was a low recurrence rate of significant MR, good LV functioning and, excellent quality of life assessed with a SF-36 questionnaire, comparable with the general Dutch population.

In **Chapter 10** we evaluated the clinical and echocardiographic outcome in symptomatic MR patients after minimally access MV surgery (MAMVS) versus conventional surgery. The overall successful MV repair rate was >90%. Echocardiography at 6 months follow-up showed that MR severity was significantly reduced, with no difference between conventional surgery and MAMVS. However, left atrium remodeling was greater in the MAMVS group. No significant differences between conventional surgery and MAMVS were seen in

in-hospital complications, NYHA class and quality of life assessment before and 6 months after surgery. Tricuspid regurgitation decreased after concomitant TVP, whereas in patients with no TVP no significant changes occurred.

Despite these surgical treatment options, a significant part of the patients with severe MR are not referred for surgery because of their advanced age or the presence of comorbidities. Therefore, the morphology of the MV complex is described in **Chapter 11** with the developing catheter-based techniques for MV repair in mind.

In **Chapter 12** patients with HF symptoms and at least moderate MR who underwent MitraClip® implantation were studied. To assess a potential learning curve, echocardiographic and clinical responses were analyzed for three subgroups classified by treatment period. Mean device implantation time decreased significantly in time and the percentage of echocardiographic responders after 3-6 months increased from 18% to 69%. Despite an increase in echocardiographic responders after MitraClip® implantation in time the number of clinical responders did, in particular in patients with functional MR, not increase.

SAMENVATTING EN CONCLUSIES

In dit proefschrift wordt de hedendaagse rol onderzocht van echocardiografie bij mitralisklepinsufficiëntie in het bijzonder in relatie tot de identificatie van het mechanisme, kwantificatie van de ernst van mitralisklepinsufficiëntie en de evaluatie van behandeling van mitralisklepinsufficiëntie.

Identificatie van het mechanisme van mitralisklepinsufficiëntie

De algemene introductie (**Hoofdstuk 1**) van dit proefschrift geeft een korte samenvatting van de aetiologie, pathofysiologie, diagnostische mogelijkheden en therapieën van mitralisklepinsufficiëntie. De anatomie van de mitralisklep wordt beschreven met de oorzaken van mitralisklepinsufficiëntie, evenals de echocardiografische criteria om de ernst van de mitralisklepinsufficiëntie te kwantificeren en de invasieve therapieën zoals mitralisklepchirurgie en percutane mitralisklepreparatie worden beschreven.

Een overzicht van een nieuwe, bijgewerkte echocardiografische classificatie van mechanismen van mitralisklepinsufficiëntie wordt gegeven in **Hoofdstuk 2** om een uitgebreidere en gedetailleerdere beoordeling te geven van mitralisklepaandoeningen die relevant zijn voor moderne mitralisklep reparatietechnieken. We hebben speciale aandacht besteed aan de toegevoegde waarde van driedimensionale (3D) echocardiografie in elk type mitralisklepathologie.

Mitralisklepannulus dilatatie is een belangrijke oorzaak van mitralisklepinsufficiëntie. In **Hoofdstuk 3** bestudeerden we deze om te beoordelen in welk transthoracaal tweedimensionaal (2D) echocardiografisch beeld en op welk specifiek tijdstip in de hartcyclus de mitralisklepannulus het best moet worden gemeten. Tweedimensionele metingen van de mitralisklepannulus werden gevalideerd tegen 3D mitralisklepoppervlak in transoesofageale echocardiografie (TEE). Geconcludeerd werd dat mitralisklepannulus metingen het beste kunnen worden gedaan eindsystolisch in het parasternale lange-as beeld. De bovengrens van de normale mitralisklepannulus in dit beeld was 35 mm.

Voor het nauwkeurig verkrijgen en interpreteren van de 2D-beelden van een mitralisklep prolaps is een hoog niveau van expertise vereist. In **Hoofdstuk 4** hebben we getracht de relatieve waarde van transthoracale 2D, 2D xPlane en 3D echocardiografie te bepalen voor de definitie van de lokalisatie en de omvang van de mitralisklepprolaps bij patiënten die een mitralisklepoperatie hebben ondergaan. Tweedimensionele xPlane-beeldvorming bleek een nauwkeurige beeldvormingsmodaliteit te zijn om de lokalisatie en de uitgebreidheid van de mitralisklepprolaps correct te diagnosticeren. Driedimensionele echocardiografie zou de meer intuïtieve techniek moeten zijn, in het bijzonder voor niet-deskundigen.

In **Hoofdstuk 5** werd de waarde van standaard 2D transthoracale echocardiografie (TTE), 2D-TEE en 3D-TEE voor de identificatie van prolaps van het achterste mitralisklepblad beoordeeld door drie groepen beoordeelaars met verschillende echocardiografische ervaring.

Verschillen tussen beoordeelaars in het bepalen van de precieze lokalisatie en omvang van het prolaberende deel van het mitralisklepblad bestonden met name in de 2D-TTE analyse met een verhoogde diagnostische nauwkeurigheid van student tot cardioloog in opleiding tot cardioloog. Driedimensionale TEE toonde de beste diagnostische nauwkeurigheid met identificatie van P1 en P3 prolaps met dezelfde verbetering tussen de beoordeelaars. Deze analyse was ook sneller in vergelijking met de 2D analysemethoden.

Kwantificatie van de ernst van mitralisklepinsufficiëntie

In **Hoofdstuk 6** werd de cirkelvormige geometrische aanname van de mitralisannulus en het linker ventriculaire uitstroomkanaal (LVOT) geanalyseerd en werd de fout, gemaakt bij de traditionele 2D-TTE pulsed wave Doppler flow methode voor het berekenen van het insufficiëntievolume, ingeschat. We hebben deze methode vergeleken met dwarsdoorsneden van de mitralisannulus en LVOT die rechtstreeks in de “en face” views van 3D-TEE beelden zijn gemeten. De ovale mitralisannulus en LVOT gebieden hadden significant verschillende grote en kleine as diameters. Bovendien werd aangetoond dat het mitralisannulusoppervlak door de 2D-methode met ongeveer 13% wordt overschat en het LVOT oppervlak wordt onderschat met ongeveer 23%. De fout bij het berekenen van de insufficiëntievolumes is zelfs nog groter omdat de gemaakte fouten in verschillende richtingen zijn met een overschatting van ongeveer 54% volgens de 2D-methode.

In **Hoofdstuk 7** is de informatie aan de chirurg over mitralisklepinsufficiëntie, tricuspidalisannulus en tricuspidalisklepinsufficiëntie van patiënten doorverwezen voor een mitralisklepoperatie, gedetailleerd onderzocht. Het vergelijken van deze gegevens met de richtlijnen toont een belangrijke kloof tussen de richtlijnen en de praktijk. De ernst van de mitralisklepinsufficiëntie is vaak niet gebaseerd op vena contracta en de proximale isovelocity surface area (PISA) metingen, met twijfelachtige technische kwaliteit van deze parameters. Gegevens over de grootte van de tricuspidalisannulus, die bij de meeste patienten essentieel zijn om de noodzaak voor bijkomende tricuspidalisklepplastiek te bepalen, waren vrijwel afwezig.

Evaluatie van behandeling van mitralisklepinsufficiëntie

In **Hoofdstuk 8** worden de resultaten beschreven van de optimalisatie van de medicamenteuze therapie bij patiënten met therapieresistente symptomatisch chronisch hartfalen en belangrijke mitralisklepinsufficiëntie die verwezen werden naar onze polikliniek voor tertiair hartfalen, in het bijzonder voor de ernst van mitralisklepinsufficiëntie, het volume van de linker ventrikel, de linker ventrikel ejectiefractie en de klinische uitkomst. Bij de meeste patiënten konden angiotensine-converterende enzymremmers / angiotensinereceptorblokkers en bètablokkers worden geïntroduceerd of geüptriteerd. Als gevolg hiervan werden aanzienlijke verbeteringen in de ernst van de mitralisklepinsufficiëntie, de linker ventrikel ejectiefractie, linker ventrikel volumes en New York Heart Association (NYHA)

klasse gezien. De verbetering van de NYHA klasse was het best gecorreleerd met reductie van de ernst van de mitralisklepinsufficiëntie.

In **Hoofdstuk 9** werden de valvulaire en klinische resultaten bestudeerd bij asymptomatische patiënten (NYHA klasse I en in sinusritme) met ernstige mitralisklepinsufficiëntie en een normale linker ventrikel ejectiefractie die een mitralisklep reparatie hebben ondergaan. Mitralisklep reparatie bij deze patiënten is veilig en heeft een bevredigende overleving op lange termijn (93,3% na 12 jaar, vergelijkbaar met de algemene leeftijd van de Nederlandse bevolking). Er was sprake van een lage herhalingsfrequentie van belangrijke mitralisklepinsufficiëntie, een goede linker ventrikel functie en een uitstekende kwaliteit van leven beoordeeld met een SF-36-vragenlijst, vergelijkbaar met de algemene Nederlandse bevolking.

In **Hoofdstuk 10** evalueerden we de klinische en echocardiografische resultaten bij patiënten met een symptomatische mitralisklepinsufficiëntie na minimaal invasieve mitralisklepchirurgie (MIMKC) versus conventionele mitralisklep chirurgie. Bij >90 % van de patiënten was de mitralisklep succesvol gerepareerd. Echocardiografie met een follow-up van 6 maanden toonde aan dat de ernst van de mitralisklepinsufficiëntie significant verminderd was, zonder verschil tussen conventionele chirurgie en MIMKC. De linker atrium remodellering was echter groter in de MIMKC groep. Er werden geen significante verschillen waargenomen tussen conventionele chirurgie in vergelijking met MIMKC voor complicaties in het ziekenhuis, de NYHA-klasse en de beoordeling van de levenskwaliteit voor en 6 maanden na de operatie. De tricuspidalisklepinsufficiëntie nam af na gelijktijdige tricuspidalisklepplastiek, terwijl er bij patiënten zonder tricuspidalisklepplastiek geen significante veranderingen optraden.

Ondanks deze chirurgische behandelingsmogelijkheden wordt een significant deel van de patiënten met ernstige mitralisklepinsufficiëntie niet doorverwezen voor een operatie vanwege hun hoge leeftijd of de aanwezigheid van comorbiditeiten. Daarom wordt de morfologie van het mitralisklepcomplex beschreven in **Hoofdstuk 11** met het oog op de ontwikkeling van kathetergebaseerde technieken voor het herstel van de klep.

In **Hoofdstuk 12** zijn patiënten met symptomen van hartfalen en tenminste matige mitralisklepinsufficiëntie die een MitraClip® implantatie hebben ondergaan, onderzocht. Om een mogelijke leercurve te beoordelen, werden de echocardiografische respons en de klinische respons geanalyseerd voor drie subgroepen, ingedeeld naar behandelperiode. De gemiddelde tijd voor bediening van het apparaat nam significant af in periode 1 tot 3 en het percentage echocardiografische respondenten na 3 tot 6 maanden steeg van 18% tot 69%. Ondanks een toename van het aantal patiënten met echocardiografische verbeteringen na een MitraClip® implantatie na verloop van tijd, nam het aantal patiënten met een klinische verbetering niet toe, met name niet bij patiënten met een functionele mitralisklepinsufficiëntie.

GENERAL DISCUSSION AND FUTURE PERSPECTIVES

Identification of MR mechanism

The number of patients with significant MV disease will increase due to the aging population and the lack of effective preventive strategies for degenerative valve disease, the most common etiology for MR [1,2]. In the industrialized world, MV prolapse as leading cause of MR is also the most frequent reason for MV surgery [1]. The site and extent of MV prolapse is essential in defining the suitability for MV repair. For accurate acquisition and interpretation of the 2D images of the prolapse a high level of expertise is required. In this thesis the added value of 2D xPlane imaging and 3D echocardiography as a more comprehensible technique, also for non-experts is shown. Considering the aging population, frequently with comorbidities, determination of MR mechanism becomes even more important and therefore we recommend the use of the updated MR mechanism classification as described in this thesis. Since 3D echocardiographic images are still not frequently recorded in patients referred to the heart team in which the intervention indication and method is discussed awareness of the newer echocardiographic modalities has to grow.

Quantification of MR severity

The guidelines for heart valve disease clearly state that an interventional class I indication only exists when MR is severe [3,4]. Quantification of MR severity should be performed in an integrative way, including qualitative, semi-quantitative and quantitative parameters. This requires an integration of Doppler blood flow data with morphological information, as well as careful cross-checking on the validity of such data against the consequences on left atrial dimension, LV dimension and function and systolic pulmonary artery pressure. Quantitative parameters such as the vena contracta and the PISA are recommended [5]. However, in this thesis it is shown that in patients referred for MV surgery in the real-world the severity of MR is often not based on these recommended criteria. This may well be because faith in these parameters is low because of the difficulties in recording and inherent limitations in PISA acquisition and analysis such as dynamic PISA and non-hemi-spherical aspect in functional MR. Also, the original validation of the PISA method may be questionable since the used gold pulsed-wave Doppler standard has serious limitations as was shown in these thesis.

To evaluate practices and show how physicians act in the diagnosis and management in patients with valvular heart disease the European Society of Cardiology has started the Valvular Heart Disease II survey [6]. Practices with the existing guidelines will be compared and changes in practices since the first European survey on valvular heart disease performed in 2001 will be evaluated. In line with this, we plan to initiate a new study in the Rijnmond area to investigate further the gap between real-life practice and guidelines. In this study

cardiologists in different hospitals will evaluate the same patient for MR and differences in acquisition and analysis will be analyzed.

Evaluation of MR outcome

For severe primary MR, surgical MV repair is the guideline-recommended standard treatment in symptomatic patients [3]. In asymptomatic patients, surgery is indicated when LV dysfunction is present and should be considered if well-defined triggers are present. In this thesis it is shown that endorsement of these recommendations in asymptomatic patients results in a satisfactory long-term survival with a good quality of life and a low recurrence rate of MR. However, for patients with secondary MR and HF with reduced LV-EF surgical repair entails heightened procedural risk [7] and has been associated with a high MR recurrence rates [8]. Therefore, most patients with HF and secondary MR are nowadays treaded conservatively [9]. In this thesis it is shown that this is an acceptable strategy, provided that medical therapy is optimized by heart failure experts, such as Caliskan and co-workers[10].

With the advent of catheter-based techniques, percutaneous treatment of secondary MR with MitraClip® has been studied in two randomized controlled clinical trials. Unfortunately, these trials provide discordant results. The COAPT (Cardiovascular Outcomes Assessment of the MitraClip® Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation) trial concluded that transcatheter MV repair resulted in a lower rate of hospitalization for HF, lower mortality and better quality of life and functional capacity during 24 months of follow-up than medical therapy alone. The prespecified goal for freedom from device-related complications was met [11,12]. In contrast, in the MITRA-FR (Percutaneous Repair with the MitraClip® Device for Severe Functional / Secondary Mitral Regurgitation) trial percutaneuos MV repair had no significant impact on mortality or unplanned hospitalization for HF at 1 year [13,14]. In line with these results we found in this thesis that in patients with functional MR MitraClip® interventions, despite an increase in echocardiographic responders in time, did not result in an improvement in the clinical course. Important differences were seen between the two trials in particular in HF treatment changes during follow-up, LV characteristics and MR severity. In the MITRA-FR trial enrolled patients had MR proportionate to the degree of LV dilatation, in contrast to the COAPT trial in which patients had more MR whereas their LVs were smaller, indicative of disproportionate MR [15]. In these latter patients transcatheter MV repair may be more useful. Apart from the future results from the ongoing RESHAPE-HF2 (A Randomized Study of the Mitraclip Device in Heart Failure Patients With Clinically Significant Functional Mitral Regurgitation) trial [16] a more in depth analysis of our (now much larger) MitraClip® patient cohort is in progress and may contribute to clarify the role of percutaneous MV repair in improving prognosis in HF patients.

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Appendix

Dankwoord

Curriculum vitae

List of publications

Portfolio

DANKWOORD

Waarom aan het eind van je cardiologie opleiding aan een promotietraject beginnen? Een samenloop van omstandigheden leidde tot deze keuze: mijn zwangerschap waardoor ik de laatste stage met nachtdiensten van de opleiding cardiologie op dat moment niet kon doen, een erg leuk onderwerp met 3D echocardiografie in de kinderschoenen, een krappe arbeidsmarkt en samenwerken in het thoraxcentrum met cardiologen, thoraxchirurgen en anesthesisten. Na het afronden van mijn opleiding was het een uitdaging om dit promotietraject, naast een baan als cardioloog en gezin, te voltooien. Dit was niet gelukt zonder steun en hulp van vele personen in de afgelopen 10 jaar, waarvoor ik hen allen heel hartelijk wil bedanken. Tot een aantal hiervan wil ik me richten met een persoonlijk dankwoord.

Allereerst gaat mijn dank uit naar mijn co-promotor Dr. M.L. Geleijnse. Beste Marcel, bij een poging mij na het afronden van mijn opleiding de vacature op de CCU te laten opvullen, wist jij als een van de eersten dat mijn opleiding langer zou duren vanwege een zwangerschap. Daarmee kon een al langer bestaand plan op de afdeling cardiologie voor een promotieonderzoek met 3D echocardiografie doorgang vinden. Mijn tweede zwangerschap dacht ik langer voor me te kunnen houden, maar toen kwam jij met de vraag de 3D TEE's bij de mitraclipimplantaties op het cathlab te doen en weer wist jij het eerder dan de rest. Want dat is wat ik zeker ga missen aan mijn vrijdagse tripjes naar het Erasmus MC: alle nieuwtjes van wat er speelt in heel cardiologisch Rotterdam en omstreken. Ik sluit me aan bij je eerdere promovendi die al memoreerden aan je heldere wetenschappelijke blik, feitenkennis en goede manier van schrijven, want zonder die bijdrage was dit proefschrift nu nog steeds niet af geweest. Maar nu het eindelijk af is zal ik op vrijdag niet meer (voor jou onverwacht, maar toch reeds ergens op een (papieren) agenda wel eerder aangekondigd) voor je neus staan, maar zal ik zorgen dat dit verrassingseffect op de refereeravonden nu er wel zal zijn.

Mijn promotor professor A.J.J.C. Bogers wil ik bedanken voor de gelegenheid die ik heb gekregen om dit onderzoek te doen. Beste Ad, ontzettend bedankt voor het vertrouwen dat ik, als assistent cardiologie, van jou heb gekregen om via de afdeling thoraxchirurgie een promotietraject te starten en het ook in mijn eigen tempo heb kunnen voltooien. Zelfs toen ik kwam vertellen dat ik in het Maasstad ging werken, zag jij mogelijkheden en bleef mij stimuleren de artikelen af te maken. Dank voor je snelle reacties en fijne commentaar.

Professor J.W. Roos-Hesselink, professor F. Zijlstra en professor R.J.M. Klautz wil ik bedanken voor het beoordelen van mijn proefschrift en samen met professor P.P.T de Jaegere, professor J.W. Deckers, Dr. F.B. Oei en Dr. P.C. Smits voor de bereidheid zitting te nemen in de promotiecommissie.

Zonder de hulp van het thoraxsecretariaat met Jos, Carolien en Maureen zou ik geen patiënten hebben kunnen includeren en daarbij ook vooral dank voor het beantwoorden van alle vragen rondom de operatieplanning en het bewaren van de echobeelden op CD.

Ook wil ik de thoraxchirurgen, anesthesisten en medewerkers van het ok complex thoraxchirurgie bedanken voor hun medewerking met extra metingen tijdens de mitralisklepoperaties en vooral voor hun geduld zodat ik de uitgebreide echocardiografische beelden op de operatiekamer kon maken.

Beste Frans, met de introductie van de minimaal invasieve mitralisklepchirurgie kwam er voor mij een aparte onderzoekgroep bij, die ik met veel interesse heb bestudeerd. Dank voor je hulp met het onderzoek en je waardevolle bijdrage aan de manuscripten.

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Voor een onderzoek over mitralisklepinsufficiëntie zijn echocardiografische beelden onmisbaar. Daarom wil ik de echolaboranten, Debbie, Marianne, Linda, Anja, Lourus en Beata bedanken voor alle hulp en de flexibiliteit als ik weer eens van kamer wilde ruilen of een echoapparaat mee naar de ok wilde nemen. Speciale dank gaat uit naar Ellen, Wim en Jackie.

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Beste Wim, tijdens mijn eerste onderzoeksperiode in het Thoraxcentrum heb ik veel over de echocardiografie van jou geleerd en een prettige tijd bij jou, Folkert en Tjebbe op de kamer gehad. Voor het huidige onderzoek heb je ook veel echo's gemaakt en daarmee een belangrijke bijdrage geleverd, waarvoor dank.

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Speciale dank gaat uit naar René Frowijn. Beste René, dank voor al je hulp als de computer niet deed zoals ik dat wilde en voor het maken van de echo-afbeeldingen met voor elk tijdschrift weer andere instructies.

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Zonder de steun van een liefdevol thuisfront, lijkt mij een promotieonderzoek onmogelijk. Lieve Michael, een opleidingstraject vergt al begrip en aanpassing van je partner, maar dan is het bijna klaar en toen volgde nog een promotietraject in combinatie met een jong gezin. Zonder jouw steun, tijd en aanmoediging zou ik dit niet hebben kunnen voltooien. Nu kunnen we nog meer genieten van elkaar, onze twee schatjes en met z’n viertjes leuke dingen gaan ondernemen.

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CURRICULUM VITAE

Lotte Elisabeth de Laat was born on November 9th, 1975 in Eindhoven, the Netherlands. After graduation from secondary school (Eckart College in Eindhoven) she started medical school at the Radboud University Nijmegen in 1994. After obtaining the degree of Medical Doctor she worked as a resident (AGNIO) in the Albert Schweitzer Ziekenhuis Dordrecht, department of Internal Medicine, and Erasmus Medical Center Rotterdam, department of Cardiology.

In 2004 Cardiology Residency started with 2 years at the department of Internal Medicine followed by 1 year at the department of Cardiology in the Albert Schweitzer Ziekenhuis Dordrecht. The last 3 years of her training she worked as a resident at the department of Cardiology at the Thoraxcenter in Rotterdam and training in three-dimensional echocardiography was initiated in cooperation with the department of Cardiothoracic Surgery, resulting in this thesis.

As of April 2013 she is working as a general cardiologist with special attention to echocardiography at the Maasstad Hospital in Rotterdam.

She is married to Michael de Groot and they have a son Tim and a daughter Isabelle.

LIST OF PUBLICATIONS

1. Snelder SM, van de Poll SWE, **de Groot-de Laat LE**, Kardys I, Zijlstra F, van Dalen BM. Optimized electrocardiographic criteria for the detection of left ventricular hypertrophy in obesity patients. Clin Cardiol 2020 Jan 28. Epub ahead of print.

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14. Tangerman A, Winkel EG, **de Laat L,** van Oijen AH, de Boer WA. Halitosis and Helicobacter pylori infection. J Breath Res 2012 Mar;6(1):017102.

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PORTFOLIO: SUMMARY OF PHD TRAINING AND TEACHING ACTIVITIES

		EC
2019	Regionale hartfalen bijeenkomst	0,6
	Refeeravond Cardiologen Club Rijnmond 2019	0,1
	Tour d'Horizon	0,4
	NVVC Jubileumcongres	0,6
	Trechter training	0,1
	Haagse Cursus Echocardiografie	0,6
2018	Refeeravond Cardiologen Club Rijnmond 2018	0,1
	Tour d'Horizon	0,4
	Kick-off Connect Hartfalen Regio Rotterdam Rijnmond	0,1
	TTE screening voor patienten met een MR	0,1
2017	Tour d'Horizon	0,4
	Cardio Cogress Highlights ACC	0,1
	Haagse Cursus echocardiografie	0,6
2016	Masterclass Toegepaste ICH-GCP	0,3
	Refeeravond Cardiologen Club Rijnmond 2016	0,2
	Regionale Hartfalen Bijeenkomst	0,2
	Tour d'Horizon	0,4
	Voorjaarscongres NVVC	0,3
2015	EuroEcho Imaging 2015	1,0
	Lustrum symposium Cardiologen Club Rijnmond	0,1
	Tour d'Horizon	0,4
	Voorjaarscongres NVVC	0,3
	Haagse Cursus Echocardiografie	0,6
2014	Refeeravond Cardiologen Club Rijnmond 2014	0,1
	Teach the teacher	0,3
	Voorjaarscongres NVVC	0,3
	Echomiddagen 2013-2014	0,1
2013	EuroEcho Imaging 2013	1,0
	Refeeravond Cardiologen Club Rijnmond 2013	0,2
	Najaarscongres NVVC	0,3
	Update hypertrofische cardiomyopathie en contrast echocardiografie	0,1
	Echo-avond Dordrecht 2013	0,1
2012	EuroEcho 2012	1,0
	Biomedical English writing course	4,0
	Echoavond Dordrecht 2012	0,2

	Refeeravond Cardiologen Club Rijnmond 2012	0,1
	Symposium harttransplantatie en hartfalen 2012	0,2
	NVVC najaarscongres	0,3
	PhDday	0,1
2011	EuroEcho 2011	1,0
	Cardiale CT in de praktijk	0,2
	Basic Introduction Course on SPSS	0,8
	Echoavond Dordrecht 2011	0,1
	NVVC voorjaarscongres	0,3
	Refeeravond Cardiologen Club Rijnmond 2011	0,1
	COEUR	1,9
	Minisymposium Hypertrofische cardiomyoapthie	0,1
2010	Acute Myocardial infarction: the next decade	0,1
	EuroEcho 2010	1,0
	COEUR	0,4
	Echoavond Dordrecht	0,1
	Cursus ABCDE method	0,3
	Juniorkamerdag	0,3
	Workshop Endnote	0,1
	iCi-Catheter Interventions in Congenital & Structural heart disease	0,3
	Drie Dimensionele Echocardiografie, huidige toepassingen en indicaties	0,6
Totaal EC		**24,1**

Lectures and teaching activities on mitral regurgitation

- Echoavond: Mitralisklepinsufficiëntie: echocardiografie, welke metingen? (2011)
- Echoavond: Ernst en mechanisme mitralisklepinsufficiëntie: 2D en 3D echocardiografie (2012)
- Onderwijs 3D echocardiografie (2012)
- Onderwijs TI wel of niet opereren? (2012)
- Hartfalen bijeenkomst: Mitralisklep insufficiëntie, medicamenteuze therapie (2019)