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Advanced Imaging Techniques for Mitral Regurgitation☆

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ABSTRACT

Mitral regurgitation (MR) is one of the most commonly encountered valvular lesions in clinical practice. MR can be either primary (degenerative) or secondary (functional) depending on the etiology of MR and the pathology of the mitral valve (MV). Echocardiography is the primary diagnostic tool for MR and is key in determining this etiology as well as MR severity. While clinicians usually turn to 2 Dimensional echocardiography as first-line imaging, 3 Dimensional echocardiography (3DE) has continually shown to be superior in terms of describing MV anatomy and pathology. This review article elaborates on 3DE techniques, modalities, and advances in software. Furthermore, the article demonstrates how 3DE has reformed MR evaluation and has played a vital role in determining patient management.

Contents

Mitral regurgitation (MR) is a commonly encountered valvular lesion in modern clinical practice and is increasing in prevalence as the average life expectancy rises.[1,2] MR can be classified as primary or secondary depending on the underlying cause. Primary MR (PMR), also referred to as degenerative MR, results from pathology of the mitral valve (MV) apparatus, such as in rheumatic

Abbreviations and acronyms: 2D, 2 Dimensional; 2DE, 2 Dimensional echocardiography; 3D, 3 Dimensional; 3DE, 3 Dimensional echocardiography; ASE, American Society of Echocardiography; AV, aortic valve; CMR, cardiac magnetic imaging; EROA, effective regurgitant orifice area; FMR, functional mitral regurgitation; LA, left atrium or atrial; LV, left ventricle or ventricular; MPR, multiplanar reconstruction; MR, mitral regurgitation; MV, mitral valve; MVC, mitral valve complex; PISA, proximal isovelocity surface area; PM, papillary muscle; PMR, primary mitral regurgitation; TTE, transthoracic echocardiography; TEE, transesophageal echocardiography; VCW, vena contracta width.

☆ Statement of conflict of interest: see page XX.

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disease, endocarditis, etc.[3] In secondary MR, also known as functional MR (FMR), the MV apparatus is anatomically intact, and the MR is due to geometric displacement of the papillary muscle leaflets due to left ventricular (LV) dysfunction and remodeling.

Echocardiography is the primary diagnostic tool for MR. In addition to evaluating MR severity, the modality is helpful in discerning the etiology of MR and can be used to evaluate the morphology, geometry, and function of the MV apparatus.[1] Visualization of these characteristics is key and plays a vital role in determining the management of patients. While 2-Dimensional (2D) echocardiography (2DE) is recognized as first-line in diagnostic imaging of MR, 3-Dimensional (3D) echocardiography (3DE) has continually shown to be superior in terms of describing MV anatomy and pathology, especially with the development of software packages. Thus, this review discusses 3DE techniques and modalities and how they have revolutionized MR evaluation.

Anatomy and pathophysiology

To understand the pathophysiology of MR and the complexity of MR imaging, clinicians should have a strong grasp of the anatomy of the MV. The MV apparatus consists of the following structures: anterior and posterior leaflets, mitral annulus, chordae tendinae, and two papillary muscles (anterolateral and posteromedial). These structures together with the left atrial (LA) myocardium, the LV myocardium, the LA and LV endocardium, and the aorto-mitral curtain make up what is known as the MV complex.[4,5] For the MV to function normally, the structures within this complex must interact in a coordinated fashion.

MV closure, for example, requires two opposing yet balanced forces.[6] During systole, the LV cavity contracts and the mitral annulus moves towards the apex. This drives blood up against the leaflets and acts as a ‘closing force,’ leading to leaflet coaptation. This closing force is opposed by the ‘tethering force’ caused by the contraction of the papillary muscles pulling the leaflets apically via the chordae tendinae.[7] When the tethering and closing forces are balanced, the leaflets will naturally come together at the level of the plane of the mitral annulus; any imbalance will lead to MR. If the tethering forces prevail, the leaflet coaptation will be abnormally below the annular plane into the LV. Conversely, if the closing forces are greater, the mitral leaflets will come together above the annular plane towards the LA.[8]

Primary mitral regurgitation

Primary or degenerative MR is the most common valvular abnormality, affecting about 1.7% of the world's population.[9] While PMR can have a wide variety of presentations, its main distinction from FMR is the structural disruption of one or more components of the MV apparatus. The two leading causes are myxomatous degeneration (also called Barlow disease) and fibroelastic deficiency.[10]

Barlow disease, which typically occurs in middle aged patients, is thought to be a genetic condition, in which the leaflet and chordal tough, fibrous structure is replaced with a loose mucopolysaccharide-rich material. This leads to progressive thickening, redundancy, and billowing of multiple leaflet segments.[11,12] Fibroelastic deficiency, on the other hand, is associated with the elderly and usually involves one segment that becomes thick and redundant while the remaining mitral leaflet becomes translucent in appearance and thinner than normal.[12,13] Other less common causes of PMR include connective tissue diseases, such as Marfan's disease and Ehlers-Danlos syndrome, and loss of papillary muscle support secondary to endocarditis or acute coronary syndrome.[14]

Secondary mitral regurgitation

Secondary or functional MR is also commonly encountered in clinical situations. Given its broad definition and multiple etiologies, its precise prevalence has been difficult to calculate[15,16]; its prevalence has been reported to be up to 60% of cases in ischemic cardiomyopathy and 40% in non-ischemic cardiomyopathy.[17,18] In this disease state, the MV apparatus is structurally normal, and the MR is a consequence of LV remodeling leading to dilation of the mitral annulus and displacement of the papillary muscles (PM). This displacement alters the normal perpendicular tension applied by the PM on the MV and results in impaired systolic excursion by one or both leaflets, causing incomplete coaptation and regurgitation.[19,20]

Echocardiographic evaluation

2DE and Doppler are the first-line modalities in evaluating MR. However, 3DE, especially real time 3D transesophageal echocardiography (TEE), has greatly enhanced MR evaluation and aided in visualization during surgical and percutaneous MV procedures.

2D echocardiography

MR, like other regurgitant flows, consists of the following three elements: (1) flow convergence proximal to the MV orifice; (2) flow through the orifice, referred to as the vena contracta; and (3) disorderly flow past the regurgitant orifice, referred to as the regurgitant jet.

Clinicians first characterized MR severity with angiography by visualizing the regurgitant jet, which was indicated by the amount of contrast media that was ejected from the LA into the LV. However, the technique is costly and time consuming, and exposes the patient to radiation and iodinated contrast.[21,22] Thus, angiography in this setting has become virtually obsolete. With the advent of color Doppler, clinicians can visualize and quantify all three elements to determine MR severity (Table 1) using the techniques described below . The guidelines from the American Society of Echocardiography (ASE) discuss these techniques and their limitations in further detail.[3]

Jet area

Historically, clinicians used color Doppler echocardiography to characterize the regurgitant jet by estimating its size either in absolute terms or relative to the left atrial size. This method is primarily applicable to cases involving a single central jet and is significantly affected by hemodynamics and technical aspects, which are further detailed in Table 2.[22] Given these limitations, techniques were developed to measure the vena contracta width (VCW) and to calculate the effective regurgitant orifice area (EROA) using the flow convergence.

Vena contracta

The vena contracta is the highest-velocity region of the flow jet and is typically located at or just downstream of the regurgitant orifice.[23] The VCW directly reflects the EROA and can be measured in the long-

Table 1
Echocardiography parameters and their determination of severe MR.

MR Parameter	Value Indicating Severe MR
Regurgitant jet area	Large central jet (usually < 10 cm^2 or < 40% of LA area) or variable size wall-impinging jet swirling in LA
Vena contracta width	≥0.7 cm
EROA	≥0.40 cm^2
Regurgitant volume	≥60 mL/beat
Regurgitant fraction	≥50%

EROA = effective regurgitant orifice area; MR = mitral regurgitation; LA = left atrium.

Table 2
2D echocardiography methods and their limitations.

Regurgitant jet area	• Primarily applicable to central jet • Eccentric jets appear smaller • Subject to hemodynamic variation (e.g. hypertension leads to a larger jet) • Affected by technical aspects (e.g. lowering the Nyquist limit gives the appearance of a larger jet)
Vena contracta width	• Primarily useful for one jet • Intermediate values require confirmation by CMR • Assumes a circular orifice
PISA method (for EROA calculation)	• Less accurate with eccentric jets • Cannot be used with multiple jets • Assumes a circular orifice

Abbreviations: CMR = cardiac magnetic imaging; PISA = proximal isovelocity surface area.

axis imaging plane perpendicular to the mitral leaflet closure.[24] This allows clinicians to provide a more quantitative assessment of MR severity. Furthermore, because the method involves a high velocity area and a fixed orifice, this method is not as affected by hemodynamics and technical aspects.

Effective orifice area

The flow convergence can be utilized to calculate the EROA by using the proximal isovelocity surface area (PISA) method, which applies the principle that blood approaching a circular orifice will form concentric, hemispheric shells of increasing velocity and decreasing surface area.[25] This is the most quantitative method of the three described thus far and has been shown to have a high correlation with MR severity. The major limitation of this method is the assumption that the EROA is circular in shape, which is often not the case. In secondary (functional) MR, for example, the orifice tends to be ovoid in shape.

Once the EROA is calculated, it can then be multiplied by the velocity time integral of the MR jet on continuous wave spectral Doppler to obtain the MR volume.[25] Subsequently, the MR fraction can be calculated by comparing the MR volume to the flow volume across a non-regurgitant orifice, such as the left ventricular outflow tract. The ASE guidelines emphasize the importance of these values, whether obtained by Doppler 2DE or by cardiac magnetic imaging, since they often correlate to symptom severity.[3]

3D echocardiography

Several studies have demonstrated that 3D transthoracic echocardiography (TTE) and TEE are superior to their 2D counterparts in terms of describing MV anatomy and identifying MV pathology.[26,27] For example, one study found that in an unselected population undergoing MV prolapse, 3D TEE had an overall accuracy of 96% compared to 87% when 2D TEE was utilized.[27] This difference in accuracy is to be expected since 2D imaging cannot portray the exact spatial location of each structure in the MVC and forces the examiner to create a complex mental depiction of the anatomy and pathology.

3DE's high accuracy can be attributed to the different modalities available for visualization, which are as follows: volume-rendered, biplane/multiplane, and color Doppler. Volume-rendered imaging has three spatial dimensions and can be further divided into three modalities of imaging (live 3DE, full volume, and zoom) depending on the magnitude of each dimension. Live 3DE, or narrow angle, imaging is the best for demonstrating the MV anatomy, but it cannot capture the entire MV apparatus in one live 3DE slice. Full-volume, or wide angle, imaging is more well suited to demonstrate leaflet movement since it has the best temporal resolution. However, it has poor spatial resolution and frequently has misalignment of individual slices (stitching artifact). Zoom imaging is the most useful for visualizing the MV since if sacrifices frame rate for good spatial resolution.[16]

The biplane/multiplane reconstruction and color Doppler modalities improve the accuracy of describing MV anatomy, but contribute more to the quantification of MR, which is essential in determining proper management and prognosis. 3DE color Doppler, for example, can determine the size, direction, and shape of the MR jet even if the shape is complex and eccentric.[28] This modality can also allow the clinician to more clearly visualize the proximal flow convergence of the regurgitant jet and reveal multiple regurgitant jets.[29,30] Even though the size of the regurgitant jet cannot be measured directly, the MR severity can be quantified by measuring the VCW (Fig. 1).[31] This measurement can be performed using either multiplanar reconstruction or color Doppler.[32,33] Moreover, one can use planimetry to measure the EROA

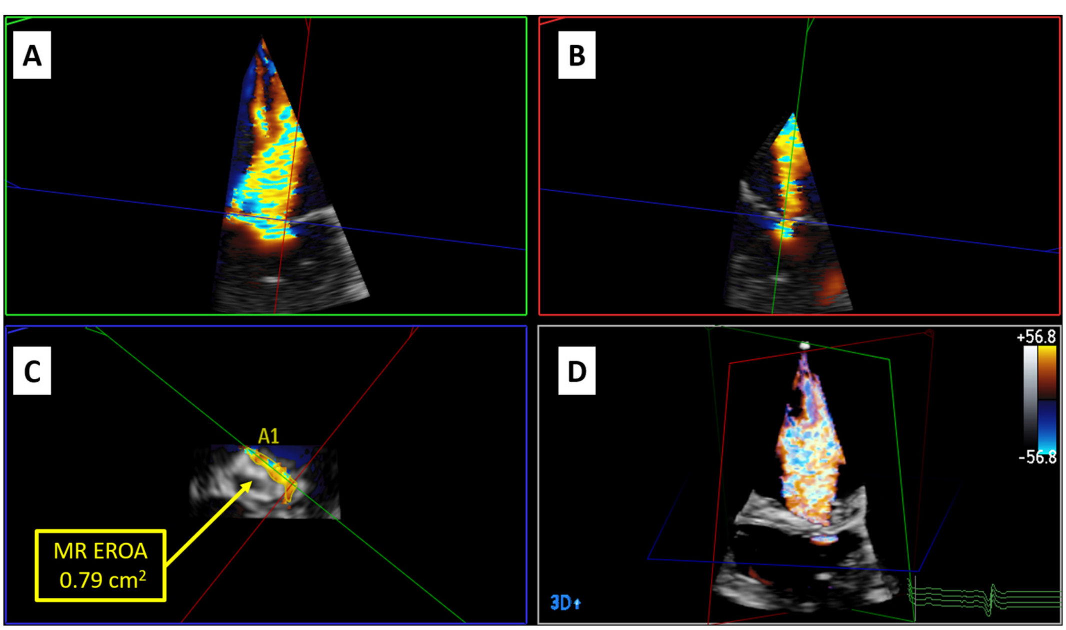

Fig 1. 3D color Doppler multiplanar reconstruction (MPR), planimetry of vena contracta area. Panels A and B – 2D color Doppler derived from a 3D color Doppler data set demonstrates severe mitral regurgitation in the long axis. Panel C – Measurement of the 3D vena contracta area (also referred to as the effective regurgitant orifice area, EROA) in the short axis. Panel D – 3D color volume rendering of severe mitral regurgitation. Abbreviations: MR, mitral regurgitation; EROA, effective regurgitant orifice area.

directly, regardless of its shape. Thus, these 3DE methods more precisely portray MR severity compared to 2D techniques, which incorrectly assume a circular EROA.[34]

The *en face* images on 3DE (Fig 2), which are equivalent to how surgeons see the MV, are the most clinically useful 3DE images. These images can also be rotated along the plane perpendicular to the imaging monitor to allow clinicians to visualize the entirety of the MV apparatus, facilitating the diagnostic process. By utilizing *en face* images in MVP evaluation, for example, one can survey the number of prolapsing segments, their location, and their extent, and the presence or absence of flail segments.[14]

Companies have also developed specific modeling and quantification software packages for 3DE. These packages can create unique models of the mitral valve by isolating it from the rest of the cardiac anatomy, allowing for better visualization and more accurate measurements (Fig 3). Moreover, companies, such as Siemens and Philips, have developed automatic software that can analyze several MV parameters in one frame and throughout the cardiac cycle. This reduces the time needed for image analysis and increases reproducibility among practitioners. The new eSieValves software, for example, has already demonstrated significant correlation with manual measurements and good intra-observer variability with a better level of agreement than manual measurements.[35] Another study found that using a computer-learning algorithm software by Philips had high accuracy when compared to expert manual measurements and surgical findings and that the software significantly improved reproducibility and efficiency of MV quantification by novice users.[36]

3D echocardiography in primary mitral regurgitation

As mentioned above, software packages for 3DE imaging have allowed for further quantification of MV parameters. These parameters include anterior and posterior leaflet area, billowing height and volume of prolapsing segment, anterio-posterior annular diameter, etc.[37,38]

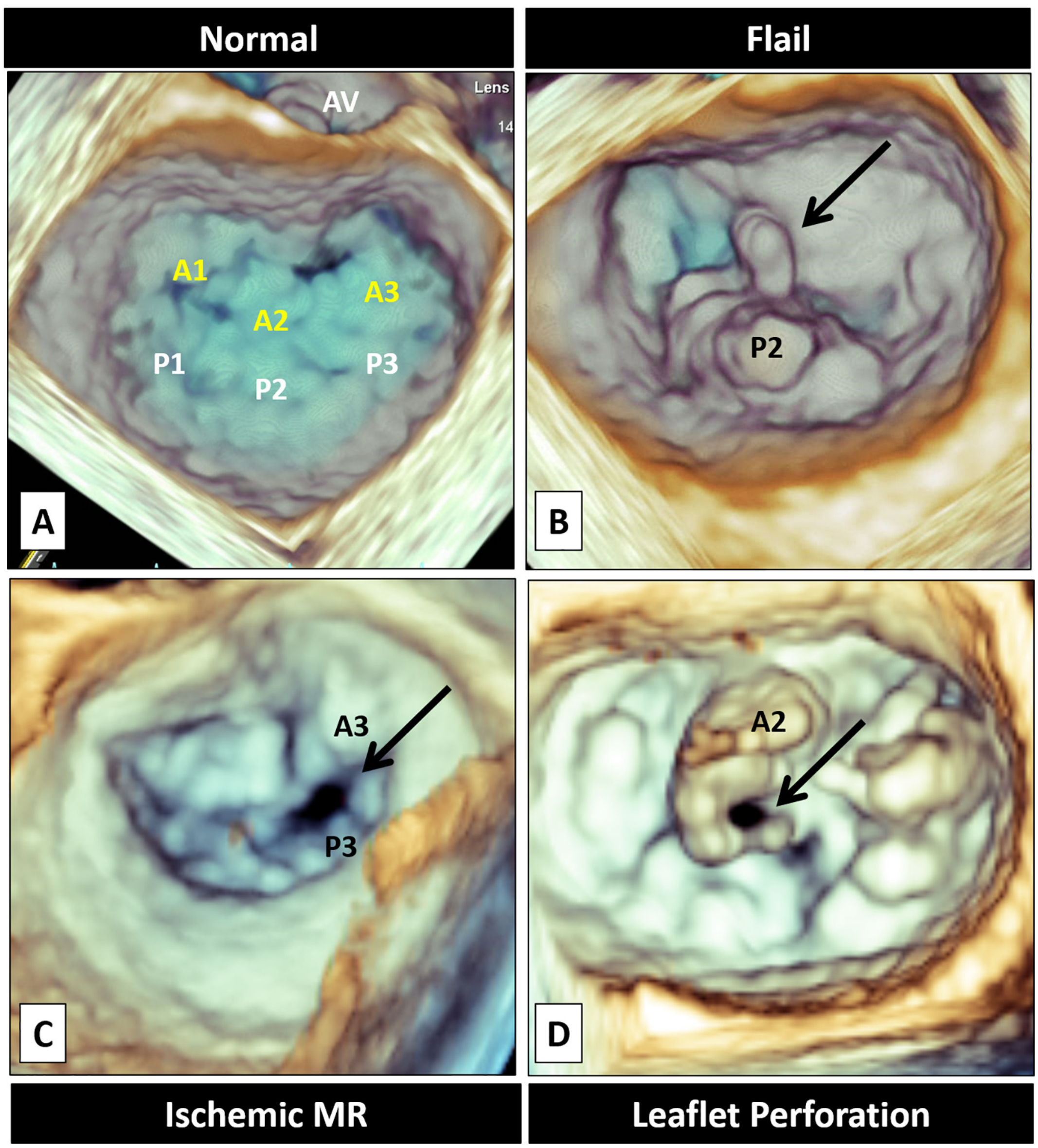

Fig 2. 3D mitral valve en face (surgeon's) view; normal vs. abnormal. Panel A – 3D imaging in the surgeon's view demonstrates a normal mitral valve. Individual scallops of the anterior (A1, A2, and A3) and posterior (P1, P2, and P3) mitral valve leaflets are depicted using the Carpentier classification. Panel B – 3D imaging in the surgeon's view demonstrates prolapse with flail of the P2 scallop of the posterior mitral leaflet. The black arrow points to the flail portion of the scallop. Panel C – 3D imaging in the surgeon's view demonstrates ischemic mitral regurgitation. A so-called "crooked smile" is produced due to asymmetric tethering (medial > lateral) of the mitral valve leaflets. Black arrow points to the regurgitant orifice, visualized along the A3-P3 coaptation line. Panel D – 3D imaging in the surgeon's view demonstrates mitral valve leaflet perforation in a patient with streptococcal endocarditis. Black arrow points to a focal point of perforation within the A2 scallop of the anterior mitral leaflet. AV, aortic valve.

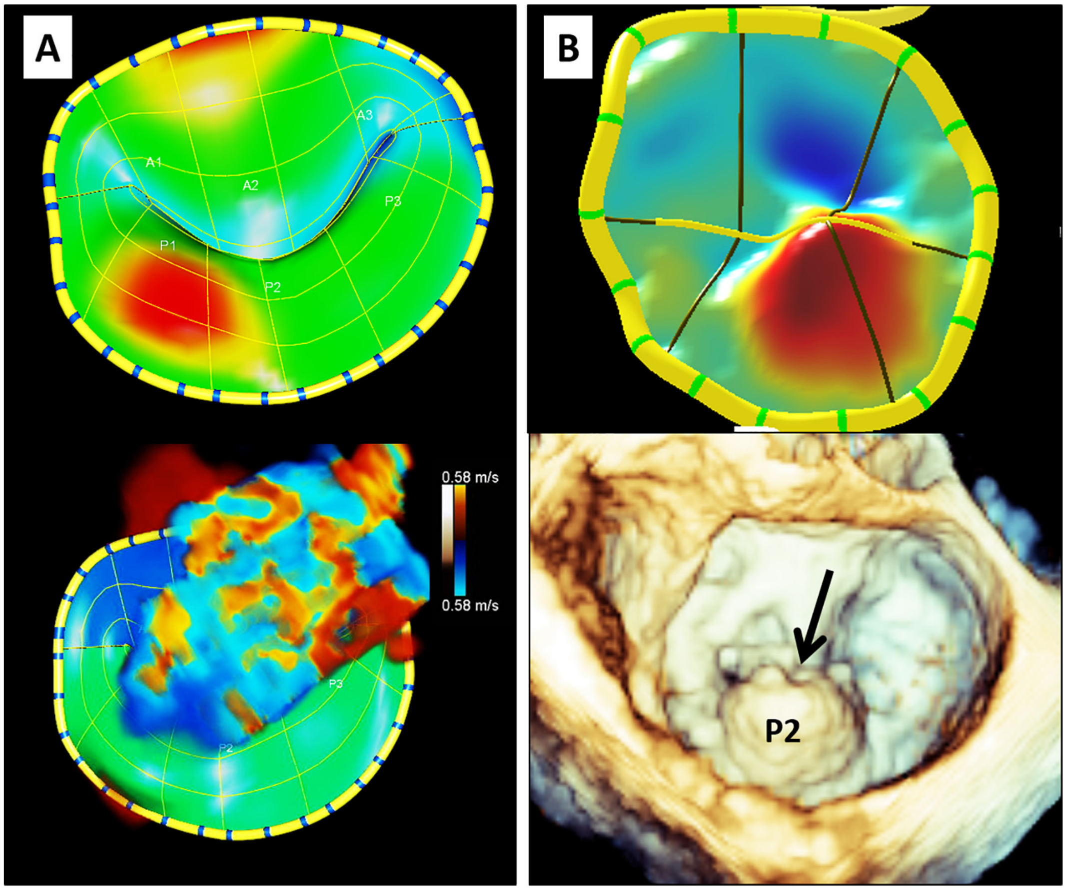

Fig 3. 3D mitral valve modeling. Panel A – 3D mitral valve modeling using Siemens system demonstrates posterior mitral leaflet prolapse with and without superimposed color Doppler. This system uses machine learning to automatically produce a 3D model of the mitral valve annulus and leaflets. Panel B – 3D mitral valve modeling using Philips system demonstrates posterior mitral leaflet prolapse. On the 3D mitral valve en face view, the black arrow points to prolapse of the P2 scallop of the posterior mitral leaflet.

With these values, physicians can distinguish Barlow's disease (which has a marked increase in overall leaflet area, leaflet billowing height and volume, and annular size) from fibroelastic deficiency (in which these changes are not as drastic).[39,40] Defining the etiology of primary MR can then determine the type of repair and the level of surgical expertise required.

Furthermore, 3DE can more accurately measure end-diastolic volume and end-systolic volume than 2D techniques.[41] Assessing these parameters is key because a LV ejection fraction (EF) <0.60 signifies LV systolic dysfunction, which correlates with poor long-term prognosis and is an indication for surgical management even if the patient is asymptomatic.[3]

3D echocardiography in secondary mitral regurgitation

Even though the role of 3DE in diagnosing and determining management in FMR is not defined, it is evident that 3D imaging (especially *en face* images) can provide unique views of the MV apparatus, the spatial relationship between the MV and LV, and even the bimodal/saddle shape of the mitral annulus that are not possible with 2DE imaging.[42] In addition to being able to quantify the severity of FMR using the methods described above, clinicians can measure the coaptation depth, the tenting area, and the angle subtended by the posterior MV leaflet.[43] These measurements can be used to predict successful MV repair. For example, a coaptation depth of ≥1 cm, tenting area of ≥1.6 cm^2, and a posterior leaflet angle of >45% predict significant recurrent MR after annuloplasty.[44]

With these details, it is also possible to elucidate the etiology of FMR. In ischemic cardiomyopathy, typically only the posteriomedial PM is displaced, leading to asymmetric tethering and restricted closure of the medial portion of the posterior leaflet. On 3DE images, this has the appearance of a 'crooked smile' as shown in Fig 2. Nonischemic cardiomyopathy, on the other hand, usually involves displacement of both PMs and leads to central MR. This can further be demonstrated on 3D TEE by measuring the tethering lengths, which are uneven in ischemic MR.[45]

3D echocardiography in mitral valve repair or replacement

Given the precision of 3DE, it is not surprising that 3D TEE has become the preferred technique for guiding the percutaneous repair of the MV using a mitral clip.[46] This modality allows surgeons to assess the results of the repair, visual possible complications, such as paravalvular and para-annular leaks, and allow more precise delivery of the catheter towards the leaflet edges (Fig 4).[41,47]

Visualization of MV characteristics during surgery with 3D TEE is also key to successful MR annuloplasty or replacement. The modality allows surgeons to tailor choices according to the patient's annuloplasty ring characteristics.[48,49] This individualized approach to surgery can greatly affect post-operative outcomes since the likelihood of success depends on how closely the post-surgical mitral annulus is restored to its natural saddle shape and function.[50] Without this consideration, patients can experience recurrent MR and continued LV remodeling, which ultimately leads to poor outcomes.[51]

Conclusion

Current imaging modalities have contributed greatly to not only visualizing the details of the MV apparatus, but also understanding the

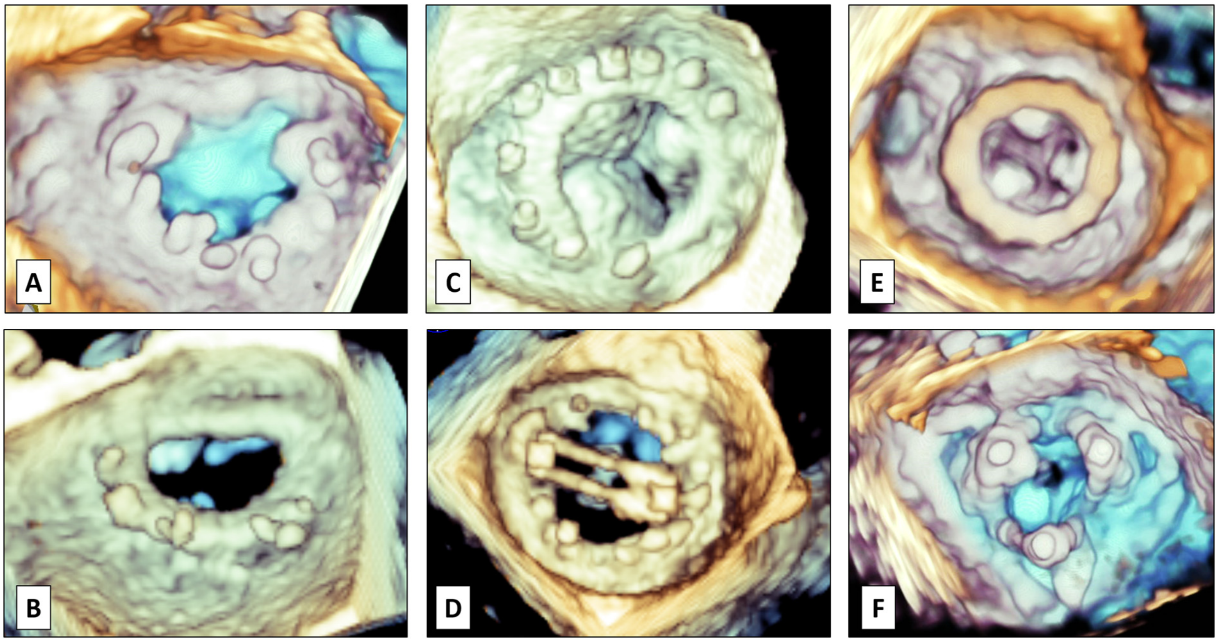

Fig 4. 3D mitral valve repairs and prostheses. 3D imaging in the surgeon's view demonstrates the left atrial aspect of surgical mitral valve repairs and replacements. (A) Annuloplasty band (incomplete ring); (B) complete annuloplasty ring; (C) mitral bioprosthesis; (D) bileaflet mechanical mitral valve prosthesis; (E) percutaneous mitral valve-in-valve (placement of a Sapien transcatheter bioprosthesis within a degenerated surgically implanted mitral bioprosthesis); (F) Percutaneous transfemoral-transseptal mitral valve replacement using a Caisson bioprosthesis within a native mitral valve.

etiology and pathomorphology of MR. While 2DE originated as the gold standard for evaluating MR, the enhanced visualization of the MV apparatus and the quantification techniques available in 3DE speak to 3DEs all-encompassing superiority over 2DE imaging. 3DE's correlation to clinical outcomes should further encourage clinicians to take advantage of this modality in order to be more well informed when discussing a patient's prognosis and determining the next steps in management.

Statement of conflict of interest

There are no conflicts of interest.

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