Past, current and future management of secondary mitral valve disease: the importance of anatomic staging

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Introduction

Mitral valve (MV) repair is superior to replacement for treating primary mitral disease (1-3). In appropriately selected patients, repair is also optimal for secondary disease (4). Mitral valve repair is potentially curative and is associated with long-term survival similar to that seen in patients without heart disease (5,6). When compared to repair, MV replacement is associated with increased operative mortality, stroke and bleeding complications, prosthetic device failure, and decreased long-term survival (6,7). However, the rate of mitral repair is decreasing (6,8). This trend may be explained by the results of Cardiothoracic Surgical Network (CTSNet) trial for treating severe mitral regurgitation (MR) (9). The CTSNet trial demonstrated a 33% rate of recurrent MR 12-months following simple reductive ring annuloplasty. The authors concluded that valve replacement achieved greater freedom from recurrent MR. However, valve distortion from secondary disease was not quantified prior to enrollment in the study and repair was not image-guided. The authors subsequently reported that left ventricular (LV) remodeling following durable repair was superior to valve replacement (10). Like CTSNet, the Percutaneous Repair with the MitraClip Device for Severe Functional/Secondary Mitral Regurgitation (Mitra-FR) trial did not quantify tethering prior to enrollment (11). Percutaneous edge-to-edge repair was used to treat the full spectrum of secondary disease. Neither trial favored MV repair.

Most recently, the Cardiovascular Assessment of MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation (COAPT) trial used transesophageal echocardiography (TEE) prior to enrollment to select patients with valve anatomy that was suitable for percutaneous edge-to-edge repair (12). Using image guidance, the COAPT investigators achieved a 95% freedom from recurrent MR at 12 months and demonstrated improved survival at 24 months. The CTSNet and COAPT trials demonstrate that durable repair for severe secondary mitral regurgitation improves LV remodeling and prolongs survival. These trials also demonstrate that image guidance is mandatory for optimal results. The role and application of image guidance have not been defined. Evidence-based, anatomic staging of secondary mitral disease is urgently needed (13).

Repair of secondary mitral valve disease

Surgical repair of secondary mitral disease is evolving. The historical approach of simple reductive ring annuloplasty for the full spectrum of secondary disease has largely been abandoned due to recurrent MR (2). Recurrent MR is common following ring annuloplasty if significant tethering is present or remodeling continues (14,15). Consequently, the indications for simple ring annuloplasty repair are specific and relatively infrequent (14,16). Valve replacement increases perioperative mortality, increases morbidity and decreases long-term survival (6,7). Therefore, for most patients with secondary MR, the binary approach (simple ring annuloplasty versus valve replacement) is not ideal (2). Several more complex techniques for repair of advanced secondary disease have been validated (4,14,17). These procedures use image guidance and complex reconstructive

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techniques to repair of the full spectrum of secondary disease.

Contemporary percutaneous MV repair is based on the surgical edge-to-edge repair (18,19). Mitral competence is restored by securing the free edges of the anterior and posterior leaflets together to create a double orifice valve. The early surgical results for treating secondary MR showed 95% freedom from recurrent MR at 18 months (20). Ring annuloplasty and reverse remodeling were both independently associated with durable surgical repair. However, concerns over high gradients and limited durability prevented widespread adoption of the edge-to-edge repair in the surgical community (21). The edge-to-edge technique reduces maximum flow rate across the valve by up to 50% and doubles stress on the leaflet free margin (22). Mitral valve gradients >5 mmHg following percutaneous edge-to-edge repair are associated with increased long-term mortality (23). When compared to percutaneous edge-to-edge repair, surgical repair results in greater freedom from recurrent MR (24). Nonetheless, the percutaneous edge-to-edge technique is effective when imaging is used to carefully select patients with no more than moderate tethering (12).

Recently, newer surgical techniques have been validated for repair of advanced tethering. Image-guided subvalvular procedures—including chordal cutting, papillary approximation/alignment and ventriculoplasty—have been effective for severe tethering (4,14,25). The future of valve repair will likely center on leaflet augmentation because it is the logical extension of naturally occurring adaptive growth and, unlike papillary approximation, does not exacerbate diastolic dysfunction (4,26-28).

Imaging secondary mitral valve disease

Secondary mitral disease can be subdivided into pathoanatomy and pathophysiology. Pathoanatomy is summarized in Carpentier's classic pathologic triad: *disease* causes *lesions* that result in leaflet dysfunction (29). For example, cardiomyopathies cause papillary displacement that results in leaflet motion restricted in systole (Carpentier Type IIIb). Pathoanatomy results in pathophysiology. The pathophysiology of secondary mitral disease is valve regurgitation. The severity of MR can be stratified to identify the need for intervention (30). For example, severe MR is an indication for intervention. However, the pathophysiologic severity does not identify the *appropriate*

intervention. Surgical or percutaneous intervention for secondary mitral disease must be guided by pathoanatomy (4,12,31). This is no different than cancer. For instance, the pathophysiology of bronchogenic carcinoma indicates the need to intervene. But it is the anatomic stage of the disease that determines the most appropriate intervention. Lobectomy is indicated for anatomic stage I neoplastic disease. Similarly, simple reductive ring annuloplasty is indicated for annular dilation with minimal tethering. Like cancer, secondary mitral disease must be anatomically staged and used to guide intervention (13,31). Again, like cancer, separate and unique imaging techniques are required to stratify the pathoanatomy and the pathophysiology of MV disease.

Standardized imaging

Anatomic stage-based intervention requires careful standardization of imaging. The concept of *axial imaging* for surgical mitral intervention was introduced in 2014 (*Figure 1*) (4,31). Currently, axial imaging is used almost exclusively for guiding percutaneous intervention (12).

Axial imaging is based on the mathematical description of the MV. During systole, the atrial surface of the valve resembles a riding saddle, which can be modelled as a hyperbolic paraboloid with three cartesian axes, x, y and z. The z-axis extends in an apical-basal basal orientation, from the LV apex to center of the mitral valve (*Figure 1*). The z-axis is referred to as the mitral-left ventricular apex axis. The x-axis extends from the anterior horn to the posterior mitral annulus and the y-axis extends between the two commissures of the valve. With TEE, the in mid-esophageal long axis and commissural views image the MV along the x- and y-axes respectively, intersecting at the center of the valve and running parallel to the mitral LV apex axis. The basal short axis view runs perpendicular to all three axes at the level of the mitral annulus. The left atrial "surgeon's" view ensures that the long-axis and commissural views are traversing the center of the valve. Landmark recognition and the elimination of parallax are mandatory. Axial imaging yields highly reproducible results. Leaflet tethering is quantified in axial long axis. The imaging techniques have been described in detail (31). The mid-esophageal four- and two-chamber views have long been known to underestimate tethering and overestimate prolapse (32,33). Consequently, there is little if any role for the four- and two-chamber views in guiding mitral intervention (31). Automated algorithms
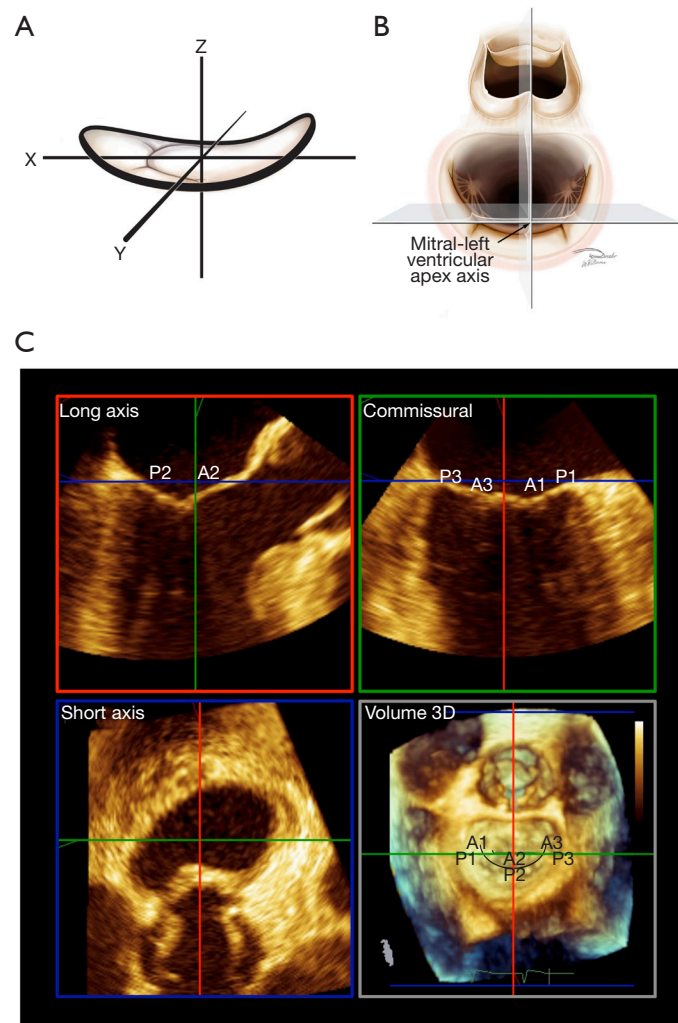
Figure 1 Axial imaging. (A) the mitral annulus in systole. Mathematically it is described as a hyperbolic paraboloid. A hyperbolic paraboloid has three orthogonal axes; the anteroposterior x-axis, the commissural y-axis, and the vertical z-axis; (B) the mitral-left ventricular apex axis. It is defined as a line that passes through the anterior leaflet such that the orthogonal long axis (xz) and commissural (yz) planes traverse the three coaptive surfaces A1/P1, A2/P2, and A3/P3. Extension of the intersection of these two planes through the ventricular apex defines the mitral-left ventricular apex axis. Imaging parallel or perpendicular to the mitral-LV apex axis minimizes geometric distortion from oblique orientation. Normally, the vertical z-axis of the hyperbolic paraboloid is not perfectly aligned with the mitral-LV axis. Angulation between the annular z-axis and the mitral-LV apex axis is important for understanding degenerative disease, hypertrophic cardiomyopathy, and aortopathies and their relationship to postoperative systolic anterior motion; (C) an example of post-acquisition axial three-dimensional multiplanar reconstruction. The valve should be displayed from the atrial aspect in the surgical orientation with the aortic valve above the MV. Imaging for 3D acquisition is the same as 2D and the long axis and commissural views are used as 2D reference frames to identify essential landmarks (31). A late systolic frame should be chosen for analysis. In the zoomed dataset shown, three orthogonal 2D slices are demonstrated: the long axis plane is in the top left quadrant (red box), the commissural plane is in the top right quadrant (green box), and a short axis view (blue box) is in the bottom left quadrant. A volume-rendered view is shown in the bottom right quadrant. Once parallax is eliminated, in the volume-rendered view, the red line demonstrates the location of the long axis plane and the green line demonstrates the commissural plane as they traverse the valve. When the colored lines are correctly positioned, the long axis (red) slice crosses the A2/P2 coaptive surface and commissural (green) slice traverses the A1/P1 and A3/P3 coaptive surfaces. The Carpentier nomenclature system is used for segmental identification. Figures modified and reproduced with permission from Daniel H. Drake and David A. Sidebotham. All rights reserved.

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and artificial intelligence may improve reproducibility and facilitate rapid acquisition of indices in the future (34,35).

When compared to TEE, transthoracic echocardiography underestimates tenting height and overestimates tenting area (36). Current guidelines provide a class I indication for TEE to determine the mechanism of MR and status of the LV (1). Given the minimal risk of TEE examination and substantial mortality of recurrent MR, TEE should be performed well in advance of intervention and used for identifying the best options for management.

Secondary mitral regurgitation is bi-phasic with peak regurgitant flows in early and late systole (37,38). Identification of mid-systole is burdensome and intrinsically ambiguous. Arrhythmias including atrial fibrillation further complicate the consistent identification of mid-systole. For these reasons, late systole should be used for analysis.

The mitral annulus is a fibrous ring that surrounds the leaflets and is an important anatomic feature for both surgical and percutaneous interventions. Imaging for mitral intervention requires proper identification of the anatomic mitral analysis. The atrial surface of the valve identifies the plane of the annulus. The mitral annulus is 1–2 mm peripheral to the leaflet hinge point. Tenting heights, tenting areas, and leaflet closing angles should all be based on the anatomic annulus in long-axis.

Currently the literature appears to favor the end-systolic long-axis view using transesophageal echocardiography in the lightly sedated patient. Three-dimensional post-acquisition analysis greatly facilitates accurate stratification of disease (4).

Indices of secondary disease

The anatomic indices of secondary disease include direct and indirect measurements. Direct indices quantify leaflet dysfunction. They are anatomic measurements taken directly from the valve and are the most important parameters for guiding surgical and percutaneous repair (4,12,14). These indices include tenting height, tenting area, anterior leaflet closing angle, posterior leaflet closing angle, and anterior leaflet inversion angle (*Figure 2A*). Coaptive length, coaptive gap and interpapillary distances may also be useful. Indirect indices are less precise and include ventricular dimensions, contractility, scar burden, and restrictive diastology. Indirect indices are important for selecting palliative options such as surgical or percutaneous

valve replacement, transplantation, ventricular assist devices, or medical therapy alone (39,40).

Staging

Stage I identifies patients with minimal tethering. Tenting height is less than a centimeter below the plane of the annulus and the tenting area is less than one centimeter squared. Stage I is relatively infrequent and the dominant lesion appears to be annular dilation from a basil myopathy secondary to atrial fibrillation (atrial functional MR) (4,14,16,35,41). Patients with Stage I disease and stable myopathies can be expected to achieve long-term freedom from recurrent MR using either simple reductive ring annuloplasty or percutaneous edge-to-edge repair. Surgeons who choose a binary approach consisting of simple reductive ring annuloplasty repair or valve replacement, should limit repair to Stage I disease. The combined lesions of a global myopathy from chronic MR superimposed on annular dilation and bileaflet prolapse from Barlow disease (Carpentier type II + IIIb = I) can also present as Stage I (31,42). These combined lesions must be recognized prior to intervention because of the increased risk of systolic anterior motion following simple reductive ring annuloplasty.

Stage II identifies moderate leaflet tethering. Tenting height is still less than a centimeter but tenting area exceeds a centimeter squared. There is no significant leaflet angular distortion although anterior leaflet inversion from tethering of the secondary chordae tendonae may be present. Mitral repair can be accomplished with simple subvalvular techniques such as anterior secondary chord lysis. These procedures are always combined with reductive ring annuloplasty (4,17,43-45). The percutaneous edge-to-edge repair is also effective for Stage II disease.

Stage III identifies advanced tethering. The tenting height exceeds one and the tenting area is typically greater than two centimeters squared. All leaflet angles demonstrate severe distortion. Advanced tethering is associated with nearly uniform failure of both simple reductive ring annuloplasty and percutaneous edge-to-edge repair. This is reflected in the 2016 European Guidelines and the 2017 American College of Cardiology (ACC) Expert Consensus. Complex surgical procedures are required for MV reconstruction (2,46). The surgical edge-to-edge repair combined with ring annuloplasty has demonstrated excellent freedom from recurrent MR but the results from
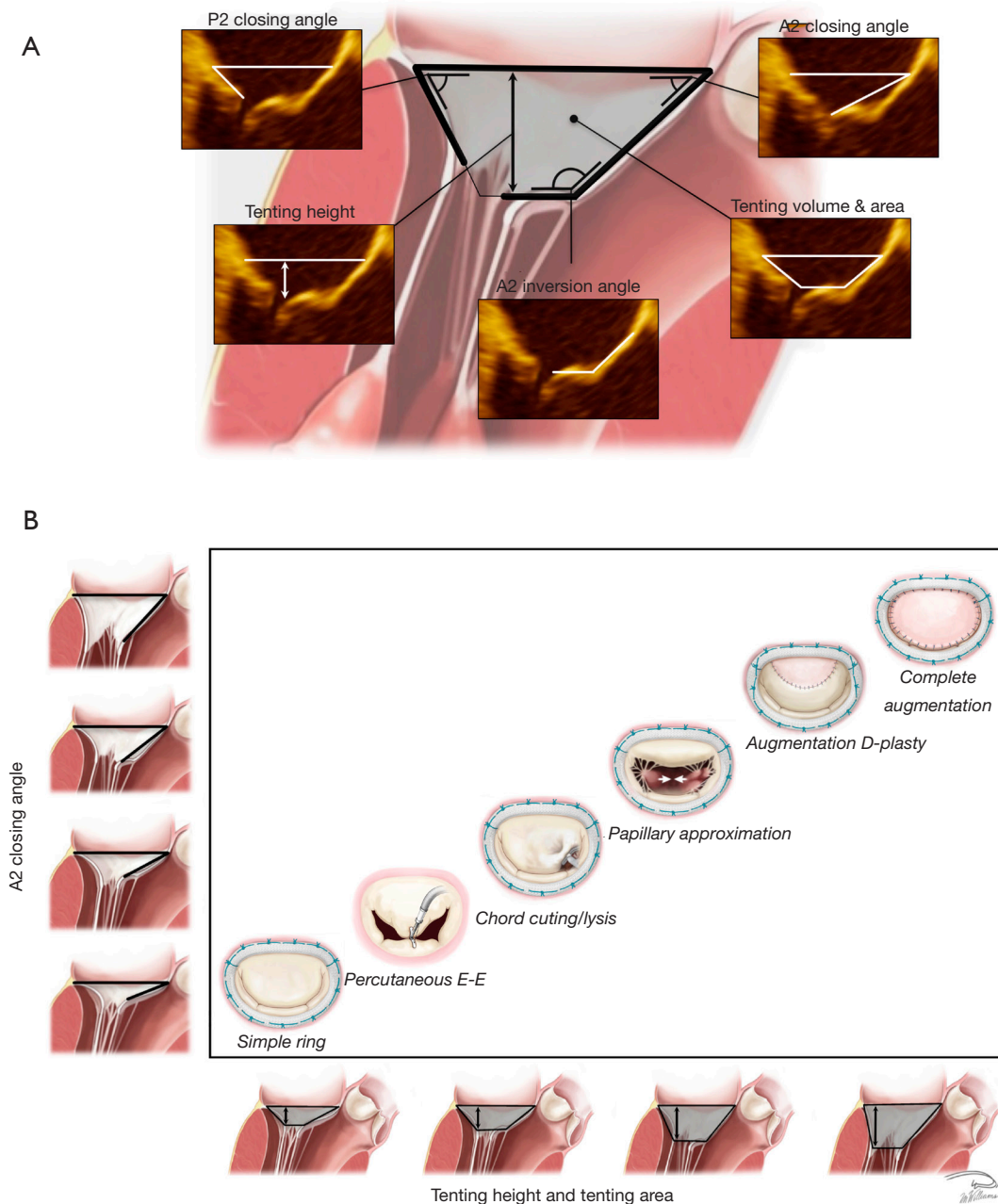
Figure 2 Image-guided mitral repair for secondary disease. (A) the LV in the axial long axis view during late systole. The direct indices of secondary distortion are identified and include tenting volume, tenting area, tenting height, A2 closing angle, P2 closing angle, and A2 inversion angle; (B) an image-guided approach for repairing the full spectrum of secondary disease. Intervention is based on anatomic staging. Tenting height, tenting area and the A2 closing angle are illustrated along the x and y axes. Although not illustrated, the other direct indices should also be considered when planning intervention. When compared to medical management, percutaneous edge-to-edge repair is effective but limited to early stage disease. Surgical procedures cover the full spectrum of disease. Surgical procedures include simple reductive ring annuloplasty, anterior secondary chord lysis/cutting, papillary muscle approximation/alignment, anterior leaflet augmentation/D-plasty, and complete anterior leaflet augmentation. Reductive ring annuloplasty is used to complete all surgical repairs. Figures modified and reproduced with permission from Daniel H. Drake and David A. Sidebotham. All rights reserved.

percutaneous edge-to-edge repair are poor (24).

Stage IV identifies patients with severe tethering and severe ventricular remodeling. These patients are likely to have recurrent MR following all repairs and may derive no benefit from mitral intervention of any type. Indirect indices are more important for identifying Stage IV disease. A basilar aneurysm, restrictive diastology or proportionate MR may also be present (47). The 2016 American Association for Thoracic Surgery and 2017 American Heart Association/ACC Guidelines indicate that MV replacement is reasonable if significant preoperative tethering is present (2,48). In patients with true end-stage heart failure, MR may no longer be of prognostic significance (49).

As demonstrated in *Figure 2B*, axial imaging can be used to anatomically stage MV disease. The direct indices provide the basis for stage-based intervention across the full spectrum of secondary disease.

Conclusions

Severe regurgitation from secondary mitral disease increases mortality (30,50). Durable repair improves LV remodeling and survival (10,12). Conversely, valve replacement is associated with increased operative mortality, bleeding and embolic complications, prosthetic device failure, and decreased long-term survival (6,7).

There is evidence to support a simple anatomic staging system for secondary mitral disease. Standardized imaging is required for staging. The first three stages use direct indices to quantify minimal, moderate and severe tethering. Each stage is associated with increasing procedural complexity for interventional success. The fourth stage is associated with failure of all repair techniques.

The historical approach of simple reductive ring annuloplasty for the full spectrum of secondary disease has been abandoned and the binary approach is far from ideal (2,9). Using image guidance, several surgical techniques for have been validated for repairing advanced disease (4,14,17). They allow for comprehensive reconstruction of the full spectrum of secondary MV disease.

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Footnote

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