Assessment of Mitral Valve Reserve Function A Structural Approach to Ischemic Mitral Regurgitation

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August 6, 2020

Abstract

Ischemic mitral regurgitation (IMR) is one of the common complications of coronary heart disease. The primary underlying mechanism is ventricular myopathy rather than disease of the valve itself. The decrease of myocardial blood supply will lead to myocardial damage, which will lead to the left ventricular remodeling, left ventricular enlargement, annular dilation, papillary muscle displacement and limited leaflet activity, resulting in mitral regurgitation. IMR has a certain effect on the prognosis of coronary heart disease, and the incidence rate of IMR has been increasing in recent years. IMR is a complex dynamic process, and it is a great challenge to deal with IMR. For patients with moderate or severe IMR, there are still many challenges and controversies in the choice of surgical methods. This article reviews the pathological process of left ventricular remodeling, the evaluation of IMR, the choice of mitral valve (MV) repair or replacement, and the reserve of MV function. Our review suggests that assessment of MV reserve function may be a predictor of IMR. In the future, assessment of MV reserve function may provide further useful information for evaluating MV function and determining MV repair or replacement in patients with IMR.

Introduction

Coronary atherosclerotic heart disease (CHD) is a common disease in the elderly. IMR is a functional mitral regurgitation secondary to the chronic coronary heart disease and LV remodeling. Up to 60% of patients with myocardial infarction have IMR[1]. The typical reason is that the geometric changes in the left ventricle following myocardial injury impede sufficient coaptation of normal mitral leaflets[2]. The MV, as a one-way valve, ensures a certain blood volume circulating from left atrium to left ventricle. The MV apparatus is a complicated structure consisting of anatomic components (leaflets, fibromuscular annulus, chords, papillary muscles and the underlying myocardium). The MV apparatus interact to maintain the MV competent during the cardiac cycle[3]. During systole, MV closure includes a dynamic interaction between anatomical and physiological factors (preload, afterload and contractility) to reach the maximum mitral coaptation so as to prevent regurgitation. The intraoperative MV function analysis should start with the quantification of mitral regurgitation (MR) and the diagnosis of related mechanism[4]. IMR is a common complication of the left ventricular global or local pathological remodeling caused by acute or chronic coronary artery disease[5]. It is a form of systolic incompetence, that is, the consequence of progressive annular dilation or leaflet retraction with gradual reduction and failure of systolic leaflet apposition[2]. It often represents the pathological results of increased tethering forces and decreased MV leaflets coaptation[6]. Therefore, the degree of apposition serves as a "mitral valve reserve" function that allows the apparatus to sustain further remodeling without overt systolic incompetence[7,8]. Ring annuloplasty is usually performed to reduce the annular area, increase the valvular coaptation zone, and reduce the severity of MR[9]. However, the remodeling of the MV apparatus in IMR can be heterogeneous that there may be a variable degree of apposition/reserve along the line of coaptation[10,11]. Depending upon the available reserve, the upper limit of the normal mitral annular diameter is MV specific and perhaps region specific within the same MV.

The appreciation of spatial variation of MV reserve brings into question the utility of normative values of mitral annular diameter routinely used for patient selection for annuloplasty[12,13]. The "mitral valve reserve" function is determined by the pathophysiology of the underlying disorder, and an extensive discussion about these changes is beyond the scope of this review. However, a brief introduction of "mitral valve reserve" function is important for surgical decisions making from the intraoperative echocardiographic perspective.

Intraoperative Mitral Regurgitation Assessment

Quantitative vs Semi-Quantitative Methods

The strong correlation between MR and prognosis underscores that the assessment of MR severity is an important part for the decision making in patients with IMR[14,15]. The recently updated guidelines of the American Society of Echocardiography (ASE) recommended an comprehensive method involving quantitative, semi-quantitative and qualitative methods to confirm the degree of secondary MR, which was divided into mild, moderate and severe[15-17]. The color Doppler is the most commonly used method for quantifying MR. The effective regurgitant orifice area (EROA), regurgitant volume and fraction can be obtained by evaluating the distal MR jet area/left atrium area ratio, vena contracta width and the proximal isovolumetric surface area (PISA)[16]. Hoverer, there are some limitations in using color Doppler to evaluate MR, such as eccentric or multiple or non-holosystolic MR jet, non-circular regurgitant orifice, non-hemispherical PISA, and the influence of load conditions[16].

Three dimensional (3D) imaging can provide supplementary information, which is an adjunct to a comprehensive examination of 2D transesophageal echocardiography (TEE). Specifically, it enhances the spatial orientation and accuracy of linear measurements, allows synchronous visualization of orthogonal views, and allows the volumetric analysis of cardiac chambers without geometric assumptions. 2D imaging can provide a wide range of methods for the identification of cardiac anatomy, physiology and structures of interest, while 3D TEE is used to obtain specific supplementary quantitative and qualitative information from the interested structures at present[18]. It is recommended to use 3D echocardiography to overcome some of the pitfalls encountered in 2D examination: the 3D image acquisition of MR enables the direct planimetry of the vena contracta (i.e., regurgitant orifice area) and thus optimizes the MR assessment in the case of non-hemispherical PISA and multiple jets[16,19,20].

General Anesthesia (GA) and Mitral Regurgitation

GA has been proved to down grade the severity of MR due to its unloading effect on the LV[21-23]. In addition, the severity of MR may vary as the result of the dynamic nature of intraoperative conditions[4]. MR is a valvular pathology affected by multiple variables such as preload, LV contractility, heart rhythm, afterload, GA and positive pressure ventilation[24,25].*Alijandro G, et al.* had done a experiment that a baseline intraoperative TEE examination was performed after GA induction to observe the effects of GA put on the grade of mitral regurgitation. They thought the reduction in MR severity was particularly pronounced when the regurgitation was due to insufficient leaflet coaptation (annular dilatation/ventricular dilatation), but did not seem to decrease when the regurgitation was due to a flail leaflet[26]. Regurgitation associated with abnormal MV structure is not significantly influenced by GA induction[24,27,28]. Functional MR is shown to be improved with GA when compared with its preoperative severity[29,30]. Although the pharmacologic simulation of hemodynamics in awake-state has been improved, the undervaluation of MR under GA has not been completely eliminated[24,31]. This is particularly challenging in functional MR cases, because there may be significant inconsistencies between the pre- and intraoperative MR severity assessments[31,32].

2、Chronic Mitral Regurgitation and Structural Remodeling

Indices of Remodeling

IMR is a common complication of the LV global or local pathological remodeling caused by acute and chronic coronary artery diseases[2]. It often represents the pathological result of increased tethering forces and decreased MV coaptation, which finally leads to IMR[33]. IMR is common and seriously affects the prognosis. Even mild IMR can have adverse effects on survival. There is a strong grade relationship between

IMR severity and survival rate[34]. The full closure of the MV leaflets is a balance between two opposing forces: the closing force of the LV contraction and the tethering force of the chordae tendineae (*Figure 1*)[35]. IMR is in a self-perpetuating cycle due to the imbalance caused by either a decrease in the closing force or an increase in the tethering force[36].

IMR occurs when the MV leaflets do not adequately cover the MV orifice in systolic period. Two main mechanisms of IMR are generally accepted: ischemic LV dysfunction and non-ischemic dilated cardiomyopathy. IMR results from LV remodeling, which directly affects the spatial relationship between LV and MV. This deformation finally affects the leaflet coaptation and valve competency. The following mechanisms play roles in the pathophysiology of IMR: 1. PM dysfunction: During systole, PM contraction is important to keep the MV leaflets close in the LV. PM ischemia can lead to hypokinesia and detectable MR[37]. The anterolateral PM has a dual blood supply, however, the posteromedial papillary muscle has a solitary blood supply[38]. Because of the vascular anatomy of the PM, the posterior PM is more susceptible to ischemia[39]. 2. MA function: The MA enlargement and flattening also contributes to the development of IMR. The abnormal MA shape, and/or the loss of the saddle-shape, would result in increase of the leaflet stress and abnormal leaflet remodeling[40]. 3. Mechanical coordination of systole: a loss of ventricular mechanical coordination after myocardial infarction would decrease the closing forces during systole, which is thought to be a factor in deteriorating IMR[41]. The disordered contraction of the LV near the PM would increase the tethering forces[42]. Dyssynchrony between atrial and ventricular systole would generate diastolic MR[43]. Due to the MR, the time required to reach the maximal coaptation during acute ischemia is prolonged, which would result in severe MR even during "early systole" and maximal coaptation[44].

IMR is believed to initiate from LV remodeling caused by increased diastolic wall stress and persistent increased end-systolic volume[45]. The lateral and apical PM displacement secondarily affects the MV coaptation, resulting in the valve incompetence. In IMR, the tethering forces exerted by the chordae are increased while the closing forces are reduced due to LV systolic dysfunction. The PM displacement result from from a regional LV remodeling or the global LV dilation after MI, so one or both PM can be affected. When abnormal wall motion and local remodeling in a specific region lead to adequate MV tethering to generate IMR[46]. MV tethering is symmetric in the global remodeling, while asymmetric tethering mainly occurs following localized LV remodeling and mostly affects the posterior PM[47].

Intraoperative Application

The presence of IMR has a negative impact on survival rate, and there is a significantly graded relationship between IMR severity and reduced survival. The use of undersized ring annuloplasty for MV repair has become the preferred treatment strategy for IMR[48,49]. Although general consensus has been reached on coronary artery bypass grafting (CABG) and MV surgery for patients with severe MR, clinical dilemma exists in patients with mild to moderate MR[50]. *Govindan* S*et al.*reported that there was no significant change in the MV nonplanarity angle in patients with mild or moderate IMR who underwent revascularization alone when they received 2D, 3D TEE and MV assessment before and immediately after the CABG (n=20)[51]. These patients who undergo CABG surgery alone may leave them with obvious residual disease, while the inclusion of MV surgery in the CABG surgery will increase the perioperative risks[52]. A growing body of literature indicates an unacceptably high risk of persistent or recurrent IMR after reduction annuloplasty[7,53]; however, in patients without recurrent IMR, MV repair may be more beneficial than valve replacement, especially in terms of LV remodeling and function. Reduction annuloplasty is an effective treatment for annular dilatation, but it can make the posterior leaflet move forward and intensify the leaflet tethering[54,55]. *Vergnat Met al.* had made comparisons of 3D TEE data before and after a flat (n=9) or a saddle annuloplasty (n=9) was implanted in patients with severe IMR. They found that the shape of the ring affects the curvature of the leaflet. Implantation of a saddle ring kept annular nonplanarity and showed higher 3D leaflet curvature across the MV surface, whereas flat rings reduced annular nonplanarity and flattened leaflet significantly in all but the P1 region[56]. This strongly demonstrates that an imaging strategy that can reliably determine the risk of annuloplasty failure and predict recurrence preoperatively would be considered during surgical decision-making, so as to improve the surgical results.

3、Ischemic Mitral Regurgitation-Repair vs Replacement

IMR is a result of adverse LV remodeling after myocardial injury, including enlargement of the LV chamber and mitral annulus, apical and lateral displacement of the papillary muscles, leaflet tethering and decreased closing forces. These processes can lead to malcoaptation of the leaflets and varying degrees of MR , which can fluctuate dynamically with heart rhythm, volume status, afterload, and residual ischemia[57]. The leaflets are normal, and the pathological changes appear in the myocardium rather than in the valve itself. Therefore, the treatment of functional IMR is quite different from that of primary degenerative MR[58]. Practice guidelines recommend that for patients with severe IMR who experience restrictive symptoms despite the best available medical treatment and possibly cardiac resynchronization, MV repair or chordal-sparing replacement should be considered[59,60]. However, these guidelines do not specify whether to do the MV repair or replacement, because there is no clear evidence on which of these intervention is better. Clinical studies have shown that MV repair is associated with lower perioperative mortality[61-63], but replacement provides better long-term correction and lower risk of recurrence (an important consideration is that recurrence of mitral regurgitation may lead to atrial fibrillation, heart failure and readmission) (*Table 1*)[64-68]. But some studies suggest the early mortality of the repair group is higher than that of the replacement group[69,70]. And some other studies have demonstrated that survival after combined surgery is mainly affected by factors related to the patient's condition during the operation, but not by the MV repair or replacement (*Table 1*)[71,72]. This perceived trade off between reduced operative morbidity and mortality with repair and better long term IMR correction with replacement has produced significant variation in surgical practice for this high-prevalence condition[58].

4、Concept of Coaptation Reserve

Definition

"Coaptation reserve" defined by the actual contact area of the leaflets is less well established, but is still crucial for the intraoperative guidance of MV repair. The leaflet coaptation failure of IMR is due to annular dilatation, leaflet tethering caused by papillary muscle displacement, or both[73]. "Mitral valve reserve" refers to the degree of apposition of the MV leaflets that allows the apparatus to maintain further remodeling without overt systolic incompetence[7,8]. Restrictive annuloplasty is performed under these circumstances to reduce annular area, provide a greater zone of coaptation between the MV leaflets, and consequently reduce the severity of MR[9]. However, in IMR, the remodeling of the MV apparatus can be heterogeneous with varying degrees of apposition/reserve along the coaptation line[10,11].

Calculation

The overall and local 3D pathological anatomy of IMR is highly complex and varies widely during patients. All patients with IMR have varying degrees of annular dilatation and leaflet tethering, but the relative contribution of these parameters to valve incompetence differs significantly among patients. This implies that depending upon the available reserve, the upper limit of the normal mitral annular diameter is MV specific and perhaps region specific within the same MV.*Mahmood Fet al.* had made regional comparisons of 3D TEE data from patients with IMR underwent MV surgery (n=66) and patients with normal valvular and biventricular function (n=10) to identify measurements that reliably differentiate normal from remodeled MVs. They found that extension of the middle potion of the anterior annulus, larger nonplanarity angle, and increased tenting angle of the posteromedial scallop of the posterior leaflet were sufficient to distinguish IMR from the control group. They thought specific 3D variations in the MV regional geometry can be used to reliably identify a significantly remodeled valve apparatus[74]. *Cho E Jet al.* suggested that MA height likely to be a useful prognostic factor in choosing the timing of surgery in patients with chronic primary MR. Annulus height/BSA can provide supplementary information for predicting the postoperative LA remodeling after successful MV repair[75].*Bretschneider* C *et al.* considered the presence of PM infarction was not associated with IMR, because the severity of mitral regurgitation was not increased compared with patients with partial or no PM infarction[76].

For the unacceptably high risk of persistent or recurrent IMR after reduction annuloplasty, what the "mitral

valve reserve" can do to predict the recurrence? *Gogoladze Get al.* had made a experiment that regional coaptation sections were analyzed in cardiac surgery patients with normal MVs (n=10) or with functional MR (n=10). They found that the anterior leaflet coaptation length (CL) was greater than posterior leaflet, the functional MR was associated with shorter leaflet CLs, the biggest difference in CLs was in A2-P2, and coaptation depth was higher in the functional MR group. They thought there was a "anterior leaflet reserve"for posterior movement of the coaptation line to compensate for annular dilation and left ventricular enlargement so as to maintain competency until the anterior leaflet CL was insufficient, followed by the functional MR[77]. *Wei Det al.* had also done a study about the association between the coaptation height of MV and MR. They measured coaptation height of patients underwent annuloplasty for mitral regurgitation (n=20). The results shown that coaptation height had a significant negative correlation with the degree of MR 12 months after operation. They made a point that MV annuloplasty induced the morphologic change of the MV structure. The coaptation height after MV repair may be one of the key factors in regulation of MR[7]. And there were still other researchers wanted to reveal the relationship between the "mitral valve reserve" and the recurrence after mitral annuloplasty. *Wijdh-den Hamer I Jet al.* performed 2D and 3D TEE on patients underwent undersized annuloplasty due to IMR (n=50). They thought that MV replacement should be strongly considered in patients with a preoperative P3 tethering angle of [?]29.9° (especially when combined with basal aneurysm/dyskinesis)[10].

A growing body of literature has documented an unacceptably high risk of IMR recurrence after reduction annuloplasty, and a growing number of researchers are interested in knowing the role of the "mitral valve reserve" in predicting the recurrence. Some echocardiographic indices derived from 2D TTE、TEE and 3D TEE modeling, have been collected in several studies during the last decade[78-81]. The most commonly used cut-offs points for determining the degree of MV tethering and the risk of MV repair failure are as following: anterior leaflet angle>25^{o}, posterior leaflet angle >45^{o}, tenting height [?]11 mm, and the tenting area [?]2.5 cm^{2}[10,14,82]. However, all of these cut-offs are obtained from the integrity of MV. For remodeling of the MV apparatus in IMR can be heterogeneous with a variable degree of reserve along the line of coaptation, the upper limit of the MA diameter is MV specific and perhaps region specific within the same MV. Maybe the cut-offs from regional MV are more important in surgical dicision making. This is worthy of further study and discussion.

5、Future Applications

In conclusion, "Mitral valve reserve" means the degree of apposition of the MV leaflets that allows the apparatus to sustain further remodeling without overt systolic incompetence. Remodeling of the MV apparatus in IMR can be heterogeneous with a variable degree of apposition/reserve along the line of coaptation. Depending upon the available reserve, the upper limit of the MA diameter is MV specific and perhaps region specific within the same MV. These regional geometric changes can be used to identify important MV apparatus remodeling that may require intervention. We need to further clarify the role of "mitral valve reserve" in patients with IMR. Preoperative echocardiographic assessment should provide the surgeons with information on the pathology and dimensions of the MV apparatus to predict disease recurrence and support the surgical decision making.

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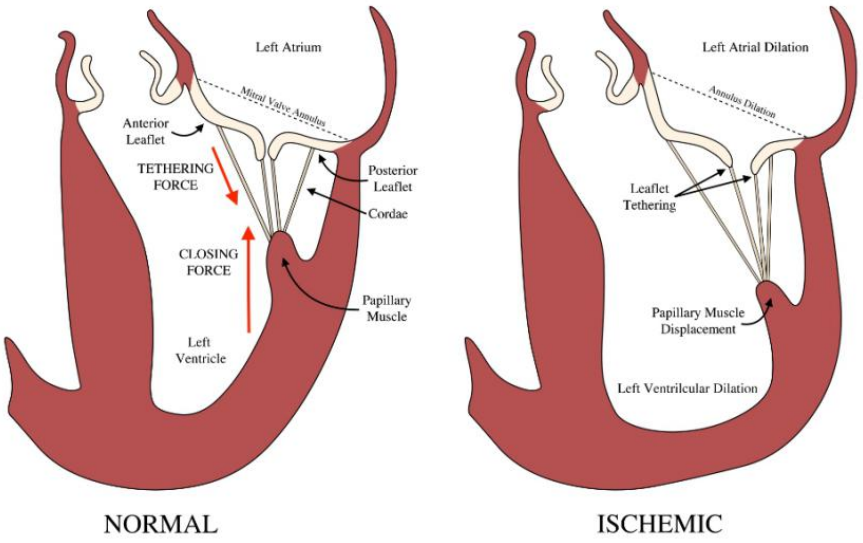

Table 1. Ischemic Mitral Regurgitation–Repair vs Replacement

Study	Summary
Hakimeh Sadeghian et al.[69]	Prospective study, CABG plus MV replacement or MV repair were performed in 49 patients
Michael A. Acker et al.[64]	Prospective study, in 251 patients with severe IMR, MV repair or chordal-sparing replaceme
Ahmet Rüçhan Akar et al.[61]	Retrospective study, 146 patients underwent MV surgery from January, 2004 to January, 200
Carlo Fino et al.[62]	Retrospective study, 121 patients with significant chronic IMR, who underwent MV repair (r
Zhibing Qiu et al.[65]	Retrospective study, 218 patients underwent either MV repair (n=112) or MV replacement (
A. Marc Gillinov et al.[63]	Retrospective study, 482 patients with IMR underwent either valve repair (n = 397) or valve
Simon Maltais et al.[71]	Retrospective study, 387 patients underwent combined CABG and MV surgery, MV repair in
Christos G et al.[66]	Prospective study, 251 patients with severe IMR underwent MV repair (n=126) or MV repla
Roberto Lorusso et al.[67]	Retrospective study, from 1996 to 2011, 1006 patients with chronic IMR and LV dysfunction
Antonio Lio et al.[70]	Retrospective study, from July 2002 to February 2011, 126 patients with IMR and LVEF <4
D Goldstein et al.[68]	Prospective study, 251 patients with severe IMR underwent MV repair or chordal-sparing re
V Shumavets et al.[72]	Retrospective study, from 2000 to 2012, 870 patients with coronary artery diseases and signi

IMR: ischemicmitral regurgitation; CABG: coronary artery bypass grafting; LVESVI: left ventricular end-systolic volume index; MV: mitral valve; LVEF: left ventricular ejection fraction.

Table 2. Studies Describing MV Reserve Function During the Cardiac Cycle in Humans

Study	Summary
Gogoladze G et al. [77]	Prospective study, 10 normal;10 with 2 to 4+ FMR. 3D TEE; data analyzed using QLAB quan
Cobey F C et al, [73]	Prospective study, 25 patients with FMR underwent cardiac operations. 3D TEE, TomTec Ima
Bouma W et al.[80]	Prospective study, 50 patients with IMR. 3D TEE; data analyzed using TomTec Imaging Syste
Dan Wei et al.[7]	Prospective study, 20 patients underwent MV valvuloplasty for mitral regurgitation were inclu
Cho E J et al. [75]	Prospective study, 47 patients with chronic severe MR and preserved LV systolic function sche
Feroze Mahmood et al. [74]	Prospective study, IMR group, n=66; control group, n =10. 3D TEE; measurements taken usi
Bretschneider C et al. [76]	Prospective study, 48 patients with chronic MI. The Magnetic Resonance Imaging (MRI) proto

FMR: functional mitral regurgitation; 3DTEE: 3-dimensional transesophageal echocardiography; MA: mitral annular; MV: mitral valve; IMR: ischemicmitral regurgitation; MI: myocardial infarction; PM: papillary muscles.