Acta Biomed 2015; Vol. 86, N. 1: 17-26

Review

Surgical treatment for functional ischemic mitral regurgitation: current options and future trends

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Summary. There is an increasing number of patients with mitral regurgitation secondary to dilated cardiomyopathy. Ischemic mitral regurgitation is a common complication of left ventricular dysfunction related to chronic coronary artery disease: it is present in 10–20% of these patients and is associated with a worse prognosis also after coronary revascularization. Currently, coronary artery bypass grafting combined with restrictive annuloplasty is the most commonly performed surgical procedure, although novel approaches have been used with varying degrees of success. The suboptimal results obtained with the commonly used surgical approaches require the development of alternative surgical techniques with the aim to correct the causal mechanisms of the disease. In fact the pathophysiology of ischemic mitral regurgitation is multifactorial involving global and regional left ventricular remodeling, as well as the dysfunction and distortion of the components of the entire mitral valve apparatus. The purpose of this review is to present the current surgical techniques available for the treatment of ischemic mitral regurgitation and to discuss novel approaches to the repair of this complex disease. (www.actabiomedica.it)

Key words: cardiac surgery, ischemic mitral regurgitation, cardiomyopathy

Introduction

Nearly 6 million Americans suffer from heart failure (1) and many of these patients have a dilated cardiomyopathy caused by ischemic or idiopathic dilated etiology. Functional mitral regurgitation (MR) is a frequent complication of dilated cardiomyopathy and it is caused by a dilated annulus with tethered papillary muscles resulting from a dilated, nonelliptical, spherical ventricle, in the presence of a structurally normal valve and subvalvular apparatus. Functional MR worsens the symptoms of chronic heart failure and it has been well demonstrated that it is a significant factor for increased mortality in the natural history of these patients (2).

The exact prevalence of ischemic MR remains unclear. Left ventricular angiography performed after an episode of myocardial infarction found at least moderate or severe MR in 3% of these patients. Doppler-echocardiographic studies reported a prevalence of ischemic MR ranging from 35% to 59% after MI, and from 6% to 17% of moderate to severe MR (3-4).

Patients with ischemic MR have a worse prognosis than those presenting with coronary artery disease alone, and this poor outcome is related to the progression of severity of valve regurgitation (5). Medical therapy is limited in its efficacy. A combination of angiotensin-converting enzyme inhibitors and beta-blockade reverses negative left ventricular remodeling, although a decrease in the incidence or severity of IMR has not been demonstrated by this approach (3).

It remains a matter of debate whether simple mitral annuloplasty could allow improved long-term

survival in chronic ischemic cardiomyopathy. Some authors supported undersized annuloplasty ring implantation, stressing the concept that a small ring can facilitate reverse remodeling to a more elliptical ventricular shape (6-7). However, the optimal management of patients with concomitant functional MR remains to be established (8-10).

Moreover, the persistence and recurrence rates of mitral regurgitation remain high in patients undergoing restrictive annuloplasty and coronary artery bypass grafting (CABG). No survival benefit has been demonstrated at 10 years compared with CABG alone (10).

The benefit of mitral valve plasty (MVP) compared with mitral valve replacement (MVR) has been shown convincingly in patients affected by degenerative mitral regurgitation (MR), but such an advantage remains controversial in the presence of chronic ischemic MR (11-13), particularly in case of concurrent left ventricular dysfunction (14).

To cast further light to these issues we have reviewed the scientific literature in order to examining historical and current surgical approaches to this disease, and to better elucidate successful repair strategies and target future improvements.

Mechanisms of mitral regurgitation secondary to chronic ischemic cardiomyopathy

Regardless of the specific etiology of heart failure, all patients with left ventricular dysfunction experience remodeling of the ventricle towards a progressive dilation (15). Normal function of the mitral valve apparatus depends on a correct interaction among the mitral annulus, the leaflets, the sub-valvular apparatus, and the subtending myocardium (16).

Systolic tethering of mitral leaflets is a very important causative mechanism of ischemic MR (3, 17). As a consequence of MI, the left ventricle (LV) becomes less elliptical and more spherical. This remodeling displaces apically and laterally the papillary muscles, thereby causing a tethering of the mitral leaflets. The displacement of papillary muscles and the wall motion abnormalities of the underlying myocardium induce valve tethering and restrict systolic leaflets motion, resulting in apical and posterior displacement of mitral valve. Another important concept is that the severity of MR is closely correlated to the mitral valve tenting area, that is the surface enclosed between the annulus and the leaflets (18), which is a reliable marker of tethering severity.

Two main patterns of leaflet tethering have been reported in patients affected by ischemic MR (19). Asymmetric tethering is characterized by a regional LV remodeling with displacement of the posteromedial papillary muscle causing posterior leaflet restriction. As a consequence, the MR jet is generally eccentric and oriented toward the posterior wall of the left atrium. The second pattern is based on a symmetric tethering generally resulting from a global LV remodeling with a displacement of both papillary muscles and with annular dilatation: this condition results typically in a central MR jet. There is a correlation between both these patterns and the localization of MI. Whereas the asymmetric pattern is often related to inferior or posterior MI, the symmetric one is predominantly related to anterior MI or to both anterior and posterior MI. Ischemic MR is a dynamic lesion that may vary over time. MR severity may change dynamically during exercise (20). Moreover, the MR severity, which increases during exercise, may limit the increase in LV stroke volume and the exercise capacity of patients with congestive heart failure (21). The presence of such a functional MR creates a vicious cycle, worsening left ventricular volume overload, leading to further dilatation and then to a more severe MR.

Treatment of ischemic mitral regurgitation

1) Medical treatment

The main purpose of the medical therapy in patients with ischemic MR is to prevent, delay or reverse LV remodelling and heart failure, as well as to prevent myocardial ischemia. Nevertheless, ACEIs, nitrates, and diuretics may reduce the severity of MR acutely (22) or in the longer term (23). The combination of β blockers and ACEIs inhibits progressive LV remodeling, and is associated with a significant reduction in MR severity in patients with chronic heart failure (24).

2) Cardiac resynchronization therapy

Cardiac resynchronization therapy (CRT) has a beneficial effect on functional MR, through reverse LV remodeling, improved LV systolic function (25), and improved coordinated timing of electro-mechanical coupling of papillary muscles. However, this effect of CRT is reversible: in fact CRT withdrawal after 6 months of implantation acutely leads in MR recurrence (26). Non-responders patients represent approximately 30% of chronic heart failure patients treated by CRT, and ischemic heart disease is an independent predictor of poor clinical response (27). Thus, the benefit of CRT may be only limited in patients with ischemic MR, especially in those with important LV dilation and leaflet tethering, or in the presence of a scar at the LV pacing lead tip (28), which may obstacle resynchronization. The long-term impact of CRT on LV remodeling and MR severity remains to be determined. However, in a study involving a population including a high percentage of patients with functional nonischemic MR, cessation of biventricular pacing after long-term implantation led to impaired LV systolic function and worsening of MR, providing indirect evidence to support of the long-term benefit of CRT (29).

3) Surgical strategies

a) Indications

Mitral valve plasty (MVP) or mitral valve replacement (MVR) can lead to the interruption of the cyclic problem related to the progressive worsening of MR, preventing further ventricular dilation and thus prolonging survival and improving quality of life. The choice to repair or replace the mitral valve concomitant with the coronary revascularization is controversial because of the retrospective nature of the available scientific results and the lack of evidence of the optimal timing and the correct indications for the correction of functional MR. Severe MR (4+) associated or not with symptoms of heart failure remains a mandatory indication to surgical correction, independently from the need for coronary revascularization. On the other hand the benefits of treating moderate (3+) MR in the absence of heart failure symptomatology remains a matter of debate.

In the setting of coronary artery bypass grafting (CABG), myocardial revascularization alone in patients with chronic ischemic MR has a higher hospital mortality than in patients without valve insufficiency (30). These data suggest that concomitant severe ischemic MR should be addressed during CABG to improve survival and quality of life.

In patients with moderate functional MR, several studies have compared the results of CABG alone versus CABG with concomitant MVR (31-33) . Some of them proved no improvement in survival after CABG with concomitant MVR (31-32, 34) whereas others found a significant improvement in follow-up survival (33, 35) . Although it remains unclear whether there is a survival benefit with repair, it is well known that there are improvements in symptoms, exercise tolerance, and reverse ventricular remodelling (35). Regardless of the controversial evidence, there is an increasing trend toward performing MVR at the time of CABG (36).

The current indications regarding mitral valve intervention in patients with severe left ventricular dysfunction are controversial because no prospective randomized trials exist that demonstrate a survival benefit. The current American College of Cardiology/ American Heart Association valve disease guidelines state that MV repair is recommended in preference to MVR when surgical treatment is indicated for patients with chronic severe primary MR limited to the posterior leaflet (Class of recommandation I, Level of evidence B). Moreover, MV repair is recommended in preference to MVR when surgical treatment is indicated for patients with chronic severe primary MR involving the anterior leaflet or both leaflets when a successful and durable repair can be accomplished (Class of recommandation I , Level of evidence B) (37).

Even though MVP has been demonstrated to be feasible with limited mortality, patients unlikely to benefit from mitral valve intervention include those with irreversible pulmonary hypertension and chronic advanced right ventricular dysfunction. Ideal operative candidates have a less spherical ventricle, have a less fibrotic myocardium, and demonstrate contractile reserve (38). Several studies have demonstrated large left ventricular end-diastolic volume (>65 mm), large left

ventricle end-systolic volume (>51 mm), large left atrial volume, poor left ventricle sphericity index, and very low ejection fraction as predictors of lack of reverse remodeling after MVP or MVR and hence reduced physiological benefit to the patient (39-40).

b) Type of surgery

In patients with mild to moderate ischemic MR, a consistent rate of persistent MR was reported early after isolated CABG (41-42), although improvement in MR severity could be predicted by a large extent of viable myocardium and absence of dyssynchrony between papillary muscles. These data suggest that isolated CABG is not sufficient to reduce MR and to improve outcome in many patients with mild moderate ischemic MR, arguing for concomitant MVP. Two large studies reported discrepant results showing that adding MVP to CABG significantly reduces the degree of MR without affecting long-term survival (43). These results therefore suggest that it is LV impairment rather than MR severity that is the main prognostic determinant in patients with ischemic MR, and that adding MVP to CABG reduces MR and improves functional outcome in the early postoperative phase but has no or minimal long-term functional and survival impact. However, these studies were limited by their retrospective nonrandomized design and by the lack of quantitative MR assessment.

One of the questions not completely answered in patients with ventricular dysfunction and MR is if the optimal choice for the treatment of ischemic MR is to repair or replace the mitral valve. Prosthetic valve function is not influenced by worsening LV negative remodeling. Therefore, MVR might provide a good alternative to MVP in this setting, but it carries on an increased risk of several complications including prosthesis patient mismatch, structural valve failure, thromboembolism, and anticoagulant-related bleeding. Unadjusted short- and long-term survival is generally reported to be lower with MVR than with MVP (44-45), but patients undergoing MVR are frequently older and have more comorbidities. Moreover the results in patients with ischemic MR seem strictly related to the baseline characteristics (46), particularly to the underlying pathophysiology of MR and the patient's clinical status rather than to the type of procedure.

There are many types of repair, without a clear consensus in the literature. Two large studies suggest that patients undergoing MVP had improved perioperative survival, shorter length of stay, and improved long-term survival than those undergoing MVR, although they did not include patients with heart failure (47-48). Another study showed a similar trend favoring MVP over MVR in terms of 5-year survival as long as the mitral valve coaptation depth was less than 10 mm (49). When it exceeds this depth, replacement should be performed taking care to preserve the subvalvular apparatus. The preservation of the subvalvular apparatus seems to result in superior left ventricular remodelling (50). MVP has also been associated with greater improvement in NYHA functional class (51). Gillinov et al (14) reported 5-year survival of 58% for valve repair and 36% for replacement. However, the MVP group had significantly fewer NYHA class IV patients and less severe MR preoperatively. In the propensity matched poorer risk groups (more severe congestive heart failure, MR, and emergency surgery) and for the group as a whole, there was no difference between repair and replacement, and 5-year survival was uniformly <50%.

On the other hand in a recent propensity-based analysis, MVR provided similar freedom from moderate-to-severe MR than MVP following a mean 2.5-year follow-up, suggesting that MVR remains a viable option for the treatment of ischemic MR (52). About the question on the optimal surgical strategy for the correction of ischemic MR, recently, an Italian multicenter, 15-year, retrospective, propensity score (PS)-matched analysis of a robust patient cohort was designed to elucidate comparative effectiveness of MVP and MVR in association with coronary artery bypass grafting (CABG) and in the presence of left ventricular dysfunction (53). Careful patient selection was carried out purposefully to focus on a homogeneous patient population, eliminating some common confounding factors characterizing published series on the matter, and to define early and long-term outcomes. Of 1006 patients with chronic ischemic MR and impaired left ventricular function 298 (29.6%) underwent MVR whereas 708 (70.4%) received MVP. Propensity scores were calculated and 244 pairs of patients were matched.

Early deaths were 3.3% in MVP versus 5.3% in MVR (P=NS). Eight-year survival was 81.6% ±2.8% and 79.6% ± 4.8% (P = 0.42), respectively. However, actual freedom from all-cause reoperation and valve-related reoperation were 64.3%±4.3% versus 80% ± 4.1%, and 71.3% ±3.5% versus 85.5% ± 3.9 in MVP and MVR, respectively (P <.001). Actual freedom from all valve-related complications was 68.3% ± 3.1% versus 69.9% ±3.3% in MVP and MVP, respectively (P = 0.78). Left ventricular function did not improved significantly, and it was comparable in the 2 groups postoperatively. The authors concluded that MVR is a suitable option for patients with chronic ischemic mitral regurgitation and impaired left ventricular function. It provides better results in terms of freedom from reoperation with comparable valve-related complication rates.

c) Persistence/Recurrence of MR following MVP

A high rate of persistent and/or recurrent MR following restrictive MVP was observed, which was correlated with the length of follow-up (4). Whereas the prevalence of ≥2+ MR ranges between 15% and 25% in the early postoperative phase (<6 months), it increases thereafter to reach approximately 70% at 5 years. De Bonis et al (54) reported a MVP failure rate of 9%, although other studies, such as that from the Cleveland Clinic, have demonstrated very high recurrence (30%-40%) of severe (3-4+) MR after annuloplasty as soon as 6 months after surgery (55). These results are in contrast to the findings by Spoor and Bolling (56) in which minimal recurrent MR was seen up to 4 years after MR with rigid annuloplasty by using a ring that was down-sized by 2 sizes.

The persistence of MR following MVP seems to be related to the persistence or worsening of the tethering of mitral valve leaflets, particularly of the posterior leaflet. Because the anterior portion of the mitral annulus is fixed to the aortic root, restrictive MVP displaces the posterior annulus anteriorly but the posterior leaflet remains tethered posteriorly, changing the valve closure in a single anterior leaflet process (57). This persistent tethering of the posterior mitral leaflet is the cause of the residual MR early after MVP (58) in both symmetric or asymmetric tethering patterns. Conversely, MR recurrence likely relates to progression of LV remodeling, with increased LV volume and sphericity and thereby valve tethering (59). The postoperative persistence or recurrence of even mild MR may contribute to negative LV remodeling, leading to a "vicious circle" and has been demonstrated to be associated with worse outcome (60).

Critiques of the failure after annuloplasty are based on the use of a partial rather than complete ring, and on the use of a flexible rather than rigid ring. It has been found that there is an almost 4-fold increase (9.5% vs 2.5%) in recurrence rate of ischemic MR by using a flexible ring as compared with a nonflexible ring in patients with a preoperative ejection fraction <30% (56). Restrictive MVP may create some degree of functional mitral stenosis (61), a hemodynamic sequela associated with higher pulmonary arterial pressure and reduced functional capacity. In conclusion, restrictive MVP combined with CABG may provide good results in selected patients (ie, in patients with a mild or moderate dilated left ventricle and with mild-to-moderate alteration of mitral valve geometry), but the procedure is associated with a high rate of persistent/recurrent MR and seems to guarantee no survival benefit in the other complex patients.

Several investigators have attempted to identify the preoperative predictors of MVP failure. A preoperative LV end-systolic diameter ≤51 mm or LV end-diastolic diameter ≤65 mm was found to be predictors of successful reversal of LV negative remodeling following restrictive MVP in patients with chronic ischemic MR, because they demonstrated high sensitivity (81% and 89%) and specificity (81% and 89%). (62). A larger preoperative mitral annulus diameter, a mitral valve tenting area, and MR severity on preoperative transesophageal echocardiography independently predicted MVP failure (63). Using transthoracic echocardiography, a mitral valve tenting area ≥2.5 cm2, a coaptation distance ≥1 cm, and a posterior leaflet angle ≥45° predicted persistent MR following MVP (49, 58). The tethering of the distal anterior mitral leaflet was found to be even a best predictor of recurrence of functional MR following annuloplasty (64). Finally, systolic sphericity index, myocardial performance index, wall motion score index, and end-systolic volume were also found to be independent predictors of recurrent MR (65).

Novel approaches in the treatment of ischemic mitral regurgitation

New annuloplasty rings specifically have been designed for functional MR (66-67), characterized by various shapes with the aim to improve the durability of valve repair in this setting.

New surgical therapeutic strategies have been directed at the mitral leaflets. Kincaid et al. introduced anterior leaflet augmentation with a pericardial patch combined with annuloplasty and CABG to address the problem of tethered leaflets in chronic ischemic mitral regurgitation (68). Others have advocated patch enlargement of the posterior leaflet which seems to provide good early and intermediate-term mitral valve competence (69).

Another area of directed focus is the subvalvular apparatus. Division of secondary chordae (chordal cutting) has shown effectiveness in decreasing leaflet tethering and MR without altering LV function (70). Subvalvular techniques that address the papillary muscle displacement of chronic IMR include relocation of the posterior papillary muscle, papillary muscle approximation, the papillary muscle sling, and papillary muscle repositioning by infarct plication (71-72). Plication of an infarct zone resulted in repositioning of the papillary muscle toward the mitral annulus, reducing chronic IMR (73).

External ventricular restraint devices continue to be used in order to reverse negative left ventricular remodeling. Hung et al (74) reported their experience with the use of a localized patch with an inflatable epicardial balloon, placed posteriorly on the beating heart. The volume in the balloon of the patch can then be adjusted allowing a modification of the movement of the ventricular wall reducing papillary muscle displacement. Another external restraint device, the Corcap Cardiac Support Device (Acorn Cardiovascular Inc, St. Paul, MN, USA), has been shown to have a long-term beneficial effect on left ventricular reverse remodelling (75). A third restraint device, the Coapsys device, treats papillary muscle displacement via inward tension on a transventricular strut anchored epicardially. Trials of the Coapsys device have demonstrated significantly greater left ventricular reshaping than annuloplasty alone (76).

Several percutaneous strategies for treating functional MR are being investigated. A percutaneous mitral annuloplasty device (CARILLON) has been designed to be inserted into coronary sinus to improve leaflet coaptation. In animal models of ischemic MR, this device has demonstrated to be effective (77). Initial data from clinical trials have demonstrated safety and feasibility for the CARILLON device (78). Additional percutaneous devices have attempted to improve valvular competence by using a clip (MitraClip, Abbott Laboratories, Abbott Park, IL) to re-approximate the valve leaflets, much like an Alfieri-type repair. Analysis in a high surgical risk population demonstrates feasibility and a hemodynamically significant reduction in MR, although many patients are left with lesser degrees of MR, limiting its widespread use. Since the publication in 2011 of the results of the Everest II trial (79) (primarily designed to investigate patients with organic MR and a principal regurgitant jet originated from malcoaptation of the middle scallops of the anterior and posterior leaflets) showing a trend toward a better outcome – compared to surgery – with percutaneous Mitraclip device in patients with functional mitral regurgiation, percutaneous replication of the surgical edge-to-edge technique by Mitraclip device has widened in the cardiological community. However, the subanalysis of patients with functional mitral regurgitation in that trail was not prespecified in the study protocol; thus, those results must be considered as only exploratory and descriptive. Apart from the Everest II trial, few data from a single-center experience exist comparing surgery with percutaneous techniques for functional mitral regurgitation. In particular, Taramasso et al. (80) recently demonstrated that Mitraclip resulted in lower hospital mortality and shorter length of stay compared to surgery in patients with functional mitral regurgitation, although higher freedom from residual mitral insufficiency was found in the surgical group both at discharge (0 vs 9.6 %) and at follow-up.

It is an exciting time in the management of heart failure because technology applied to heart surgery is continually evolving and will allow more interesting cellular and novel device therapies for the treatment of functional MR secondary to dilated cardiomyopathy.

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Received: 1 April 2014
Accepetd: 19 January 2015
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