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Mitral valve repair in heart failure

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Abstract

Mitral regurgitation (MR) is a frequent complication of end-stage heart failure. Historically, these patients were either managed medically or with mitral valve replacement, both associated with poor outcomes. Mitral valve repair via an 'undersized' annuloplasty repair is safe and effectively corrects MR in heart-failure patients. All of the observed changes contribute to reverse remodeling and restoration of the normal left-ventricular geometric relationship. Mitral valve repair offers a new strategy for patients with MR and end-stage heart failure. © European Society of Cardiology. All rights reserved.

Keywords: Mitral regurgitation (MR); Mitral valve repair; Annuloplasty

1. Introduction

Heart failure is currently one of the leading causes of hospitalization. Heart failure will become even more of a medical challenge as average life expectancy continues to rise. Despite significant improvements in maximal medical management, approximately 50% of patients with heart failure are dead within 3 years of clinical presentation. While heart transplantation is now considered standard treatment for selected patients with severe heart failure, it is only applicable to a small % of these patients. Transplantation is limited, both by the small number of donor hearts available, and its inapplicability in the older patient or those with comorbid medical conditions that would preclude them from consideration for transplantation.[1] In an effort to address this problem, alternative and new surgical strategies have evolved, including coronary artery revascularization [2,3], mechanical circulatory support [4–6], cardiomyoplasty [2,7], left ventricular myoreduction [8,9], and mitral valve repair [10–14].

Functional mitral regurgitation is a significant complication of end-stage heart failure, and may affect almost all heart-failure patients as a pre-terminal or terminal event. The mitral regurgitation develops secondary to an alteration in the annular-ventricular apparatus [15] and altered ventricular geometry [16], which results in incomplete leaflet coaptation. In ischemic heart failure this can be attributed to papillary or lateral wall muscle dysfunction, and in non-ischemic heart failure it can be ascribed to annular dilation and chordal tethering [17], all as a result of dysfunctional remodeling. Mitral regurgitation exacerbates the volume overload [18] of the already dilated ventricle, with further progression of annular dilation, increased left ventricular wall tension, worsening mitral regurgitation and increased failure, which predicts a poor outcome [19].

Historically, the surgical approach to patients with functional mitral regurgitation was mitral valve replacement, and little was understood of the adverse

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consequences that interruption of the annulus-papillary muscle continuity had on left ventricular systolic function [20]. This procedure was associated with very high mortality rates [21,22]. It is in this population of patients that the concept of the 'pop-off' effect of mitral regurgitation originated, that is, reversal of blood flow was somehow beneficial to the patient in heart failure. It has been demonstrated in a number of studies that preservation of the annulus-papillary muscle continuity is of paramount importance to preservation of left ventricular function [23,24]. It was the excision and disruption of the subvalvular apparatus that accounted for the significant loss of systolic function and led to the poor outcome in the earlier patients who underwent mitral valve replacement [25,26]. Preservation of the mitral valve apparatus and left ventricle in mitral valve repair (in rheumatic and degenerative mitral valve disease) has been demonstrated to enhance and maintain left ventricular function and geometry with an associated decrease in wall stress [27,28]. This procedure has been shown to be safe, with a significant decrease in operative morbidity and mortality, and good long-term outcomes [29–32].

In order to address the issue of heart failure and mitral regurgitation, the anatomy of the mitral valve must first be understood. The determination of mitral competence depends on an understanding that the mitral valve apparatus consists of the annulus, leaflets, chordae tendinae, papillary muscles, and the entire left ventricle. Maintenance of the chordal, annular and subvalvular continuity and mitral geometric relationships are important in the preservation of overall ventricular function, and may be even more important in those patients with compromised left-ventricular function. When selecting a surgical approach to the problem of heart failure, it must, therefore, first be recognized that this is a ventricular problem, and therefore a solution directed solely at the mitral valve, neglecting the left ventricle, is not ideal. Excision of a portion of the left ventricular wall does not address the issue directly, and in fact can further disrupt the mitral valve apparatus by disruption of the left ventricular wall.

2. Surgical procedure

At the University of Michigan between June 1993 and January 1999, 92 patients with end-stage heart failure and refractory severe mitral regurgitation were studied prospectively. All patients had NYHA class III or IV heart failure despite receiving maximal medical therapy (digoxin, diuretics, and afterload-reducing agents), and had severe left ventricular systolic dysfunction as defined by an ejection fraction $< 25\%$ on angiography or radionuclide studies. Patient ages ranged from 33 to 81 years (mean 60 ± 5 years). Patients were equally divided between non-ischemic dilated heart failure and end-stage ischemic heart failure without ongoing ischemia, as defined by a negative dobutamine echocardiogram and/or a negative positron emission tomography scan, and therefore would not be expected to gain any improvement from a coronary artery revascularization procedure. The mean duration of documented heart failure was 3 ± 6 years (range 0–16). Pre-operative ejection fraction ranged from 8 to 24% (mean 14%). At surgery, all patients underwent mitral valve reconstruction with implantation of an undersized flexible annuloplasty, remodeling ring; no patients underwent a complex mitral valve repair. Additional procedures included, 38 DeVega tricuspid annuloplasties, seven single coronary artery bypass grafts in patients with coronary artery disease discovered as an incidental finding, and implantation of one ICD patch. Mitral valve reconstruction was performed via median sternotomy with cardiopulmonary bypass, utilizing hypothermic, blood cardioplegic arrest in patients undergoing a first operation, and via right thoracotomy, utilizing cold fibrillatory arrest in 38 redo patients who had undergone prior coronary artery bypass grafting.

3. Results

Intra-operative transesophageal echocardiography revealed no mitral regurgitation in most patients, and mild regurgitation in seven at the end of the procedure. All patients were weaned from cardiopulmonary bypass and maintained in the immediate post-operative period on milrinone and norepinephrine infusions.

There was one intra-operative mortality from right ventricular failure, in a patient who died despite both the use of the intra-aortic balloon pump (IABP) and mechanical right ventricular assist device support. Five patients required IABP support, but none required the use of a left ventricular assist device.

In the postoperative period in our study, seven patients required longer than 24 h of mechanical ventilator support, and only three patients for longer than 48 h. There was one late wound infection. There were no other in-hospital deaths and the mean length of stay following the procedure was 9 ± 4 (range 4–37) days. There were five 30-day mortalities (overall operative mortality was 5%), one due to cardiac failure, one due to a stroke, two due to multisystem organ failure, primarily related to underlying pulmonary failure, and the one intra-operative death mentioned previously.

We followed these patients for 1–68 months (mean 38), with a 1- and 2-year actuarial survival of 80 and 70%, respectively. All patients remained on medical therapy for their heart failure. Patients did not undergo routine placement of ICD devices, nor were they placed on amiodarone therapy unless clinically indicated. On immediate post-operative echocardiograms, the mean trans-mitral diastolic gradient was 3 ± 1 mm Hg (range 2–6), there were no cases of mitral stenosis or systolic anterior motion (SAM). At 24-month follow-up all remaining patients, without loss to follow-up, were in NYHA Class I or II, with a mean ejection fraction of 26%, and with a demonstrated improvement in ejection fraction in every patient. A marked reduction in regurgitant volume and fraction was demonstrated. The NYHA class improved for every patient individually, and from a mean of 3.2 ± 0.2 to 1.8 ± 0.4 for the entire group. All patients reported subjective improvement in functional status. In those patients for whom preoperative data was available for comparison, peak maximal volume of O_2 use during a 6-min walk rose significantly, from a mean of 14.5 to 18.6 ml O_2/kg/min. The matched preoperative and 24-month postoperative echocardiographic data are recorded in Table 1. All patients had a reduction in sphericity index and regurgitant fraction. All patients demonstrated improvement in left ventricular ejection fraction, cardiac output, and end diastolic volumes. There have been 26 late deaths in this group of patients. This number includes three patients who had further progression of disease and had undergone transplantation, and two related to complications following other operative procedures. The other deaths have resulted from progression of heart failure ($n = 8$), despite no significant return of mitral regurgitation, sudden ventricular arrhythmia ($n = 12$, 8 in ischemic patients) and one suicide.

4. Discussion

For patients with dilated heart failure, mortality is directly related to the severity of left ventricular systolic dysfunction [19]. In addition, increased chamber sphericity and, more importantly, the presence of mitral insufficiency [33] are markers of a worse prognosis. In review of these types of patients, 1-year mortality has been reported between 54 and 70%. Furthermore, in a study of 28 patients awaiting transplantation, with an ejection fraction of 25% or less, 1-year survival was only 46%, and independent predictors of death were low forward-stroke volumes, a history of ventricular arrhythmia, and mitral regurgitation [34]. The patients presented in our study therefore represent a group with a very high-predicted mortality.

The pathogenesis of mitral regurgitation-related myopathy is multifactorial. In the absence of organic disease, mitral regurgitation is predominantly thought to occur as a result of progressive dilation of the mitral annulus, with subsequent loss of coaptation of the valve leaflets. A large leaflet area is normally required for coaptation, because mitral leaflet area is 2.5 times greater than the area of the mitral valve orifice. As more mitral leaflet tissue is utilized for coverage of the enlarging mitral valve orifice, a critical reduction in the leaflet tissue available for coaptation is reached, and a central regurgitant jet of 'functional' insufficiency begins to develop [15,35]. Therefore, the most significant determinant of mitral valve coaptation, leaflet orifice area, and mitral regurgitation is the dimensions of the mitral valve annulus. The left ventricular dimension appears to be a less important factor in functional mitral regurgitation; chordal length and papillary muscle length are not significantly different in people with idiopathic heart failure with or without mitral regurgitation [15].

In ischemic heart failure, the mechanisms that contribute to mitral regurgitation are complex. They may include 'functional' mitral regurgitation, through dilation of the mitral valve annulus, and 'papillary muscle dysfunction', which is an unsuccessful coordination of the entire mitral valve apparatus rather than simply an isolated disorder of the papillary muscle [36]. These ischemia-related changes are also thought to result in an insufficient area of coaptation of the mitral leaflets.

In a recent study of patients with severe heart failure who were managed with pharmacological agents (diuretics, nitrates and afterload-reducing

Table 1
Echocardiographic data in heart-failure patients

ECHO parameter	Pre-operative	Post-operative[a]	P value
End diastolic volume (ml)	281 ± 86	206 ± 88	< 0.001
Ejection fraction (%)	16 ± 5	26 ± 8	0.008
Regurgitant fraction (%)	70 ± 12	13 ± 10	< 0.001
Cardiac output (l/min)	3.1 ± 1.0	5.2 ± 0.8	0.001
Sphericity index (D/L)	0.82 ± 0.10	0.74 ± 0.07	0.005

[a] 24 months.

Table 2
Cytokine and receptor levels in heart-failure patients

	TNF-α (pg/ml)	TNF-R1 (pg/ml)	TNF-R2 (pg/ml)	IL-6 (pg/ml)	IL6-R (ng/ml)
Pre-op.	3.5 ± 1.3	931 ± 187	1989 ± 381	6.1 ± 6.6	36.0 ± 5.2
Post-op. (6 month)	2.8 ± 1.1	774 ± 177	1450 ± 254	2.9 ± 1.8	31.2 ± 8.1
P value	0.02	< 0.01	< 0.01	0.13	0.15

agents), the observed decrease in filling pressure and systemic vascular resistance led to a reduction in the dynamic mitral regurgitation associated with their heart failure. This was attributed to a reduction in the regurgitant orifice area related to the decrease in left ventricular volume and annular distension [37]. This complex relationship between mitral annular area and leaflet coaptation may explain why, paradoxically, an undersized 'valvular' repair can help a 'muscular' problem. Although significant undersizing of the mitral annulus was employed in our study to over-correct for the zone of coaptation, no mitral stenosis was induced, nor was any SAM of the anterior leaflet noted. SAM was avoided, due to widening of the aorto-mitral angle and increased left ventricular size seen in myopathic patients. In addition, acute remodeling of the base of the heart from the undersizing of the mitral annular ring may also contribute to the improvement seen in these myopathic hearts. This may re-establish the ellipsoid shape and somewhat normal geometry to the base of the left ventricle.

Increases in left ventricular preload, wall tension, diastolic volume, and stroke volume, are all documented ventricular adaptations to severe mitral regurgitation. Maintenance of forward flow becomes difficult, because up to 50% of the stroke volume is ejected into the left atrium, even before the aortic valve opens [38]. Eliminating the regurgitant volume can increase ventricular efficiency dramatically.

Successful mitral valve repair may have beneficial effects on coronary flow. One study assessed coronary flow in patients without coronary artery disease before and after mitral valve reconstruction [39]. Coronary flow reserve was limited in patients with mitral regurgitation due to an increase in basal coronary flow and flow velocity, which was related to hypertrophy and increased preload (left ventricular wall stress). The restriction in coronary flow reserve improved following mitral valve reconstruction because of a reduction in the basal coronary flow and flow velocity once the left ventricular preload, work and mass were reduced [39]. Based on this study, a restriction in the coronary flow reserve would seem probable in patients with mitral regurgitation and heart failure, and an improvement in flow reserve and velocity would be expected following mitral valve repair.

Heart failure is a clinical syndrome resulting from diverse and complex mechanisms. Proinflammatory cytokines, including tumor necrosis factor-α (TNF-α), IL-1, IL-2 and IL-6, may not only be produced by the stressed myocardium, but also be responsible, in part, for myocardial depression [40–43]. Studies have demonstrated that this proinflammatory cytokine may play a role in the development of left ventricular dysfunction, heart failure, hypotension, and pulmonary edema [44–47]. There are two forms of TNF-α-specific receptors: TNF-R1 and -R2. Both receptors are found in equal proportions in the normal myocardium and TNF-α binds with equal affinity to both receptors. The negative inotropic effects of TNF-α are mediated primarily by its interaction with TNF-R1. The expression of myocardial TNF-Rs is down-regulated in the presence of heart failure, similar to that seen with the β-adrenergic receptors [44,48]. The circulating, or soluble, forms of TNF-Rs are elevated in patients with heart failure, suggesting that these receptors may be 'shed' from the myocardial cells [49]. The circulating TNF-Rs can neutralize the biological effects of circulating TNF-α [50]. Based on these observations, it has been postulated that the cardiac-tissue response to increased TNF-α levels is to increase the level of soluble TNF receptors in order to decrease the amount of bioactive TNF-α that can potentially stimulate cardiac cells [44]. At the University of Michigan we have measured levels of TNF-α, soluble TNF-R1 and -R2, IL-6 and IL-6 receptors in the pre- and post-operative period in patients undergoing mitral valve repair in the presence of heart failure (Table 2). The levels of these cytokines and their respective receptors were all decreased in these patients 6 months after mitral reconstruction. Further studies are being conducted, in which the soluble recombinant form of TNF-R is being administered to heart-failure patients in the hope of decreasing some of the clinical manifestations of failure [44].

As the availability of transplantation for treatment for patients with end-stage heart failure is limited, there has been recent interest in the altered geometry of the left ventricle in patients with severe dysfunction. This innovative work was initially described by Batista, who states that all mammalian hearts share the same ratio of mass/diameter, regardless of the size of the heart. The formula that is common to all hearts should be a muscle mass that is four times the

radius cubed ($M = 4 \times R^3$). Batista proposed that those hearts that do not comply with this relationship should undergo an operative procedure to restore the ratio back to normal [8,9]. Surgeons have attempted to normalize this relationship by left ventricular myoreduction surgery, also called partial left ventricular reduction surgery, reduction myoplasty or the Batista procedure. Batista initially reported an operative mortality of 5%, a 30-day mortality of 22%, and a 2-year survival of 55%. Unfortunately, complete and long-term follow-up was not available for these patients [9,51–53]. This procedure has met with varying degrees of success in the United States and worldwide [53–57]. The Cleveland Clinic series of 62 patients (95% idiopathic dilated cardiomyopathy) reported a 3.5% hospital mortality with seven late deaths and a 1-year actuarial survival of 82% [54]. All of the cases routinely had a mitral valve repair or replacement as part of the myoreduction procedure, which may have contributed to the relative success of the procedure in this center.

Mitral valve reconstruction alone also re-establishes a more normal left ventricular mass/volume ratio without the loss of myocardial mass [11,13]. The average left ventricular volume at 24-month follow-up in our study was over 200 ml, still quite large, while with the left ventricular myoreduction procedure, Batista has demonstrated acute reduction of LV volumes to approximately 90–100 ml at the time of operation. There is no loss of ventricular mass with the mitral valve reconstruction alone; however, an appropriate mass/volume ratio is restored. Importantly, there is an acceptable surgical mortality, both at 30 days and 1 year, for mitral valve reconstruction, which is equivalent to, or lower than, that reported for left ventricular myoreduction procedures [51–57].

One must differentiate the effect of abolishing mitral regurgitation alone versus the addition of the myoreduction. In dog models, left ventricular remodeling may be rapid and complete, with resultant regurgitant fractions of less than 30% after correction of the mitral regurgitation alone [58]. In the University of Michigan study, a decrease in sphericity index and left ventricular volume measurements were demonstrated post-operatively, and it is in these patients that the negative cycle of heart failure is interrupted and the surgical unloading of the left ventricle is achieved. These patients may be undergoing slow reverse remodeling due to the alteration of the angulation of the base of the heart, stabilization of the mitral annulus, or left ventricular unloading. Beneficial remodeling tends to occur more frequently in the patients with idiopathic, as opposed to those with ischemic, heart failure. In the hearts with end-stage ischemic heart failure the potential for remodeling may be limited, due to presence of scar in the ventricular wall.

5. Conclusion

In conclusion, mitral reconstruction via an annuloplasty ring effectively corrects mitral regurgitation in heart-failure patients and is a relatively safe procedure in a high-risk population. Not only does it appear to improve survival, but also functional status, often remarkably. While longer-term follow-up is necessary with a greater number of patients, we are encouraged by these results, and feel that mitral reconstruction offers a new strategy for end-stage heart failure.

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