Surgical treatment of functional mitral regurgitation in dilated cardiomyopathy

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Received 9 March 2011; revised 7 April 2011; accepted 9 April 2011
Available online 16 April 2011

KEYWORDS
Cardiomyopathy;
Functional mitral regurgitation;
Heart failure

Abstract  Functional mitral regurgitation is a significant complication of end-stage cardiomyopathy. Dysfunction of one or more components of the mitral valve apparatus occurs in 39–74% and affects almost all heart failure patients. Survival is decreased in subjects with more than mild mitral regurgitation irrespective of the aetiology of heart failure. The goal of treating functional mitral regurgitation is to slow or reverse ventricular remodelling, improve symptoms and functional class, decrease the frequency of hospitalization for congestive heart failure, slow progression to advanced heart failure (time to transplant) and improve survival. This article reviews the role of mitral valve surgery in patients with heart failure and dilated cardiomyopathy.

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Peer review under responsibility of King Saud University.
doi:10.1016/j.jsha.2011.04.001
1. Introduction

Dilated cardiomyopathy (DCM) is usually associated with variable degrees of functional mitral regurgitation with normal valve morphology (Strauss et al., 1987; Sabbah and Goldstein, 1993; Koelling et al., 2002; Trichon and O'Connor, 2002; Carabello, 2008). Mitral regurgitation (MR) imposes a haemodynamic load on the left ventricle (LV), which, along with the underlying cardiac injury, and in association with neurohormonal activation, results in negative ventricular remodelling, which is defined as alteration in the structure (dimensions, mass, shape) and function of the heart (Cohn et al., 2000; Dorn et al., 2003), which is characterized by progressive LV dilatation and a change to a more spherical shape (Sabbah and Goldstein, 1993; Tibayan et al., 2004). Remodelling accounts for most instances of severe MR (Levine and Schwammenthal, 2005; Beeri et al., 2008; Carabello, 2008; Neilan et al., 2008). Reversal of remodelling with both medical therapy and an LV assist device is associated with marked improvements in left ventricular function (LVF) in patients with advanced heart failure (HF) (Birks et al., 2006). However, there are no curative therapies specifically for the treatment of progressive LV dilatation, which is one of the strongest predictors of mortality (Pfeffer et al., 1992; Pieske, 2004).

To-date, clinical studies have several limitations: almost all are retrospective, observational, and mostly single centre. They all suffer from potential referral, selection, ascertainment, and reporting biases and limited general application. Studies mingle patients with ischaemic and non-ischemic cardiomyopathy with patients undergoing simultaneous coronary artery bypass surgery.

Most studies have reported centre-specific techniques for repair. While it is clear that the failing ventricle would benefit from relief of severe MR, unanswered questions remain regarding appropriateness of patient selection, acceptable peroperative mortality, and long-term survival benefit. Does surgery alter the natural course of HF? Does it reduce mortality? When is the best time for surgery? How much does MR contribute to symptoms and disease progression?

It is still unclear in the absence of randomized trials evaluating MV surgery in patients with dilated cardiomyopathy and symptomatic heart failure when to intervene surgically.

2. Mechanism of FMR

The MV in FMR is morphologically thought to be “normal”. However, some suggest that the MV in DCM is biochemically different from normal with extracellular matrix changes that are influenced by the altered cardiac dimensions. This remodelling suggests that MR in patients with HF may not be purely functional and that these valves are not “normal” (Grande-Allen et al., 2005). The MV apparatus is a complex structure composed of the mitral annulus, mitral leaflets, chordae tendinae, papillary muscles and the left ventricular and left atrial walls. A competent MV needs well coordinated function of all of these structures (Perloff and Roberts, 1972). FMR mostly results from dysfunction of one or more of these components. In DCM, ventricular dilatation causes MR through annular dilation, an increase in the interpapillary muscle distance, amplified leaflet tethering (elongation and stretch on the chordae tendinae because of cardiac enlargement) causing MV tenting, and decreased closing forces from muscle weakness and asynchrony of papillary muscle contractile timing (He et al., 1997; Yiu et al., 2000; Nielsen et al., 2002; Jimenez et al., 2003; Karagiannis et al., 2003). The final common pathway is a failure of coaptation and FMR (Spoor and Bolling, 2008). MR in these patients is primarily a function of distorted LV geometry rather than a primary valve problem and results primarily from tethering of the MV leaflets due to ventricular remodelling, specifically increased LV dilation and sphericity (Levine and Schwammenthal, 2005). It should be noted that contractile dysfunction alone in the absence of ventricular dilation or increased sphericity does not result in significant MR (Gaasch and Meyer, 2008). From a physiological point of view MR in these patients will lead to LV overload and reduction of forward stroke volume. This occurs initially in response to exercise and subsequently at rest, which in turn activates systemic and local neurohormonal systems, and cytokines that worsen cardiac loading conditions and promote negative LV remodelling and dysfunction (Mann, 1999). This might create a vicious cycle where FMR begets more FMR.

There are several predictors of FMR in DCM where MV tenting and tethering length is the most powerful predictor (Otsuji et al., 1997). Increased LV sphericity (Kono et al., 1992; Sabbah et al., 1992) annular dilation and reduced closing forces primarily “modify” tethering but are not the predominant mechanisms of MR (Levine and Schwammenthal, 2005). In the ACORN trial, LV diastolic dysfunction (LVDD) was found to play a significant role in the FMR development. The major determinant of MR severity was the tenting area, and this was best related to mitral annular area, which was strongly associated with left atrial (LA) volume. In addition, the LA volume index was highly correlated with LVDD. These findings suggest that LA enlargement caused by advanced dia-
stolic dysfunction may contribute to causing significant MR by augmenting mitral annular dilatation in DCM (Park et al., 2009).

3. Prevalence and implication of FMR in HF

FMR is a significant complication of end-stage cardiomyopathy and it may affect almost all heart failure patients as a pre-terminal or terminal event. In a Mayo Clinic series of 558 patients with the New York Heart Association (NYHA) class III–IV HF, 39% had moderate or greater MR (Starling, 2007; Patel et al., 2004). Patients with significant MR had higher mortality (p = 0.03). Koelling et al. (2002) retrospectively reviewed 1421 patients with systolic dysfunction and reported that significant FMR is present in 49% of patients with HF, 20% of patients exhibited severe MR with a consequent decrease in their 1- and 5-year survival rate (59% and 35%, respectively). Patient survival at a mean follow-up of 1 year varied inversely with MR grade (Koelling et al., 2002; Levine and Schwammenthal, 2005). Nieminen et al. evaluated 3580 patients hospitalized with acute heart failure in 133 centres and found moderate or severe MR in 43% (Nieminen et al., 2006). Robbins et al. (2003) reported that 45% of outpatients and 74% of hospitalized patients with HF had echocardiographic evidence of moderate to severe MR.

Despite similar LV dimensions, patients with MR had an increased mortality compared to those without. In a Duke University series, Trichon et al. (2003) examined a cohort of 2057 patients with symptomatic HF (NYHA II–IV functional class) and noted 56.2% to have MR, 29.8% in the moderate–severe range. Survival was decreased in subjects with more than mild MR irrespective of the aetiology of HF. Survival rates at 1, 3, and 5 years were significantly lower in patients with moderate to severe MR versus those with mild or no MR (p < 0.001). MR was found to be an independent predictor of mortality and is reportedly an indicator of poor prognosis in patients with DCM (William Abraham and Waldo, 2006; Strauss et al., 1987; Blondheim et al., 1991; Conti and Mills, 1993; Otto, 2001; Koelling et al., 2002; Robbins et al., 2003; Trichon et al., 2003; Fukuda et al., 2005). In a further study of 130 patients awaiting transplantation, the 1-year survival was only 46%.

Significant independent predictors of death for these patients with idiopathic DCM were low forward stroke volumes, with an EF of less than 25%, and MR (Stevenson et al., 1987). Other predictors are episodes of heart failure, and increased LV end-diastolic volume (Anguita et al., 1993). Most patients with DCM die from heart failure despite improvements in medical therapy. The 1-year survival was 25% in a study of medically treated patients in NYHA class IV (Rose et al., 2001).

The question then is whether such patients have a worse prognosis because of the MR or because their ventricles are more intrinsically damaged to begin with. According to the updated ACC/AHA guidelines for managing patients with HF (Hunt, 2005), MR is a poor prognostic sign for patients with end-stage cardiomyopathy. Yamano et al. (2008) studied patients with FMR during exercise and concluded that FMR was significantly exacerbated during exercise, which was strongly related to their exercise intolerance, thus, the clinical impact of FMR in patients with DCM could be more serious than can be expected by its degree at rest.

Bursi et al. examined the independent prognostic role of FMR and its impact across the severity of CHF in a large population of outpatients with systolic HF. Four hundred and sixty-nine patients were followed-up for death and heart transplant according to severity of their FMR on baseline echocardiography. The 5-year transplant-free survival was 82.7% in patients with no or Grade I FMR, 64.4% in Grade II, 58.5% in Grade III, and 46.5% in Grade IV (p < 0.0001). There was a strong association between FMR and the long-term risk of death and heart transplant. The association between FMR and events was strong and independent in patients with less severe symptoms and in those at a lower overall risk based on a propensity score analysis, while it was not significant in patients with more advanced CHF or in the high-risk subgroup. This study clarifies previous apparently discrepant results by demonstrating that FMR is an independent determinant of death and heart transplantation only in less severe CHF and in patients with a lower risk profile. This finding indicates that FMR plays a major role in the early phase of HF and should therefore be the focus of therapeutic strategies attempting to reduce it (Bursi et al., 2010).

4. Treatment of FMR in HF

There are several methods to reduce MR, including optimal medical therapy, treating arrhythmias, cardiac resynchronization therapy, cardiac passive, restraints or constraint devices, and MV surgery (Starling, 2007). Advances have been made with medical therapy and cardiac resynchronization but, despite such measures, outcomes remain poor in individuals with advanced HF (Rose et al., 2001). Surgical correction of MR is not performed frequently as a stand-alone procedure in patients whose primary problem is a dilated failing heart (Enriquez-Sarano et al., 2008). Cardiac transplantation, the ultimate therapy for end-stage HF, is plagued by the limited supply of donor hearts and the need for lifelong immunosuppression (Hosenpud et al., 2000; Miller et al., 2007; Esmore et al., 2008). It was once thought that patients with LV dysfunction and MR would suffer if their MV were made competent as they would lose the pop-off effect of MR (reversal of blood flow was somehow beneficial to LV function). The high mortality in earlier studies appears mainly related to loss of LV function by disruption of the sub-valvular apparatus because valve replacement (rather than repair) was mostly performed. The “pop-off” effect has been disproved and MV repair has been found not to add to surgical mortality (Bolling, 2002).

MV repair (MVR), specifically mitral annuloplasty (MVA), has been proposed for selected patients with FMR due to systolic HF, although supportive data are limited to observational studies. Reduction of MR by MVA using partial or complete annuloplasty rings is accomplished by reducing the septal-lateral diameter of the annulus, with resulting improved leaflet coaptation.

Bolling and colleagues 1995 demonstrated that this approach was feasible and could be conducted with reasonably low morbidity. MVA using an undersized ring effectively corrects MR in HF patient and can safely be performed in patients even with the most compromised ventricles with an operative mortality of < 5% and 75% one year survival.
(Bolling et al., 1995; Bach and Bolling, 1996). Bishay et al. (2000) at the Cleveland Clinic, demonstrated an operative mortality of 2.3% in 44 patients with severe MR and severe LV dysfunction (EF < 35%) who underwent isolated MVR or replacement demonstrated reverse ventricular remodelling, improvement in NYHA functional class, and freedom from readmission for HF of 88%, 82%, and 72% at 1, 2, and 5 years, respectively, but the majority of the patients in this cohort have organic MR. These patients were also able to tolerate higher doses of medications after repair with 1, 2 and 5-year survival rates of 89%, 86% and 67%, respectively. MV surgery offered symptomatic improvement and survival benefit in patients with severe LVD and MR and more use of this surgery for FMR in DCM patients is warranted. As surgeons gained more experience and expertise with MVR, the surgical mortality improved substantially and the use of MVR for patients with DCM has become a reasonable option (Calafiore et al., 2001). In selected patients, MV surgery, specifically MVA, in which the sub-valvular apparatus is left intact can lead to reduced ventricular size, improved LVEF and HF symptoms (Rothenburger et al., 2002; Carabello, 2004), and high-risk MV surgery may be an alternative to heart transplantation in some patients, however, this is not documented or supported by current practice guidelines. Bolling (2002) reported in a landmark study from the University of Michigan in 140 patients with NYHA class III–IV and an EF < 25% who underwent a downsized MVA with an operative mortality of 5% that the 1- and 2-year actuarial survival was 80% and 70%, respectively (Bolling, 2002). This indicates that MVA is the current standard means of correcting MR associated with end-stage DCM (Bolling et al., 1995; Bach and Bolling, 1996; Bolling, 2002; Bax et al., 2004) and has been demonstrated to improve end-diastolic volume, LV performance, HF symptoms and exercise tolerance (Bolling et al., 1998; Chen et al., 1998; Konertz et al., 2001; Badhwar and Bolling, 2002a,b; Gummert et al., 2003; Romano and Bolling, 2003, 2004; Mehr and Griffin, 2005; Jessup et al., 2006). Szalay et al. (2003) compared a posterior MV annuloplasty using a flexible ring in 121 patients with significant FMR, ischaemic (75%) and non-ischaemic (25%) with an EF < 30% and found early mortality of 6.6%, which was equal for both groups and the improvement in NYHA class was equal between groups after 1 year. Hence, MVA is effective in patients with severely depressed LVF and has acceptable operative mortality and mid-term results which are superior to medical treatment alone and comparable to cardiac transplantation. Haan et al. in 2004 studied 727 patients (LVEF < 0.30) who underwent MV surgery between 1998 and 2001 and found mortality was less than 2% for mitral MV repair (Haan et al., 2004; Gammie et al., 2007). Similar results were shown by the Mayo Clinic and Cleveland Clinic teams (Mahon et al., 2004; Ngaage and Schaff, 2004). Wu et al. performed a propensity analysis to compare MVA with medical therapy in patients with severe MR and advanced HF who underwent MVR (undersized ring) and a matched control group treated medically at the University of Michigan between 1995 and 2002 where they demonstrated 4.8% 30-day mortality with no clearly demonstrable mortality benefit conferred by MVA for significant MR with severe LV dysfunction or in the combined end-point of death, implantation of an LVAD, or urgent heart transplantation (Wu et al., 2005). A study of 289 patients with an EF \( \leq 30\% \) and FMR compared flexible and non-flexible undersized complete mitral annuloplasty rings which showed an operative mortality of 5% and less recurrence of MR with rigid rings (9.5% versus 2.5%), while in a 1–5-year survival, improvement of EF and NYHA class are comparable to others (Chen et al., 1998; Bishay et al., 2000; Bitran et al., 2001; Calafiore et al., 2001; Radovanovic et al., 2002; Spoor et al., 2006). THE RESTORE Group proposed a new surgical approach that consists of implantation of a mitral prosthesis that is smaller than the annulus with preservation and traction of the papillary muscles to reduce sparsity of the LV in end-stage cardiomyopathy. One hundred and sixteen patients with DCM underwent this procedure with the following aetiologic factors: ischaemic (68), idiopathic (43), Chagas disease (3), viral (1), and post-partum (1). All patients were in an end-stage phase requiring > 2 hospital admissions over the past 3 months, despite receiving optimal medical therapy. They reported 16.3% hospital mortality and a relatively flat late survival curve with evidence of improved clinical status, better echocardiographic parameters, and reduction in ventricular sphericity (Buffolo et al., 2006). Recently, Geidel et al. reported that the early and late results of restrictive MVA in patients with chronic MR and advanced cardiomyopathy 3.3% 30-day mortality and 91% 12 months survival with no postoperative recurrence of significant MR (Geidel et al., 2008). Similarly, data from Germany showed 7.5% operative mortality and no differences in survival after MV repair or replacement indicating that high risk MV surgery in patients with cardiomyopathy and FMR offers a real mid-term alternative method of treatment for patients with drug refractory heart failure with similar survival in comparison to heart transplantation (Rukosuwew et al., 2009). The most compelling data for the safety and efficacy of mitral valve repair for FMR comes from the MV surgery arm of the prospective Acorn trial (CorCap Cardiac Support Device, a prospective, randomized, multi-centre trial). The Acorn device is a knitted polyester sock that is drawn up and anchored over the ventricles in order to limit left ventricular dilation and remodelling and improve LVEF. Preliminary data suggest that the device produces an improvement in HF symptoms, EF, left ventricular end-diastolic dimension, and quality of life (Konertz et al., 2001; Shelton et al., 2005). The Acorn trial, showed a 98.4% 30-day survival rate, 2.1% repeat re-operation, and 85.2% 24 months survival and significant improvements in quality of life, exercise performance, and NYHA class. Furthermore, MV operations lead to improvement in LV volumes, mass, and shape. All consistent with reverse remodelling with considerable safety and efficacy (Acker et al., 2006; Grossi and Crooke, 2006; Mann et al., 2007). As a result, the improvement in LV structure and clinical function, along with a very low mortality rate, justifies strong consideration for offering MV surgery to heart failure patients who are on an optimal medical regimen. The outcomes do, however, support the hypothesis that patients with cardiomyopathy benefit from the surgical correction of the FMR. The results of this study add to a growing experience of clinical improvement with mitral valve repair (Bolling et al., 1998). Unfortunately, there is still considerable scepticism about the safety and efficacy of mitral valve surgery in patients with heart failure. The ACC/AHA guidelines published in 2005 stated that “surgical treatment
of FMR results in little, if any, survival benefit or reverse remodelling” and “it is possible that MVR for FMR reduces symptoms and improves exercise tolerance but conclusive data to support this hypothesis do not exist” (Hunt et al., 2005).

5. Percutaneous therapies

The potential for mechanical relief of MR without surgery has ignited much interest. There are two primary approaches to treating MR percutaneously: performance of an edge-to edge (Alfieri) repair with a clip or a suture which opposes the centres of the two mitral leaflets producing a double-barrel opening and reducing or eliminating MR while avoiding mitral stenosis (Webb et al., 2006), and insertion of a device in the coronary sinus to mimic the effects of a surgically-placed annuloplasty ring (Block, 2005; Feldman et al., 2005).

By inserting devices into the coronary sinus that mechan- ically alter its shape, the shape of the annulus is also altered, in turn helping to restore MV competence (Dubreuil et al., 2007; Gazoni et al., 2007). Early experience shows that these devices can be effective. However, there are several possible limitations to procedure. Firstly, the percutaneous techniques will need to be as efficacious, or nearly as efficacious, as tradi- tional MVR surgery. Although early results may be very good for the percutaneous devices, their durability will need to be closely followed. Edge-to-edge procedures do not incorporate an MVA, an important determinant of durability in the Alfieri MV technique (Maisano et al., 2003). Coronary sinus-based procedures do not account for the fact that the coronary sinus has no anatomical connections to the mitral annulus, which is in fact an intra-atrial structure, which may result in continued annular dilation and recurrent MR over time (Singh and Borger, 2005). Secondly, percutaneous MVR should not preclude the subsequent possibility of open surgical repair. Although conventional MVR early after failed percutaneous techniques has already been performed in several patients worldwide, it will be important to determine whether MVR surgery is still possible many months after a percutaneous procedure, when scar tissue and adhesions have formed. Thirdly, the risk in tra- ditional MVR is very low. Several large, single-institution series (Bech-Hanssen et al., 2003; David et al., 2003; Matsumura et al., 2003; Enriquez-Sarano et al., 2005) have reported very low rates of operative mortality and morbidity in patients with non-ischaemic MR. The bar has therefore been set very high for percutaneous MV procedures. EVEREST (Endovascular Valve Edge-to-Edge Repair Study) phase 1 clinical trial (EVEREST I) (Feldman et al., 2005), was successfully completed after enrolment of 55 patients, demonstrating feasibility and initial safety of the device with a reduction in MR in a sig- nificant proportion of patients. EVEREST II, aimed to evaluate treat- ment with the percutaneous MitraClip device compared with conventional MV surgery among patients with severe MR and an EF > 25% who were candidates for MV surgery; major adverse events at 30 days occurred in 15% of the mitral clip group versus 48% of the control group (p < 0.01 for superiority). Clinical success rate at 12 months was 67% versus 74% (p = 0.05 for non-inferiority), respec- tively (Feldman et al., 2009), and 2 years result reported mea- surable improvement in LV volume and functional class (Feldman et al., 2011). At 1 year, the MitraClip device demon- strated meaningful clinical benefits for patients with significant MR including improvements in heart function, quality of life, normal physical activity, and a decrease in cardiac symptoms. In the primary effectiveness endpoint (freedom from death, surgery for MR dysfunction, and > 2+ MR at 12 months), the MitraClip device was non-inferior to surgery at 1 year (clinical success rate of 72.4% for MitraClip patients with suc- cessful initial treatment compared to a clinical success rate of 87.8% for surgery patients). With 95% confidence, the clinical success rate of the MitraClip device falls within 25.4% of the clinical success rate of the surgical control. In the per-protocol group, 82% achieved 2+ or less mitral regurgitation versus 97% in the control group. NYHA class I or II at follow-up was 98% in the clip group versus 88% in the control group. Among patients with severe mitral regurgitation, repair with a percutaneous mitral valve clip was feasible. This therapy demonstrated improved safety at 30 days compared with sur- gery, largely by reducing the need for blood transfusion. The mitral valve clip was also non-inferior for effectiveness at 12 months. If the clip implantation proves to be feasible in high-risk and HF patients with severe LV dysfunction, even in those who do not match EVEREST or high-risk registry cri- teria because of low LVEF or large dimensions and, eventu- ally, in patients that are not responding to cardiac resynchronization therapy, it could help to solve an important clinical problem. At the moment, the MitraClip device therapy appears a promising treatment option in patients with a clear indication for MVR. It also seems appropriate for heart failure patients with severe LV dysfunction, secondary functional MR, and a substantially dilated ventricle. The current Euro- pean Society of Cardiology’s guidelines recommend MV sur- gery in patients with HF whenever they have to get re- vascularized and only in selected patients with severe FMR and severely depressed LV function, who remain symptomatic despite optimal medical therapy (IIb, level C, recommenda- tion) (Vahanian et al., 2007). It seems that elective surgical procedures for FMR are mainly necessitated by the heavy symptomatic burden of these patients. Thus, lacking a clear indication for surgical repair in high-risk surgical candidates, the MitraClip therapy might be an attractive, less invasive op- tion for these patients with a major unmet clinical need.

6. Recurrence of FMR

Recent recurrence of FMR is often explained away as being the result of a “ventricular problem”. Then why do some patients with FMR manifest a benefit from alleviating their MR. We are faced with the question of whether the lack of benefit purely is the result of recurrence or is the recurrence of significant MR; a marker for a ventricle that has passed the point of no return. In FMR, previous reports document 17–29% preva- lence of recurrent MR early or late postoperatively (Tahta et al., 2002; Spoor et al., 2006). However, the surgical approach in these series either used predominantly flexible or partial rings (Matsunaga et al., 2004; McGee et al., 2004; Kuwahara et al., 2006). In the more recent CorCap study (Acker et al., 2006) in which surgeons performed mitral valve annuloplasty with predominantly undersized rigid complete annuloplasty rings, recurrent MR was reassuringly uncommon with only 4% experiencing significant MR at 18-month follow- up. Several factors have been described to account for recur-
rent MR along with further LV remodelling and progressive LV failure. Recurrent MR is often due to progressive lateral displacement of the papillary muscles and attendant chordal tethering, severe displacement of the anterior muscle may be predictive of recurrence (Tahta et al., 2002). The data from the University of Michigan identified the use of flexible rings as a risk factor for recurrent MR (Miller, 2001; Spoor et al., 2006). Roshanali et al. (2007) pointed at an interpapillary muscle distance of >20 mm as a risk factor for recurrent MR after repair. Calafiore et al. considered tent height, defined as the distance between the mitral annulus and point of leaflet coaptation, >10 mm as a risk factor for failure after annuloplasty for IMR (Calafiore et al., 2004). The coaptation depth (CD) importance in FMR recurrence was debated where the isolated undersized mitral annuloplasty improved clinical symptoms and FMR in non-ischaemic DCM, while the pre-operative CD of 11 mm or more does not always predict recurrent MR after isolated undersized mitral annuloplasty for functional MR due to non-ischaemic DCM (Miura et al., 2008). The occurrence of reverse LV remodelling is associated with longer repair durability and a better clinical outcome compared to those with persistence or progression of the remodelling process (De Bonis et al., 2008). Lee et al. (2009) examined the Acorn trial data for the mechanisms of recurrent MR after MVR for non-ischaemic cardiomyopathy and found recurrent MR was associated with greater distal mitral anterior leaflet angle, greater coaptation depth and tenting area, larger LV volumes, and poorer LVEF. Hence, the post-operative mitral competence is highly dependent on distal anterior leaflet mobility.

7. Why benefit is so hard to find?

A positive impact on the mortality of correcting functional MR is not apparent from the existing clinical studies and may reflect inadequacies of the studies (retrospective, underpowered, poorly characterized patient subsets, absence of prospective core-lab controlled data). Symptomatic relief and functional improvement occurs in most patients although the difference versus alternative therapies is not dramatic in existing observational studies. Trials with ventricular remodelling as a surrogate endpoint will not resolve clinical effectiveness of mitral intervention. Although the investigation of Wu et al. (2005) suggests that patients receive little benefit from mitral valve annuloplasty, several questions are raised: even if the MR is corrected, the underlying muscle disease will still exist. This fact must contribute to worsened prognosis of secondary MR (Carabello, 2008). Is this lack of benefit because mitral valve surgery does not work or because a different surgical approach is needed? Is annuloplasty sufficient?

Are sub-annular, three-dimensional repairs required? We simply do not know. Well-designed, randomized controlled trials are warranted to resolve these issues. The respective roles of MV repair versus replacement in patients with advanced HF continue to evolve. Compared with patients undergoing MV replacement with chordal preservation, patients undergoing MVR have lower peri-operative mortality but a higher failure rate. Because most series to date have reported patients undergoing MV repair rather than replacement, the lack of demonstrated mortality benefit in MV surgery in advanced HF may reflect, in part, the less durable relief of MR afforded by MV repair rather than replacement. MR recurrence and operative mortality, counterbalance the benefit which is limited to specific patient subgroups that have not been predefined in the current data sets (aetiology, duration of MR, LVEF, functional class, etc.).

8. Guidelines

The lack of proven, long-term benefits of mitral valve repair or replacement for FMR is reflected in published guidelines from major societies. The 2005 ACC/AHA HF guidelines note that the effectiveness of MVR or replacement for severe secondary mitral regurgitation in refractory end stage HF is not established (Hunt et al., 2009). The 2006 Heart Failure Society of America (HFSA) practice guidelines note that isolated MVR or replacement for severe FMR in the presence of severe LV systolic dysfunction is not generally recommended (Heart Failure Society of America, 2006). The 2006 International Society for Heart and Lung Transplantation (ISHLT) guidelines for cardiac transplant candidates notes that isolated MVR (not associated with revascularization or ventricular restoration) should not be routinely performed in patients with advanced LV dysfunction and HF (Jessup et al., 2006). The current updated ACC/AHA valve disease guidelines (Bonow et al., 2008) include an appropriately cautious, but generally supportive, recommendation for consideration of MV surgery in patients with advanced HF but only if MVR or MV replacement with chordal sparing are options. The authors conclude that “…even though such a patient is likely to have persistent LV dysfunction, surgery is likely to improve symptoms and prevent further deterioration of LV function”. The ESC guidelines for the diagnosis and treatment of acute and chronic HF 2008, surgery for FMR may be considered in selected patients with severe FMR and severely depressed LVF, who remain symptomatic despite optimal medical therapy-class of recommendation IIb, level of evidence C (Dickstein et al., 2008).

9. Conclusion

Given the unproven long-term mortality benefit from MV surgery, treatment of FMR should emphasize optimal medical therapy of HF and, in appropriate patients, cardiac resynchronization therapy. MV surgery with current annuloplasty techniques in carefully selected patients with advanced heart failure should be considered before end-organ dysfunction becomes irreversible or right ventricular function becomes impaired, as such conditions increase the risk of operative intervention and impact on long-term outcomes. Taking in account the limitations, MV surgery may result in significant symptomatic and reverse remodelling benefit in patients with DCM and FMR, along with survival benefit comparable to cardiac transplantation.

Finally, MV surgery in DCM is an attractive treatment which may benefit many symptomatic patients with DCM and may be an alternative option to cardiac transplantation. The percutaneous MVR, MitraClip therapy, might be an attractive, less invasive option for these high risk patients. Its role in FMR treatment is yet to be proved.
10. Future challenges

Given the heterogeneity of remodelling, it is unlikely that a “one size fits all” option will evolve for the durable correction of severe MR in patients with advanced HF. Surgeons and interventional cardiologists will require a portfolio of options for more targeted, individualized repair of the annulus, leaflets, chordae, and the remodelled ventricle. Just as more elegant measures of myocardial reserve, more elegant measures of LV reverse remodelling may improve surgical outcome of severe MR in patients with advanced HF. Future measures of reverse remodelling viability may aggregate biomarkers, novel molecular imaging modalities, and genomic and proteomic assays of myocardial tissue. By echocardiography and MRI, patients with MR exhibit flattening of the annulus due to a reduction in the saddle-horn height. Such flattening may increase leaflet closing stress and contribute to MR. Standard annuloplasty rings are planar and do not conform to the normal saddle-shaped MV annulus. Development of three-dimensional annuloplasty rings with better conformation to the saddle-shaped annulus may provide additional reduction in leaflet closing stress and MR.

Disclosures

All authors have no conflict of interests to disclose.

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