The Role of Surgical Treatment of Severe Functional Mitral Regurgitation in Heart Failure

Khalil Fattouch, MD, PhD*, Francesco Guccione, MD, PhD

KEYWORDS

• Mitral valve • Secondary regurgitation • Surgical options • Transcatheter therapy

KEY POINTS

- Patient selection is mandatory to successful mitral valve repair in functional mitral valve regurgitation.
- Preoperative echo evaluation is critical to better evaluate the anatomic modification of the mitral apparatus.
- In light of recent randomized trials, several patients could benefit from transcatheter mitral therapy.
- Mitral annuloplasty is not effective in all patients with functional mitral valve regurgitation; meanwhile, adding surgical techniques should be performed to improve the repair durability.

INTRODUCTION

Functional mitral regurgitation (FMR) is a common clinical entity that will likely increase in the future due to predicted demographic changes. It is also associated with poor long-term survival. The anatomic structure of the mitral valve apparatus is complex and consists of several components, each of which can be affected by a variety of diseases resulting in mitral regurgitation (MR).

In primary MR, the valvular incompetence is caused by compromised or structurally disrupted components of the valve apparatus.

In secondary or FMR, the mitral apparatus is structurally normal, with the regurgitation resulting from failure of coaptation of the mitral valve leaflets without coexisting structural changes of the valve itself.

As a consequence of this, we see a systolic retrograde flow from the left ventricle into the left atrium due to reduction of the normal systolic coaptation of the mitral valve leaflets. A slow progression of the symptoms is typical for this valve disease and often ends in irreversible left ventricular dysfunction.

The pathophysiology and treatment of FMR are quite complex.

Given the complexity of its pathogenesis, a solution to correct the valvular and subvalvular dysfunction, along with the left ventricular (LV) geometric distortion associated with ischemic MR (IMR) has not yet been elucidated.[1,2]

DEFINITION OF SEVERE FUNCTIONAL MITRAL REGURGITATION

In the 2017 European Society of Cardiology (ESC) guidelines, an effective regurgitant orifice area (EROA) $\geq$20 mm^2 and a regurgitant volume (RV) $\geq$30 mL are considered as cutoff values to define severe FMR,[3] whereas in the 2017 American College of Cardiology/American Heart Association (ACC/AHA) guideline update severe FMR, similarly to severe primary MR, is defined as an EROA $\geq$40 mm^2 and an RV $\geq$60 mL.[4] Current divergences between European and American recommendations confirm that assessment of FMR severity is challenging for several reasons.

Department of Cardiovascular Surgery, GVM Care and Research, Maria Eleonora Hospital, Viale Regione Siciliana 1571, Palermo 90100, Italy
* Corresponding author.
E-mail address: khalilfattouch@hotmail.com

Cardiol Clin 39 (2021) 185–188
https://doi.org/10.1016/j.ccl.2021.01.012

cardiology.theclinics.com

1. First, lower EROAs ($\geq$20 mm^2 vs $\geq$40 mm^2) have been shown to be associated with a worse prognosis in patients with FMR compared with those affected by primary MR.
2. Second, EROA may be underestimated in patients with FMR due to its semilunar instead of round shape, as in primary MR.
3. Third, in the presence of LV dysfunction and low stroke volume, smaller RVs reflect a significant regurgitation fraction.
4. Finally, FMR is a dynamic condition and its degree may change depending on the phase of cardiac cycle and loading conditions (ie, systemic arterial pressure, medical therapy, exercise). Exercise echocardiography can play a crucial role in the assessment and quantification of the dynamic component of FMR.[5]

Importantly, FMR severity should always be evaluated after optimization of guideline-directed medical therapy (GDMT). Finally, clinical and echocardiographic findings should be integrated to prevent unnecessary intervention when MR may not be as severe as documented on noninvasive studies.

CURRENT GUIDELINES

In Accordance with American Heart Association Guidelines

Class I

1. Patients with chronic secondary MR (stages B to D) and heart failure (HF) with reduced LV ejection fraction (LVEF) should receive standard GDMT therapy for HF, including angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, beta blockers, and/or aldosterone antagonists as indicated. (Level of Evidence: A)
2. Cardiac resynchronization therapy with biventricular pacing is recommended for symptomatic patients with chronic severe secondary MR (stages B to D) who meet the indications for device therapy

Class IIa

1. Mitral valve surgery is reasonable for patients with chronic severe secondary MR (stages C and D) who are undergoing coronary artery bypass grafting (CABG) or aortic valve replacement. (Level of Evidence: C)

Class IIb

- Mitral valve repair or replacement may be considered for severely symptomatic patients (New York Heart Association [NYHA] class III to IV) with chronic severe secondary MR (stage D) who have persistent symptoms despite optimal GDMT for HF. (Level of Evidence: B)
- Mitral valve repair may be considered for patients with chronic moderate secondary MR (stage B) who are undergoing other cardiac surgery. (Level of Evidence: C)

In According with European Society of Cardiology Guidelines

I C

Surgery is indicated in patients with severe secondary MR undergoing CABG and LVEF greater than 30%.

II A C

Surgery should be considered in symptomatic patients with severe secondary MR, LVEF less than 30% but with an option for revascularization and evidence of myocardial viability.

II B C

- When revascularization is not indicated, surgery may be considered in patients with severe secondary MR and LVEF greater than 30% who remain symptomatic despite optimal medical management (including cardiac resynchronization therapy [CRT] if indicated) and have a low surgical risk.
- When revascularization is not indicated and surgical risk is not low, a percutaneous edge-to-edge procedure may be considered in patients with severe secondary MR and LVEF greater than 30% who remain symptomatic despite optimal medical management (including CRT if indicated) and who have a suitable valve morphology by echocardiography, avoiding futility.
- In patients with severe secondary MR and LVEF less than 30% who remain symptomatic despite optimal medical management (including CRT if indicated) and who have no option for revascularization, the heart team may consider a percutaneous edge-to-edge procedure or valve surgery after careful evaluation for a ventricular assist device or heart transplantation according to individual patient characteristics.

It therefore appears evident that the role of mitral valve surgery for the treatment of isolated severe FMR is also unclear. European recommendations suggest surgical treatment in this scenario only for patients with severe HF symptoms despite optimal GDMT, LVEF greater than 30%, and low comorbidity burden.

SURGICAL TREATMENT OF FUNCTIONAL MITRAL REGURGITATION

The most commonly recommended surgery for patients with moderate or severe FMR is mitral valve repair or chordal sparing replacement, but a lack of conclusive evidence in favor of one or the other technique has left the choice largely to the surgeon's preference and expertise. Several randomized and observational studies have found that restrictive mitral valve repair is associated with lower perioperative mortality but has high rate of MR recurrence, which is cited at 30% to 60% at mid-term follow-up.[6,7] Undersizing valve repair is preferentially performed with closed rings, often with predetermined geometry, compared with partial ring or band. Conversely, replacement provides better long-term correction with a lower risk of MR recurrence and repeat surgery but has higher perioperative morbidity. A recent meta-analysis reported a rate of death at 35% higher in the replacement patients than in the repair subjects. This relative long-term risk has been attributed to the fact that patients undergoing mitral valve replacement tend to be older and have more coexisting illnesses than those undergoing repair.[8] Complete preservation of subvalvular apparatus is recommended.

The mitral valve repair technique most commonly performed is a restrictive annuloplasty with the use of a rigid or semirigid ring to downsize the annulus diameter. Combined restrictive annuloplasty and subvalvular procedures directly addressing papillary muscle (PM) displacement and leaflet tethering also have been successfully performed.

Procedures involving the PMs require knowledge of their anatomy and blood flow distribution, as well as recognition of the different divisions of PMs and anatomic variants. Two main procedures are performed in this context: PM approximation or "sling," and PM relocation.

TRANSCATHETER THERAPY

Percutaneous MR treatment mimics surgery by using annuloplasty, edge-to-edge repair, or prosthesis implantation.

Reduction of the severity of MR may be accomplished percutaneously by approximation of the anterior and posterior mitral leaflets, a procedure that leads to formation of a double-orifice valve. In the randomized Endovascular Valve Edge-to-Edge Repair Study (EVEREST) II, transcatheter mitral-leaflet approximation with the MitraClip device (Abbott, Chicago, IL) was safer than surgical mitral valve repair but was not as effective in reducing the severity of MR.

It should be noted, however, that patients included in EVEREST II were low-risk candidates for surgery mainly affected by primary MR (73.4%), and, hence, quite different from those undergoing MitraClip treatment in current practice in Europe.

For many years after the publication of EVEREST II results, evidence supporting the use of MitraClip for the treatment of FMR was derived only from observational studies.

Recently, 2 intensely awaited randomized controlled trials have been published. Both MITRA-FR (Multicentre Study of Percutaneous Mitral Valve Repair MitraClip Device in Patients With Severe Secondary Mitral Regurgitation) and COAPT (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation) investigated the role of MitraClip treatment in patients with ischemic or nonischemic FMR, who remained symptomatic (NYHA class II–IV) despite GDMT.[9,10]

In COAPT, device-based treatment resulted in a significantly lower rate of hospitalization for HF, lower mortality, and better quality of life and functional capacity within 24 months of follow-up than medical therapy alone. In addition, the rate of freedom from device-related complications with transcatheter mitral valve repair exceeded a prespecified objective performance goal.

A total of 614 patients with moderate-to-severe (3+) or severe (4+) FMR (EROA >30 mm^2 and RV >45 mL), NYHA class II–IV, and LVEF 20% to 50% were randomized to MitraClip plus GDMT (n = 302) or GDMT alone (n = 312). The primary effectiveness endpoint (HF hospitalizations at 24 months) was significantly lower in the MitraClip group compared with the GDMT group (35.8% vs 67.9% per patient-year; hazard ratio [HR]0.53, 95% confidence interval [CI] 0.40–0.70; P<.001) with a very favorable number needed to treat of 3.1. Importantly, significant differences between groups were also observed in the composite of death and HF hospitalization at 1 year (45.7% in the device arm vs 67.9% in the control arm; HR 0.57, 95% CI 0.45–0.72; P<.001), all-cause mortality alone at 24 months (29.1% in the device arm vs 46.1% in the control arm; HR 0.62, 95% CI 0.46–0.82), and need for LV assist device at 1 year (3% in the device arm vs 7.1% in the control arm; HR 0.34, 95% CI 0.13–0.87; P = .02).

In the MITRA-FR trial, 6304 patients with severe FMR (defined as EROA >20 mm^2 and RV >30 mL), NYHA class II–IV, and LVEF 15% to 40%, were randomized to MitraClip plus GDMT (n = 152) or GDMT alone (n = 152). The primary composite endpoint (all-cause death and hospitalization for HF at 12 months) was similar between the 2 arms (54.6% in the device group vs 51.3% in the

control group; odds ratio 1.16, 95% CI 0.73–1.84), and both single endpoints did not significantly differ between groups. No significant differences were noted across specified subgroups.

SUMMARY

In conclusion, it appears there is no agreement between the 2 trials; however, we think that the results of MITRA-FR and COAPT trials should be interpreted as complementary rather than contradictory.

To obtain a prognostic benefit, only selected patients should receive MitraClip therapy. Accurate evaluation of GDMT before intervention is essential. GDMT is also necessary after the intervention. This reinforces the importance of the heart team with active participation of HF specialists in decision making and patient management. Intervention should be considered only in the presence of severe FMR, defined as EROA >30 mm^2 and RV >45 mL according to COAPT criteria. Finally, it is important to exclude patients with advanced cardiomyopathy, defined as NYHA class IV, right ventricular failure, severe tricuspid regurgitation, as well as patients with marked LV dilatation or severely reduced LVEF. In these patients, LV assist device/transplantation should be discussed by the heart team if appropriate, whereas patients in whom no benefit could be expected from any intervention should stay on GDMT.

Percutaneous intervention (ie, MitraClip), when used in a timely manner in properly selected patients, may interrupt the vicious circle that ultimately leads to end-stage HF in patients with chronic HF.

CLINICS CARE POINTS

- Patient selection and preoperative echocardiographic evaluation are critical for successful mitral valve repair in functional mitral regurgitation.
- Transcatheter mitral valve intervention would be beneficial in selected patients with functional mitral regurgitation.
- Mitral annuloplasty alone is not effective in some patients, and additional surgical techniques should be considered to improve the repair durability.

DISCLOSURE

The authors have nothing to disclose.

REFERENCES

1. Nappi F, Spadaccio C, Nenna A, et al. Is subvalvular repair worthwhile in severe ischemic mitral regurgitation? Subanalysis of the papillary muscle approximation trial. J Thorac Cardiovasc Surg 2017;153:286–95.e2.
2. Timek TA. Sub or snub: is subvalvular repair worthwhile in severe ischemic mitral regurgitation? J Thorac Cardiovasc Surg 2017;153:296–7.
3. Baumgartner H, Falk V, Bax JJ, et al. 2017 ESC/EACTS guidelines for the management of valvular heart disease. Eur Heart J 2017;38:2739–91.
4. Nishimura RA, Otto CM, Bonow RO, et al. AHA/ACC focused update of the 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation 2017;135:e1159–95.
5. Zoghbi WA, Adams D, Bonow RO, et al. Recommendations for noninvasive evaluation of native valvular regurgitation: a report from the American Society of Echocardiography developed in collaboration with the Society for Cardiovascular Magnetic Resonance. J Am Soc Echocardiogr 2017;30:303–71.
6. Acker MA, Parides MK, Perrault LP, et al. Mitral-valve repair versus replacement for severe ischemic mitral regurgitation. N Engl J Med 2014;370:23–32.
7. Goldstein D, Moskowitz AJ, Gelijns AC, et al. Two-year outcomes of surgical treatment of severe ischemic mitral regurgitation. N Engl J Med 2016;374:344–53.
8. Vassileva CM, Boley T, Markwell S, et al. Meta-analysis of short-term and long-term survival following repair versus replacement for ischemic mitral regurgitation. Eur J Cardiothorac Surg 2011;39:295–303.
9. Obadia JF, Messika-Zeitoun D, Leurent G, et al, MITRA-FR Investigators. Percutaneous repair or medical treatment for secondary mitral regurgitation. N Engl J Med 2018;379:2297–306.
10. Stone GW, Lindenfeld J, Abraham WT, et al, COAPT Investigators. Transcatheter mitral-valve repair in patients with heart failure. N Engl J Med 2018;379:2307–18.