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Review Article

Functional Mitral Regurgitation: Review of Literature and Institutional Therapeutic Strategy

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Abstract

Functional mitral regurgitation (FMR) is associated with poor prognosis and increased morbidity in patients with left ventricular remodelling or atrial dilatation. The review is focused on the current evidence and guideline-based treatments for patients with FMR. Optimal management of patients with FMR requires early initiation and optimization of guideline-directed medical therapy (GDMT), evaluation of indication for cardiac resynchronization therapy (CRT), and timely evaluation for surgical or percutaneous intervention. A stepwise approach tailored to MR mechanism, ventricular geometry, and patient comorbidity is essential. In this paper we present a review on literature and a practical approach for the management of FMR based on currently available evidence.

Key Words: mitral regurgitation; drugs; cardiac resynchronization device therapy (CRT); functional mitral regurgitation (M-TEER)

Introduction

Mitral regurgitation (MR) is a common pathological condition worldwide and one of the most frequent typeof heart valve disease. It affects approximately 2.5% of the total population and its progression can lead to left ventricular (LV) enlargement and dysfunction, congestive heart failure and death [1]. Mitral regurgitation can be classified as primary or secondary. It is defined primary when it is due to alterations ofthe valve leaflets, chordae tendinae and annulus, while it is secondary or functional (FMR) when due to changes in the left atrium (LA), left ventricle (LV) or mitral valve annulus. FMR can be further classified in atrial (AFMR), ventricular (VFMR) and mixed FMR [2]. For FMR the main treatment is guidelines-directed medical theraphy (GDMT) and cardiac resynchronization (CRT) although some cases can benefit from surgical or percutaneous edge-to-edge transcatheter mitral valve repair. In current era M-TEER can be considered the gold standard therapy for high-risk patients with FMR [2].

Imaging for evaluation of FMR

Transthoracic echocardiography (TTE) is the initial imaging modality for the assessment of FMR; Transoesophageal echocardiography (TOE) may be required in cases of suboptimal TTE images or when is needed a more detailed evaluation of the mitral apparatus. Transoesophageal echocardiography (TOE) represents the method of choice to assess valve anatomy, leaflet quality, motion, and coaptation, as well as to confirm MR severity. Three-dimensional TOE provides an excellent morphological and functional view of the different valve segments, and should be used systematically when planning and performing surgical or transcatheter repair (Figure.1-2). Echocardiographic assessment of MR severity is based on a multi-parametric approach with qualitative, semi-quantitive and quantitative methods (Figure.3). Between semiquantive signs, vena contracta width is one of the best measures considering a cut-off of 7 mm to define severe FMR. Among the quantitative parameters, it is necessary to consider an effective regurgitant orifice area (EROA), a regurgitant volume (RVol) and a regurgitant fraction (RF). According the current European Society of Cardiology guidelines, we can define MR as severe if EROA is > 40 mm2, the RVol > 60 ml and the RF>50% [2]. When quantifying EROA and RVol in FMR, lower thresholds may apply to define severe regurgitation because of the potential elliptical regurgitant orifice and/or the low-flow state. Stress echocardiography is another modality used to assess FMR as regurgitation severity often increases during exercise due to elevated afterload or worsening tethering forces [1-4].

Ventricular Functional Mitral Regurgitation

VFMR is due to LV distortion and dysfunction and can be further classified as either ischemic or nonischemic. The ischemic form which is the most frequent etiology results from papillary muscle displacement causing systolic symmetric or asymmetric tenting of the MV [1]. Symmetric tethering is associated with substantial systolic dysfunction, global

remodeling, and increased LV sphericity with a central regurgitant jet. Asymmetric tethering most frequently results from localized remodeling affecting the posterior papillary muscle with posterior leaflet tenting and a posteriorly directed MR jet. Non ischemic MR, instead, is caused by long standing hypertension or idiopathic dilated cardiomyopathy and is characterized by global LV dilation with increased sphericity and a central regurgitant jet. The severity of FMR is dynamic and varies during the cardiac cycle and is also influenced by changes in loading conditions and inducible reversible ischemia [3].

Patients with mild/moderate MR at rest, indeed, can worsen with exercise and supine positioning for increase venous return or can worsen with systemic hypertension for increases afterload. Stress-induced ischemia of the inferior or inferolateral wall leads to worsening of leaflet tethering and subsequent MR. This variability in the degree of FMR should be taken into consideration when considering other imaging techniques, such as stress echocardiography, to assess the severity of FMR in addition to TTE [3].

Approach to Management

Guidelines-directed medical therapy (GDMT)

Since FMR occurs secondary to LV dysfunction, pharmacological therapy to optimize LV remodeling is the first line of treatment (Tab.1). All patients should receive GDMT for heart failure with reduced ejection fraction (HFrEF). The availability of four main classes of medication in the armamentarium of GDMT has focused research interest on simple mechanisms to safely and effectively initiate these four classes rapidly. Several authors have proposed rapid optimisation protocols designed to rapidly establish patients onto these 'four pillars' of heart failure therapy (beta- blocker (BB), ACE inhibitor/ angiotensin II receptor blocker/ARNI, SGLT2 inhibitor, mineralocorticoid receptor antagonist (MRA)).However, in the real world, GDMT is initiated in only a fraction of patients with HFrEF and it is mostly underdosed, compared with the doses reached in randomized clinical trials (RCTs). Triple GDMT with ARNI, beta-blockers, and MRA was prescribed in 40% of patients undergoing M-TEER in the European Registry of Transcatheter Repair for Secondary Mitral Regurgitation (EuroSMR) registry and was associated with higher survival after mitral transcatheter edge-to-edge repair (M-TEER) [4]. Heart failure guidelines recommend rapid GDMT uptitration with achievement of the maximum tolerated dose within 6 weeks and it's advisable to re-evaluate patients after 1–3 months [3].

Cardiac resynchronization device therapy (CRT)

Cardiac resynchronization therapy is an established treatment for patients with symptomatic HF despite GDMT and is indicated in patients with New York Heart Association Class II–IV, reduced LVEF ≤ 35%, and a QRS duration ≥ 130 ms with a left bundle branch block (LBBB) morphology (Class I indication according to according american and european guidelines) (Table.2). The effects of CRT on FMR are due to improvement of atrioventricular synchrony and LV contractile efficiency and to restore the electomechanical sequence of papillary muscle with a reduction of effective regurgitant orifice area (EROA) [2]. The amount of FMR reduction with CRT ranges from 23% to 35%, and the residual FMR after CRT is associated with adverse clinical outcomes. For this reason, it is important to identify CRT non-responders early, so that residual FMR can be addressed before the disease is too advanced. Therefore, in non-responders CRT patients o with low probability of CRT due to very advanced stages of HF, poor LV viability, disproportionate MR, and myocardial fibrosis), MV intervention should be considered [28]. Instead, in patients with good acute response and intermediate probability of CRT response, FMR should be reassessed after 3 months of follow-up [3].

Percutaneous transcatheter MV repair (M-TEER)

The management of patients with ventricular FMR is complex and should be discussed by a multidisciplinary Heart Team. In patients who continue to be symptomatic despite the adequate GDMT and CRT, surgical or percutaneous intervention may be considered. However, patients with FMR and HFrEF are rarely operated on surgically both for their hight surgical risk and because trials have not demonstrated a benefit of surgery over conservative therapy [5-6]. In this regard, the Multicenter, Randomized, Controlled Study to Assess Mitral vAlve reconsTrucTion for advancEd Insufficiency of Functional or iscHemic ORigiN (MATTERHORN) trial showed that, among patients with heart failure and FMR, transcatheter edge-to-edge repair was non inferior to mitral-valve surgery with respect to a composite of death, rehospitalization for heart failure, stroke, reintervention, or implantation of an assist device in the left ventricle at 1 year [5-7-8]. In current era, M-TEER can be considered the gold standard therapy for patients with severe ventricular MR without concomitant coronary disease (Tab.3). According to the current ESC guidelines 2025, M-TEER is recommended to reduce HF hospitalizations and improve quality of life in haemodynamically stable, symptomatic patients with impaired LVEF (<50%) and persistent severe ventricular SMR, despite optimized GDMT and CRT (Class I indication) [9]. There are two major randomised trials that have examined the benefits of m-TEER in patients with FMR and HFrEF: the MITRA-FR trial and the COAPT trial [10-11-12]. The MITRA-FR (Percuta-153neous Repair with the MitraClip Device for Severe Functional/Secondary Mitral Regurgi-154tation) trial showed that m-TEER did not lead to a lower rate of death from any cause or hospitalization for heart failure or a lower rate of death from any cause at 1 year and 2 years compared to medical therapy alone [9].In contrast, the COAPT ((Cardio-157vascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure 158Patients with Functional Mitral Regurgitation) trial showed that m-TEER led to both a lower rate of hospitalization for heart failure and a lower rate of death from any cause than medical therapy alone during 24 months of follow-up [11-13]. Furthermore, these results appear to be durable over 3- year and 5- year follow- up [13]. This trial has led to a specific indication, Class IIa and level of evidence B, in current guidelines, for patients fulfilling inclusion criteria adopted in the study [LVEF 20%– 50%, LV end-systolic diameter < 70 mm, and lack of advanced HF, haemodynamic instability, severe pulmonary hypertension, severe tricuspid regurgitation (TR), moderate or severe right ventricular function]. The different outcomes between these trials are due to differences in the study populations. MITRA-FR trial enrolled patients with extreme LV dilatation (mean LVEDV of 252 mL) and modest MR (EROA of 31 mm) while COAPT trial enrolled patients with MR disproportionately severe (EROA 41 mm 2) compared to their LV dysfunction (mean LVEDV of 192 mL). These differences suggest that the patients most likely to benefit from M-TEER are patients with MR disproportionately severe compared to their LV dysfunction [14-15-16]. Subsequently the RESHAPE-HF2 trial (A Clinical Evalua-175tion of the Safety and Effectiveness of the MitraClip

System in the Treatment of Clinically Significant Functional Mitral Regurgitation), which has the same inclusion criteria as those of the COAPT trial in terms of MR severity, with intermediary criteria COAPT and MITRA-FR in terms of LV dysfunction severity , have demonstrated that, among patients with heart failure with moderate/severe FMR in medical therapy, the addition of M-TEER led to a lower rate of first or recurrent hospitalization for heart failure or cardiovascular death and a lower rate of

first or recurrent hospitalization for heart failure at 24 months and better health status at 12 months than medical therapy alone [17-18-19]. The RE-SHAPE-2 trial suggests a broader application of M-TEER in addition to guideline-directed medical therapy in patients with symptomatic HF and moderate to severe functional mitral regurgitation [20-21-22-23-24]. A comparison of the salient baseline characteristics and outcomes from the 3 randomized trials are shown in Table.4.

Other transcatheter mitral interventions

Among the other percutaneous mitral interventios that have received CE mark approval, it must be consider the Tendyne valve which is a transcatheter mitral valve implanted via the transapical approach, through a left anterolateral thoracotomy. Two year outcomes of 100 patients in a non-randomised prospective study reported a 96% technical success rate, reduction in annualised HFH rates and improvement in NYHA class. Compared to the benefits of the procedure, 39% of patients died within the follow- up period and numerous cases of fatal hemorrhages and strokes have been described after the intervention. Furthermore, there are ongoing trials aimed to test the efficacy of this procedure as the SUMMIT prospective trial which is enrolling patients with severe symptomatic MR to be randomly assigned to m-TEER or Tendyne mitral valve replacement. Other percutaneous procedure include the Carillon mitral contour system and the Cardioband system. The first is a mitral annuloplasty device placed in the coronary sinus to reduce the mitral annular dimension and FMR. It is not currently FDA approved and large randomized trials are needed to assess its clinical benefits. The second is a transcatheter annular reduction system which, in a multicentre trial of 62 patients, have shown at 1 year an improvement in symptom and functional status. These devices, however, are in various stages of development and large randomised controlled trials are needed to demonstrate safety, efficacy and long term prognosis [2-3].

Atrial Functional Mitral Regurgitation

Atrial FMR (AFMR) is characterized by marked left atrial dilation which is common in patients with long standing atrial fibrillation (AF) and heart failure with preserved ejection fraction (HFpEF). LA dilatation pulls the annulus and leaflets insertion upwards, causing flattening and restriction of the anterior MV leaflet movement [1]. Echocardiographic criteria include: preserved LVEF (=50%) without regional wall motion abnormalities or leaflet tethering; no or mildly dilated LV cavity, mitral annulus (MA) and left atrium (LA) dilation [2]. AFMR may have a better prognosis than VFMR but management of AFMR is not clear because of its complicated pathophysiology and lack of data. The initial therapeutic strategy involves, in the case of AF, the restoration of sinus rhythm which can be achieved through various strategies (antiarrhythmic drugs cardioversion, catheter ablation) or GDMT for HFpEF. However, in severe symptomatic patients, refractory to medical/rhythm therapy, M-TEER find application proving to be effective as it brings to positive reverse remodeling of LA and mitral annular dimension [2].

Conclusion

FMR is a complex and dynamic condition where the best treatment depends on its cause, severity, ventricular geometry, the patient's overall condition, timely diagnosis, optimal medical therapy, and precise patient selection for intervention. There's no single "one-size-fits-all" option, the current scientific evidence suggest a stepwise and mechanism-driven approach. We propose our therapeutic algorithm guided by the guidelines finalized to rapidly optimise patients with FMR and early identify 'non- responders' patients in order to direct them to device therapy reducing morbidity and mortality (Figure.3).

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