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Surgical treatment of secondary mitral regurgitation in heart failure: a present-day view

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Abstract

Rationale. *Secondary, or functional, mitral regurgitation is the most common complication of heart failure. Dysfunction of one or more mitral valve structures occurs in 39–74% of patients thus complicating the course of the disease and significantly worsening the prognosis in patients with left ventricle dilatation. An unfavorable prognosis in patients with the development of mitral regurgitation is conditioned by the progressive changes that form a vicious circle: the continuing volume overload and dilatation of the left ventricle cause its remodeling, leading to further dilatation of the mitral valve annulus. Dysfunctions of the papillary muscles lead to the increased tension of the left ventricle wall and increased mitral regurgitation. Clinically, this process is manifested by the congestive heart failure progression and worsened prognosis of the further course, which in the future may lead to considering the inclusion of this patient group on the waiting list for heart transplantation.*

Purpose. *The purpose of this article is to review the role of surgical management in patients with heart failure complicated by mitral regurgitation.*

Conclusion. *The main principles of the treatment for functional mitral regurgitation include the reverse left ventricular remodeling and mitral valve repair or replacement surgery which lead to an improved quality of life, the transition of patients to a lower functional class, reduced hospital admission rates, and also to a regression or slower progression of the heart failure and to an improved survival.*

Keywords: secondary mitral regurgitation, heart failure, surgical treatment of mitral regurgitation

Conflict of interests Authors declare no conflict of interest

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AF, atrial fibrillation

CABG, coronary artery bypass grafting

CHF, chronic heart failure

CRT, cardioresynchronization therapy

HF, heart failure

LV EF, left ventricle ejection fraction

LV, left ventricle

MI, myocardial infarction

MIns, mitral insufficiency

MR, mitral regurgitation
MV, mitral valve

Introduction

Mitral regurgitation (MR) has been categorized into primary and secondary. Primary (or organic) MR occurs as a result of a structural or degenerative mitral valve (MV) anomaly. Organic mitral insufficiency per se is an indication for surgery, so there is no doubt about the necessity of its correction.

Secondary (functional) MR has a complex nature and is caused by the dysfunction of the left ventricle (LV) and subvalvular apparatus. Functional MR is associated with a worse prognosis.

Despite a wide variety of surgical procedures and their improvements, secondary mitral insufficiency (MIns) continues progressing in most cases. This leads to further remodeling of the LV myocardium and deterioration in patient's functional class, up to the development of end-stage chronic heart failure (CHF). This circumstance, in view of the further futility of an optimal drug therapy and surgical correction, enables us to consider such patients as potential candidates for heart transplantation [1].

Pathophysiology of secondary mitral regurgitation

Functional MR is caused by an altered geometry of the LV and subvalvular apparatus. In secondary MR, the MV leaflets usually have a normal structure, but are displaced to the apex of the heart against its usual position, in which the valve is effectively closed at the level of the mitral annulus.

In dilation, the LV cavity size increases in all directions, resulting in an increase both in the cavity volume, and also in its sphericity. As the

LV cavity expands, the papillary muscles became displaced, the chords tighten, and the configuration of the MV annulus changes from saddle-shaped to flat, which, in turn, causes MR [2-4]. Moreover, the LV systolic dysfunction reduces the MV closing strength, which also deteriorates MR.

Prognostic significance of functional mitral regurgitation

A relationship was found between the secondary MR and mortality [5].

In the study by Grigioni et al., 303 patients with ischemic heart failure (HF) were investigated; 194 patients (64.0%) had MR, the others had no MR. After 5 years of follow-up, the overall mortality in the patients with MR was higher than in the patients without MR [6].

Rossi et al. studied 1,256 patients, whose study endpoints were reduced mortality and hospitalization as related to HF progression. The study included three following groups: group 1 (27%) consisted of patients without MR, group 2 (49%) consisted of patients with grade 1-2 MR, and group 3 (24%) included patients with grade 3-4 MR. The mean follow-up period was 2.5 years. The authors found an increased mortality with an increase in the MR severity grade; the highest mortality rate was observed in the group of patients with grade 3-4 MR [6].

Ischemic and non-ischemic MR

MR in HF can be classified as either ischemic or non-ischemic.

In ischemic MR, LV remodeling after myocardial infarction (MI) leads to the displacement of papillary muscles, causing MV systolic tension, while globally the left ventricular ejection fraction (LV EF) may not decrease [7]. Depending on the location of the MI zone, symmetrical or asymmetrical displacement of the MV leaflets may occur. In case of

the symmetric displacement, remodeling in the form of LV sphericity with a central regurgitant jet is more frequently observed. An asymmetric displacement is more likely to occur as a result of the localized MI affecting the posterior papillary muscle, which causes a backward directed asymmetric regurgitant jet.

Non-ischemic MR is characterized by the LV dilatation of an increased sphericity and, as a rule, with a central regurgitant jet. Dilatation of the MV annulus is most pronounced in the septal-lateral direction and corresponds to the severity of LV dysfunction.

Atrial fibrillation as a predictor of mitral regurgitation in heart failure

Another cause of secondary MR is the left atrium enlargement with atrial fibrillation (AF), which results in the expansion of the MV annulus and an impaired coaptation of leaflets, with a normal LV function and intact MV [7]. In patients with AF, when sinus rhythm is restored, MR decreases, which indicates a causal relationship here [8].

Surgical correction of secondary mitral regurgitation

Options for surgical treatment of secondary MR include endovascular treatment, Mitral valve repair and mitral valve replacement surgery, LV reconstructive surgery, LV mechanical assist devices and aorto-coronary bypass grafting for ischemic MIns. However, given the etiological factors, the outcome of the disease may be unfavorable even despite the MR surgical treatment [9, 10].

Mitral valve annuloplasty

The most commonly performed surgical intervention is MV annuloplasty, which preserves all valvular structures and their

interrelationships. The main indication to annuloplasty is the MV annular dilatation while the valvular and subvalvular structures being intact. A proper understanding of the pathophysiology of MV annulus dilatation makes it possible to correctly select the prosthesis type and size, minimizing the impact of anterior leaflet prolapse [8, 11]. However, despite an adequate MR correction, 15-20% of patients relapse after 6-12 months; and up to 70% of patients need a repeated MV correction. within 5 years [12, 13]. The risk factors include a more severe preoperative MR, a greater degree of LV dilatation, and the anterior leaflet prolapse [12]. Relapse of MR is more common in patients after using strips or flexible support rings [14, 15]. Currently, various ring designs have been developed, including for post-ischemic MR, which correct the prolapse of the P3 segment [16]. The use of annuloplasty in patients with non-ischemic MR currently requires further studies, given that the previously conducted studies were accompanied by a rather high mortality rate, a more frequent MR relapse, and required repeated operations [1-7, 18].

Annuloplasty or mitral valve replacement surgery?

Initially, in patients with secondary MR, the MV replacement surgery with the removal of leaflets and subvalvular apparatus were used. However, those patients experienced a LV dysfunction after such interventions. Present day methods of MV replacement surgery are more gentle, salvaging the leaflets and subvalvular apparatus, which allows preserving the LV function. This type of surgery is preferable in patients with the highest MR severity [19-21]. Situations in which replacement surgery is preferred include: papillary muscle rupture in acute ischemic MR, patients in cardiogenic shock, with an extreme MR severity grade, with initially reduced LV EF, while taking into account an extent of surgeon's proper experience in MV reconstruction surgery.

From 2004 to 2009, 9 non-randomized studies were conducted, according to which data the authors of this studies compared the results of MV replacement surgery for ischemic mitral regurgitation in 1,730 patients. Meanwhile, most patients underwent combined surgery with coronary artery bypass grafting (CABG). Mortality rates in patients after MV replacement surgery and MV surgical repair in the early postoperative period did not differ. Similar results have been obtained in more recent studies, with the mortality rate in the early postoperative period being 2-3% in patients after MV surgical repair, and 12.5% after MV replacement surgery ($p=0.03$). The similar results were seen within a 3-year follow-up. In addition, the patients after MV surgical repair showed an improved LV function with reverse remodeling of LV due to the preservation of annulo-papillary continuity.

Other studies have shown that MV replacement surgery with preserving subvalvular structures lead to a similar or even lower mortality compared to the MV surgical repair, especially in patients with severe mitral regurgitation and/or a severe LV dysfunction [19]. From 1996 to 2011, 244 patients with ischemic MR were investigated. Some patients underwent MV annuloplasty, while others underwent surgical replacement with mechanical or biological implants. All patients had similar 8-year mortality rates, but patients who underwent MV surgical repair required repeated surgery 2.8 times more often [22].

In another study, a comparative assessment was performed between MV surgical repair and MV replacement surgery for the patients with severe ischemic mitral regurgitation. In this study, 251 patients with ischemic MR were investigated. All patients were divided into two groups: group 1 included the patients after MV surgical repair, and group 2 included patients after MV replacement surgery [9]. There were no significant differences in the first year of follow-up. However, MR

recurrence after 1 year was seen significantly more often after MV surgical repair compared to MV replacement surgery (32.6% vs. 2.3%, $p<0.001$). MR relapses were most frequently observed in patients with a basal aneurysm or dyskinesia of the LV existing before surgery (62.1% of patients with relapse and 20.5% relapse-free, $p<0.001$) [23]. Therefore, MV replacement surgery should be preferred in the cases of a basal LV aneurysm.

Other surgical methods for the treatment of secondary mitral regurgitation

Despite the fact that annuloplasty and MV replacement surgery are the most common surgical modalities, a number of other techniques are currently being used with varying success.

In patients with severe calcification of the MV annulus, the annuloplasty is not effective due to the restricted motion and elasticity of the valve structures, and MV replacement surgery is often impossible. In such cases, Alfieri's repair is used.

In 2001, O. Alfieri et al. proposed a method of surgical repair for MV anterior leaflet prolapse using a suture that anchored the prolapsing part of the anterior leaflet to the intact posterior leaflet. This maneuver forms a double-lumen atrioventricular orifice, restricts the anterior MV leaflet motion, and promotes a tight MV seal. Subsequently, the O.Alfieri's suture was used as a supplement to create a better MV physiology when other surgical repair methods were inadequate [24].

The effect of coronary artery bypass grafting on secondary ischemic mitral regurgitation

There is a consensus that myocardial revascularization in ischemic mitral insufficiency improves the course of MR [25, 26].

The STICH study demonstrated that although surgical correction of severe MR in patients undergoing coronary bypass grafting is usually recommended to improve the quality of life; as a result of a large-scale study, it remained unclear whether the survival improves after MV surgical repair or replacement surgery in this group of patients. The ACC/AHA *Guidelines for the management of patients with valvular heart disease* note that "Mitral valve surgery is reasonable for patients with chronic severe secondary MR who are undergoing CABG" despite the lack of strong evidence that this approach prolongs life or reduces symptoms. Meanwhile, this approach avoids leaving a patient with severe MR [26].

The MitraClip Device

The MitraClip device is a clip that under transesophageal echography guidance is inserted through the transseptal puncture, drawn via the femoral artery into the LV and applied on the free edges of MV leaflets, simulating a surgical correction [27]. If necessary, multiple clips can be applied.

In the EVEREST II study, 278 patients with severe MR were allocated into two groups. MitraClip was used in group 1 patients, and MV surgical correction was performed in group 2 patients. In the patients of MitraClip application group, improvement in mitral regurgitation was seen compared to the group where the patients underwent open surgery [28]. In group 1, a satisfactory result was achieved only in 77% of patients, of whom 21% required surgical intervention. Nevertheless, within 4 years of follow-up, NYHA functional class and overall survival rates were similar in the two groups [29].

In Europe, the MitraClip technique has been widely used in patients with a high risk of or contraindications to open MV surgery.

Numerous studies demonstrate low mortality and favorable short-term results [30-34].

The TRAMI study has been the largest published Registry to date [35]. Among the 1,064 patients implanted with MitraClip, the median age being 75 years, NYHA functional class III/IV, 69% of patients had an EF lower 50%, and secondary MR was present in 71% of patients. A satisfactory result was achieved in 95% of patients. After 3 months of follow-up, 12% of patients died and 12% were hospitalized for HF, meanwhile 66% of patients remained in NYHA functional class I/II. In the ACCESS-EU study, MitraClip was implanted in 567 patients [36]. MR was reduced to ≤2+ in 91% of patients. NYHA functional class and 6-minute exercise test results significantly improved after 1 year of follow-up. Similar results were obtained in the Pilot, EVEREST II and REALISM studies. These studies confirmed a reduction in mortality and the frequency of repeated hospitalizations, reduction in quantity of repeated MV operations, and also reduction in MR was associated with reverse LV remodeling, an improved quality of life and the improvements in NYHA functional class. MitraClip was also used successfully in the HF patients, non-responders to cardioresynchronization therapy (CRT) (especially high-risk groups), with subsequent improvements in MR and reverse remodeling of LV [37].

Currently, there are studies confirming the successful use of MitraClip in patients with severe MIns and severe HF who are on the waiting list for heart transplantation [38].

Left ventricle assist devices

Two of the investigational cardiac support devices, CorCap (Acorn Cardiovascular) and Coapsys (Myocor, Maple Grove, Minnesota), were used to achieve the LV remodeling that could have reduced the secondary

MR severity. The CorCap Cardiac Support Device is a mesh device fitted around the LV and designed to reduce the wall stress; its advantage is that it can be implanted on the beating heart without resorting to extracorporeal circulation [17]. The ACORN study, which included only 300 patients, showed a reduction in LV size, but the MR severity and mortality did not decrease versus the comparison group [18]. The Coapsys LV reshaping device also alters the shape of the LV and involves reverse LV remodeling in addition to reconstructive operations on MV [36]. The RESTOR-MV study showed a reduction in LV size, but there was no significant difference in the reduction of MR severity when compared with conventional MV reconstruction [39].

Cardioresynchronization therapy for the correction of secondary mitral regurgitation

Along with reverse LV remodeling and improved EF [40], most studies demonstrated a reduction in overall MR severity with restoring the synchronous ventricular contraction. In the MIRACLE study of 450 patients with HF of NYHA functional class III/IV having an ejection fraction of lower 35% and a QRS duration of at least 130 ms, the CRT resulted in a marked decrease in end diastolic and end systolic volume an improved EF, and a sustained decrease in MR [41]. Similarly, in another study of 610 patients with HF of NYHA functional class I/II and QRS duration of at least 120 ms, the CRT resulted in a sustained reduction in MR severity at 3 and 6 months with a parallel reduction in LV dimensions [42]. In a study of 63 patients with heart failure and moderate/severe MR, 43% showed an immediate improvement in MR, and another 20% showed a later improvement after 6 months [43]. Thus, the CRT is an acceptable treatment option for secondary MR in patients with HF.

Conclusion

Despite numerous advances in therapeutics, the mortality in end-stage heart failure remains exceptionally high. Functional mitral regurgitation is the most common complication of heart failure. Regardless of the etiology, the secondary mitral regurgitation development dramatically complicates the course of the disease and significantly worsens the prognosis in patients with heart failure. An accurate assessment of the mitral regurgitation severity in such patients can be a difficult diagnostic task, but it is important for evaluating the patient's severity and deciding on further treatment tactics.

Heart transplantation remains the main treatment option for this group of patients, but the shortage of donor organs limits the use of this treatment. Over the past decade, a pharmacological therapy, combined with cardioresynchronization therapy, the mitral valve replacement surgery or surgical repair, and/or arterial revascularization of the myocardium can reduce secondary mitral regurgitation, improve the patient's prognosis, or can be used as a "bridge" to heart transplantation. Meanwhile, some patients may be completely excluded from the waiting list for heart transplantation, given the good clinical and physiological effects of the described technique.

Currently, there is no consensus on the surgical treatment tactics for such patients. There are a number of surgical treatment methods, and each of them should be applied on an individual basis. The main goals of surgical treatments are reverse remodeling of the left ventricle and the normalization of its function leading to a regression or slower progression of the heart failure. Further randomized trials in this area will help to optimize the surgical treatment in this category of patients.

Regardless of the drug therapy and surgical correction effects, such patients should be monitored more closely for their heart failure

progression to provide their timely placement on the waiting list for heart transplantation, which should lead to improved treatment results for this category of patients.

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