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REVIEW

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Minimally invasive mitral valve repair for functional mitral regurgitation

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Key question

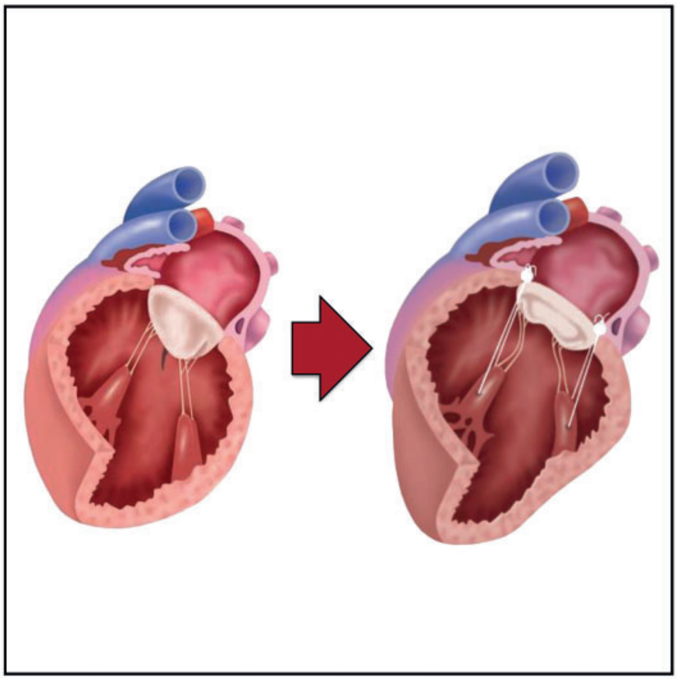
What is the pathophysiological background of functional mitral regurgitation (MR)?

Key finding(s)

Functional MR cohort is inhomogeneous and comprises 2 subgroups of patients who may require tailored surgical treatment.

Take-home message

Modern mitral valve surgery for functional MR combines the benefits of an endoscopic minimally invasive approach with standardized subannular repair.



Summary

Systolic heart failure is frequently accompanied by a relevant functional mitral valve regurgitation (FMR) which develops as a direct sequela of the ongoing left ventricular remodelling. The severity of mitral regurgitation is further aggravated by progressive left ventricular enlargement causing leaflet tethering and reduced systolic leaflet movement. The prognosis of such patients is obviously limited by an underlying left ventricular disease, and the correction of secondary FMR has been previously suggested as predominantly 'cosmetic' surgery in the setting of ongoing cardiomyopathy. Inferior results of an isolated annuloplasty in type IIIb FMR supported the philosophy of malignant course of progressive cardiomyopathy and resulted in increasingly restricted indications for mitral valve surgery for FMR in the guidelines. The lack of a standardized pathophysiological approach to correct type IIIb FMR led to the development of valve replacement strategy and edge-to-edge catheter-based mitral valve procedures, which became the most frequent procedures in the FMR setting in Europe. Modern mitral valve surgery combines the advantages of 3-dimensional endoscopic minimally invasive surgical approach with

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standardized subannular repair to address the pathophysiological background of type IIIb FMR. The perioperative results have been significantly improved, and there is a growing evidence of improved long-term stability of subannular repair procedures as compared to isolated annuloplasty. This review article aims to present the current state-of-the-art of the modern mitral valve surgery in FMR and provides suggestions for future trials analysing the potential advantages in these patients.

Keywords: Functional mitral regurgitation • Subannular repair • Mitral valve surgery

INTRODUCTION

The progression of chronic heart failure is associated with ongoing left ventricular (LV) remodelling and subsequent changes in the geometry of the mitral valve apparatus. While LV deformation and enlargement progress, a complex remodelling process of the whole 'ventriculo-mitral unit' occurs and results in geometrical distortion of the subvalvular mitral apparatus [1]. Because of the ventricular origin of resulting mitral regurgitation (MR), the definition of functional or secondary mitral regurgitation (FMR) has been adopted to differentiate this entity from the degenerative (i.e. primary) mitral valve disease primarily caused by the structural changes of mitral valve leaflets. Despite the univocal evidence of underlying left ventricular disease in FMR patients, the standard surgical treatment of FMR for decades has been an isolated annuloplasty using various ring designs, all of them aiming to reduce the anteroposterior (i.e. so-called septolateral) diameter of the mitral valve annulus. Given the well-documented long-term ineffectiveness of an isolated annuloplasty in the advanced FMR and MR recurrence rates up to 60% at 2 years postoperatively [2], the focus has shifted towards the mitral valve replacement strategy and towards a worldwide boom in catheter-based percutaneous edge-to-edge therapy [3]. The basic tenor of irreparable end-stage left ventricular disease has been often used to justify the failure of annuloplasty concept in type IIIb FMR and has resulted in a stepwise downgrading of the level of evidence for mitral valve repair in secondary MR in the recent updates of consensus guidelines [4].

Modern mitral valve surgery for FMR combines the benefits of well-established full-endoscopic minimally invasive surgical approach with the standardized subannular repair to address the distorted geometry of the subvalvular mitral valve apparatus. While routinely using these techniques, the evidence of improved echocardiographic and functional outcomes in FMR treatment is evolving and is summarized in the present review article. The clinical adoption is still limited due to unproven reproducibility of subannular techniques in well-designed, prospective multicentre trials and lack of data regarding prognostic benefits in the FMR treatment.

FUNCTIONAL MITRAL REGURGITATION: A HOMOGENEOUS ENTITY?

Carpentier's classification describes MR in relation to the mitral valve leaflet motion: type I, normal leaflet motion; type II, leaflet prolapse; type IIIa, restricted leaflet motion in the diastole; and type IIIb, restricted leaflet motion in the systole [5]. According to this classification, 2 distinct pathophysiological entities of FMR patients with the structurally normal mitral valve can be classified: (i) FMR patients presenting with predominant mitral annular dilatation (i.e. type I MR lesion) (Fig. 1A and B) versus (ii) FMR patients with regurgitation predominantly caused by LV remodelling, papillary muscle displacement and tethering of mitral leaflets (i.e. type IIIb MR lesion) (Fig. 1C and D). The synonyms used by interventional cardiologists refer to 'atrial type' [6] and 'ventricular type' of FMR, which intuitively indicate major differences in the pathogenesis of these 2 diseases. Type I FMR is common in patients with relevant left atrial dilatation (e.g. those presenting with long-standing permanent atrial fibrillation), which consecutively leads to mitral annular dilatation and central coaptation defect of mitral leaflets. Left ventricular geometry and systolic LV function are preserved, and there is no relevant systolic tethering of mitral leaflets [6]. As opposed to this 'atrial-type' FMR, type IIIb FMR results from a geometric LV remodelling (i.e. of ischaemic or non-ischaemic origin) and distortion of the subannular mitral apparatus and is associated with a relevant LV dysfunction and systolic tethering of mitral leaflets [7]. It is intuitive that these 2 FMR entities should differ not only in terms of their pathophysiological background but also, even more importantly, in their surgical treatment strategy and finally in their long-term prognosis. Therefore, a word of caution is warranted when analysing published data on surgical or catheter-based treatment of 'universal' FMR cohorts, as they may potentially consist of various combinations of type I and type IIIb FMR subgroups.

PATHOPHYSIOLOGICAL BACKGROUND OF FUNCTIONAL MITRAL REGURGITATION: WHAT DOES IT MEAN FOR THE TREATMENT STRATEGY?

Although the definition of FMR generally implies the presence of structurally normal mitral valve leaflets, the treatment strategy for secondary MR depends on the specific pathophysiological mechanism and may, therefore, be different in type I versus type IIIb lesions.

The development of type I 'atrial' FMR correlates with the progressively increasing left atrial volume (e.g. persistent atrial fibrillation patients), which causes an incremental dilatation of atrioventricular continuity and subsequently leads to a central leaflet coaptation defect and central regurgitation jet [7]. Given the fact that LV geometry is sufficiently preserved in these patients and mitral leaflets move normally to the annular level during the systole, the surgical or interventional treatment strategy aims to simply reduce mitral annular diameter (and thereby mitral valve orifice) to re-establish the competence of mitral valve [8] (Fig. 2A and B).

Type IIIb 'ventricular' FMR, defined as secondary MR with reduced systolic leaflet motion, is a primary disease of the left ventricle and results from a complex remodelling process of the whole 'ventriculo-mitral unit' [9]. It is a sequela of geometrical distortion of the subvalvular mitral apparatus caused by LV dilatation and remodelling in dilated or ischaemic cardiomyopathy [1]. From the pathophysiological point of view, type IIIb FMR results from the increasing distance between the tips of both papillary muscles and mitral annular plane due to apicolateral displacement of the papillary muscles in the progressively enlarging left ventricle (Fig. 3A) [10]. Quite independent of the primary

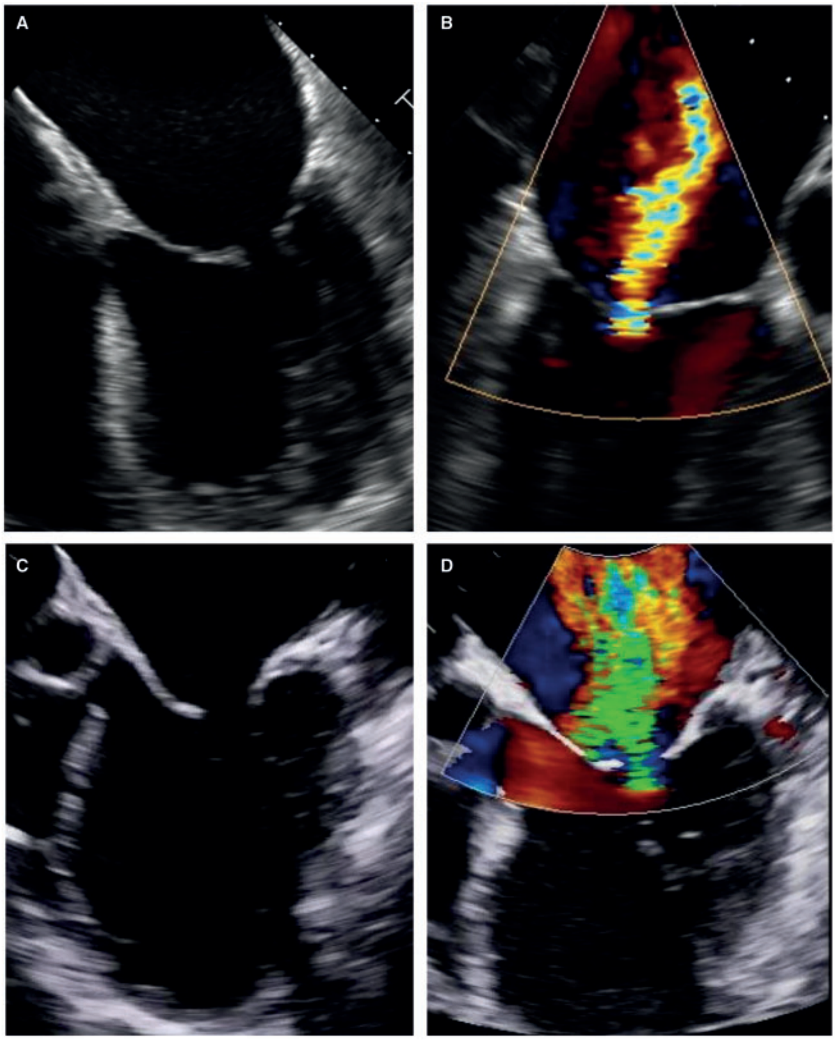

Figure 1: Two different entities of functional mitral regurgitation (FMR). (**A** and **B**) Type I 'atrial-type' FMR and (**C** and **D**) type IIIb 'ventricular-type' FMR.

LV disease (i.e. ischaemic or non-ischaemic origin), there is a severe left ventricular remodelling, which leads to restricted movement of mitral leaflets during the systole and coaptation line well below the mitral annular plane. The severity of restriction in the systolic leaflet movement can be quantitatively graded by so-called tenting parameters, which are summarized in Fig. 4.

Keeping this in mind, standard surgical technique of restrictive annuloplasty which has been used for decades to treat type IIIb FMR [11] is pathogenetically unable to address the underlying regurgitation mechanism of reduced leaflet movement towards the mitral annular plane in the systole and, therefore, to reproducibly restore leaflet coaptation plane (Fig. 3B). One of the basic principles of Carpentier's mitral valve repair 'to restore free leaflet motion' [5] is, therefore, not achieved by an isolated annuloplasty in FMR patients with a predominant type IIIb lesion. Quite the contrary, there is emerging evidence from the literature that the reduction in septolateral dimension by restrictive annuloplasty in type IIIb FMR aggravates leaflet tethering and even further restricts leaflet mobility in the systole [12, 13]. This phenomenon is explained by the fact that restrictive annuloplasty brings in the posterior mitral annulus towards aortomitral continuity and thereby increases the distance to the papillary muscle tips [12]. Consequently, the posterior mitral leaflet becomes completely straightened, immobilized and is completely excluded from coaptation in the systole [12, 13].

In accordance with these pathophysiological findings, clinical data convincingly indicate that an isolated restrictive annuloplasty leads to high reoccurrence rate of FMR after mitral valve repair [2, 14]. Of note, recent prospective randomized Cardiothoracic Surgical Trials Network (CTSN) trial by Acker *et al.* [2] showed an almost 60% reoccurrence rate of MR $\geq$2 in the annuloplasty group at 2 years postoperatively. Such dismal results of an isolated mitral valve (MV) annuloplasty in type IIIb FMR patients have been often justified by an irreversible course of end-stage LV disease and shifted the focus towards the MV replacement strategy as a more reproducible procedure which would basically eliminate the risk of recurrent MR. Several prospective cohort studies and meta-analyses were performed to compare the surgical strategy for isolated annuloplasty versus mitral valve replacement in FMR patients [15, 16]. Although all these studies demonstrated significantly higher FMR recurrence in the annuloplasty cohort, most of them revealed an increased perioperative mortality rate in the MV replacement group [15, 16]. Even though the randomized trial by Acker *et al.* [2] found no

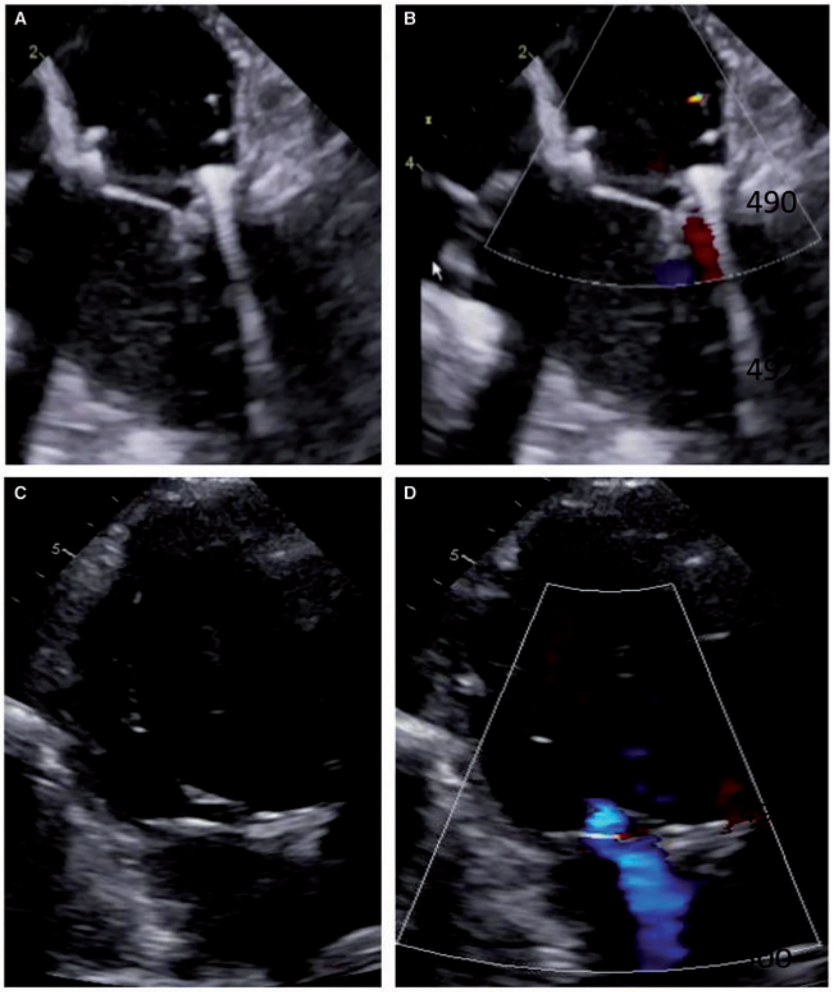

Figure 2: The functional result of an isolated annuloplasty in 2 different functional mitral regurgitation (FMR) entities. (**A** and **B**) The appropriate result after an isolated annuloplasty in type I FMR. (**C** and **D**) Residual leaflet tethering and mitral regurgitation after an isolated annuloplasty in type IIIb FMR (postoperative echocardiography at hospital discharge).

significant differences in 2-year mortality and adverse cardiac events when comparing isolated annuloplasty versus mitral valve replacement cohorts in ischaemic MR, the authors of the current review interpret these results in a different way. On the basis of the findings from this randomized controlled trial, one may conclude that an isolated annuloplasty in type IIIb FMR results in the dismal postoperative results that are comparable to those of mitral valve replacement (i.e. 42% major adverse cardiac and cerebral events (MACCE) rate in the annuloplasty cohort vs 42% MACCE rate in the MV replacement cohort at 2 years postoperatively, $P = 0.96$) [2]. Interestingly, in a *post hoc* analysis of aforementioned randomized controlled trial, those patients with successful annuloplasty (i.e. no MR recurrence at 2-year follow-up) versus those with recurrence of MR >2 demonstrated an evidence of significantly improved reverse LV remodelling [i.e. left ventricular end-systolic volume index (LVESVI) 42.7 ± 26.4 ml/m^2 (successful repair) vs 62.6 ± 26.9 ml/m^2 (MR >2 after repair), $P < 0.0001$] [2]. This finding may indicate the prognostic importance of the long-term stability of mitral repair in type IIIb FMR patients.

An urgent need for pathophysiological correction in type IIIb FMR has led to the development of several subannular repair techniques that aim to correct a distorted subvalvular LV geometry and thereby to better maintain the long-term stability of MV repair. Subannular techniques are very heterogeneous; however, they can be subdivided by their mechanism of action which points out the anatomical structures addressed by subannular repair. Although several groups focused primarily on the augmentation procedures of posterior mitral leaflet [17, 18] and the secondary chordae cutting [19], the majority of subannular reconstruction techniques focused directly on the repositioning of the papillary muscle [20–24]. Our recent meta-analysis on subannular reconstruction in type IIIb FMR demonstrated that MV annuloplasty with simultaneous subannular repair was associated with a 4-fold reduction in the late reoccurrence of MR ≥2 after mitral valve repair as compared to MV annuloplasty alone [25]. Although 'papillary muscles techniques' were the most commonly used manoeuvres in the included studies [i.e. 411/743 (55.3%) patients], our meta-analysis was not powered to analyse the most appropriate subannular manoeuvre in the type IIIb FMR treatment [25]. In addition, our meta-analysis did not include any comparative data of mitral valve replacement versus subannular repair in type IIIb FMR which could be of major interest. Unfortunately, no prospective cohort studies comparing the outcome of subannular mitral valve repair techniques versus mitral

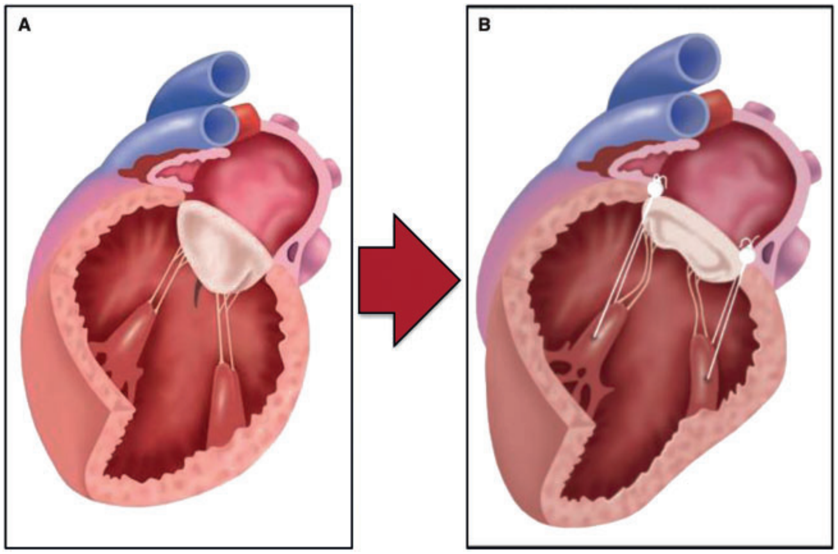

Figure 3: (**A**) Functional impact of left ventricular remodelling on mitral valve geometry in type IIIb functional mitral regurgitation. (**B**) The principle of pathophysiological correction of type IIIb functional mitral regurgitation by repositioning of both papillary muscles using polytetrafluorethylen (PTFE) sutures [10].

valve replacement in type IIIb FMR patients have yet been published.

The main drawback of all subannular manoeuvres is marked heterogeneity and the lack of standardization and, therefore, limited reproducibility. We recently introduced a subannular repair technique, which is intended to be standardized and reproducible, does not significantly prolong aortic-cross-clamp or cardiopulmonary bypass (CPB) time and could be easily performed via a full-endoscopic and non-rib-spreading MV repair approach [10].

MINIMALLY INVASIVE VALVE REPAIR FOR FUNCTIONAL MITRAL REGURGITATION: WHAT IS THE EVIDENCE?

Minimally invasive mitral valve surgery through a right anterolateral minithoracotomy approach became increasingly a standard of care in the setting of isolated mitral valve surgery [26]. In particular, very high mitral valve repair rates and an excellent safety profile using a minimally invasive approach were achieved in patients with degenerative mitral valve disease [27, 28]. For example, a total of >6000 isolated surgical mitral valve procedures were performed in Germany in 2016, 50% of which were treated through a minimally invasive access [29]. Multiple studies worldwide confirmed the hypothesis that minimally invasive mitral valve surgery does not increase the surgical risk as compared to conventional sternotomy [28, 30].

In contrast to degenerative mitral valve disease, surgical data on the systematic use of minimally invasive techniques in the FMR setting are very sparse. Only few case series have been reported by single high-volume and high-expertise institutions [30, 31]. Even though Penicka *et al.* [31] reported on 167 type IIIb FMR patients with left ventricular ejection fraction <45% who underwent minimally invasive mitral valve repair in a single institution during a 12-year period, their surgical strategy has been an isolated annuloplasty in all patients, and no subannular repair was used. Despite significant long-term mortality in mitral annuloplasty subgroup (i.e. 44% all-cause mortality during the median follow-up of 7 years), the aforementioned study demonstrated a significant long-term survival benefit in the minimally invasive surgery cohort as compared to the conservative cohort that received the best medical treatment [31].

The implementation of additional subannular manoeuvres for minimally invasive mitral valve repair surgery of FMR has been reported in small case series only [32, 33]. Santana *et al.* [33] reported on 19 consecutive patients with severe FMR who underwent minimally invasive mitral valve repair using a papillary muscle sling + annuloplasty technique in a single institution. Study population included represent a typical patients' cohort with a type IIIb FMR and severely reduced left ventricular systolic function (i.e. mean left ventricular ejection fraction of 23%). Despite relatively long aortic-cross-clamp and CPB times [i.e. the median aortic-cross-clamp time 106 (interquartile range, IQR, 76–120) min and median CPB time 163 (IQR 119–170) min], which were required to place a papillary muscle sling properly around the base of all the papillary muscles, the authors reported a very satisfying 30-day outcome (0% mortality) and an excellent mitral valve competence at 3-month echocardiographic follow-up [33]. However, the aforementioned report represents a limited single-centre experience with a very short follow-up, and therefore, no definite conclusions can be drawn.

Because type IIIb FMR patients will often require subsequent cardiac surgical interventions due to progressive heart failure (e.g. left ventricular assist device (LVAD) implantation, heart transplantation and coronary artery bypass graft surgery), the specific focus on minimally invasive mitral valve surgery in these patients is well considered and may significantly simplify subsequent reinterventions. On the other hand, we strongly believe that subannular manoeuvres should be adopted in the minimally invasive valve surgery setting and should, therefore, be simple and reproducible not to significantly increase perioperative risk in these severely compromised patients with multiple comorbidities. Therefore, we briefly describe in the following sections our current surgical strategy for minimally invasive mitral valve repair for type IIIb FMR which includes a standardized subannular reconstruction manoeuvre [10].

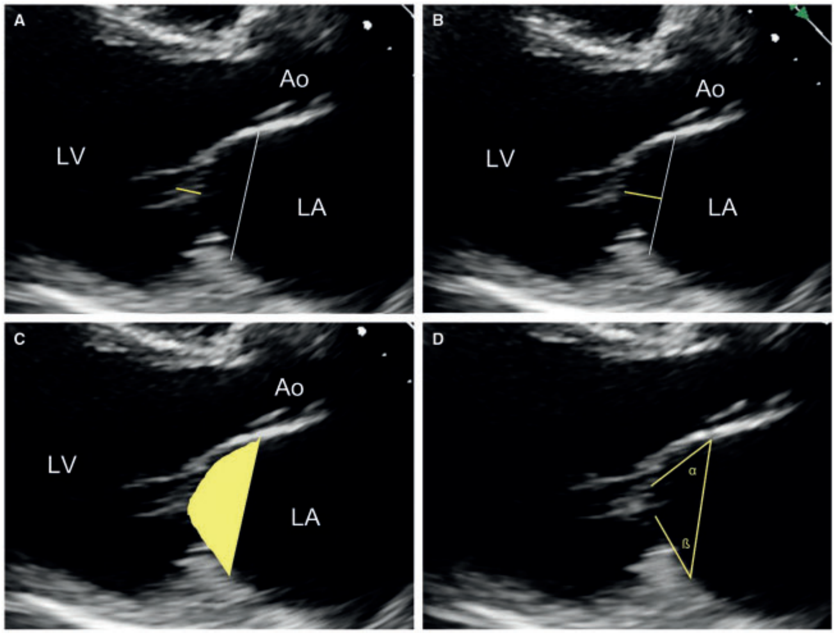

Figure 4: Echocardiographic quantification of tenting parameters in the parasternal long-axis view. (**A**) Coaptation length: distance of overlap between the anterior mitral leaflet and posterior mitral leaflet during the systole; (**B**) tenting height: distance between the annular plane and the most atrial margin of the coaptation line; (**C**) tenting area: area between the mitral annular plane and mitral leaflets at the end systole; and (**D**) tenting angles: angle between the mitral annular plane and anterior mitral leaflet angle and between the mitral annular plane and posterior mitral leaflet angle at the end systole. Ao: ascending aorta; LA: left atrium; LV: left ventricular.

Nowadays, routine diagnostic workup for minimally invasive surgery includes a native chest and abdomen computed tomography scan to exclude relevant calcifications in the thoracic/abdominal aorta in older patients and those with signs of systemic atherosclerosis (e.g. coronary artery disease, carotid artery disease, peripheral artery disease or s/p cerebrovascular accident). Antegrade arterial perfusion by right axillary artery cannulation to prevent retrograde flow in the diseased atheromatous aorta may be potentially advantageous in such patients. Preoperative echocardiography in FMR patients should specifically differentiate between type I and type IIIb valve lesions and quantify the tenting parameters (Fig. 4).

A right anterior minithoracotomy and non-rib-spreading endoscopic approach became the most commonly used technique for surgical exposure [34]. After surgical exposure of the mitral valve and intraoperative confirmation of type IIIb mitral valve lesion, pledgeted 3-0 polytetrafluorethylen (PTFE) sutures are passed in a U-form fashion through the trunks of both papillary muscles (Fig. 5A). Both PTFE sutures are then advanced behind the posterior mitral valve annulus from the ventricular to the atrial side in the corresponding segments (Fig. 5B). Mitral annuloplasty is then performed in the standard fashion using a complete undersized annuloplasty ring. After the annuloplasty ring is completely secured by sutures, both PTFE sutures are passed through the posterior aspect of the annuloplasty ring (Fig. 5C). In the following step, the left ventricle is pressurized with a cold saline to induce the maximal possible tenting of mitral leaflets. Stepwise traction is then applied on both PTFE sutures aiming to bring the anterior leaflet to the level of the annuloplasty ring. After reaching the appropriate position of the anterior leaflet, both sutures are tightly secured on the annuloplasty ring (Fig. 5D) and thereby fixing the distance between the papillary muscle tips and mitral annular plane.

The procedural success of subannular reconstruction may be defined as a nearly complete disappearance of anterior leaflet tenting (i.e. the coaptation line reaches the level of the annuloplasty ring), tenting height of <5 mm and no/trivial residual MR in the intraoperative transoesophageal echocardiography (Fig. 6). The interim analysis of 100 consecutive patients over a period of 2 years showed that our subannular manoeuvre can be safely performed and without significant prolongation of aortic-cross-clamp/CPB times. Over a period of 2 years, this manoeuvre has become the standard surgical procedure in type IIIb FMR patients at the University Heart Center Hamburg and is now routinely performed by 5 mitral valve surgeons.

PROGNOSTIC IMPLICATIONS OF SURGICAL FUNCTIONAL MITRAL REGURGITATION TREATMENT: WHAT KIND OF EVIDENCE DO WE NEED?

The main drawback of surgical and interventional FMR treatment is the lack of appropriate prognostic evidence that convincingly demonstrates the benefits of reducing MR on the long-term prognosis of FMR patients as compared to the guideline-directed medical therapy [35]. In other words, the key question regarding FMR treatment—how many survival years and how much quality of life does the competent mitral valve add for the patients with a primary ventricular disease—is still unanswered. Also, does the progression of cardiomyopathy slow down in the setting of surgically or interventionally corrected MR? The available data for the treatment of secondary MR are sparse and controversial [35]. Several retrospective studies including 1 propensity score-matched analysis [36] revealed a significant survival benefit for

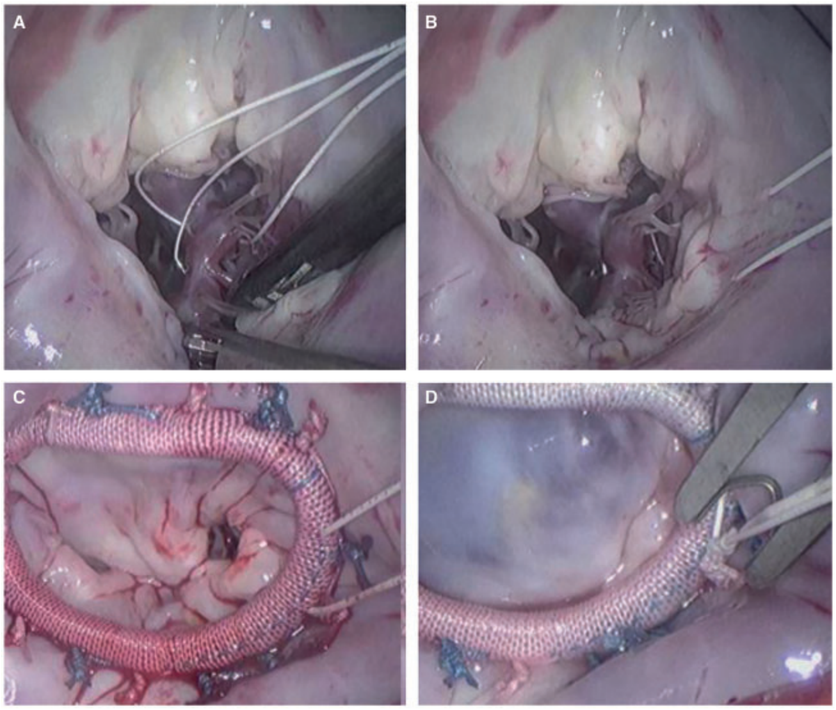

Figure 5: Intraoperative steps of standardized subannular repair for repositioning of both papillary muscles. (**A**) The placement of PTFE sutures in both papillary muscles. (**B**) Advancement of PTFE sutures behind the posterior mitral valve annulus. (**C**) Annuloplasty and anchoring of polytetrafluorethylen (PTFE) sutures on the annuloplasty ring. (**D**) Repositioning of both papillary muscles and fixation of the distance between papillary muscles tips and mitral annuloplasty ring.

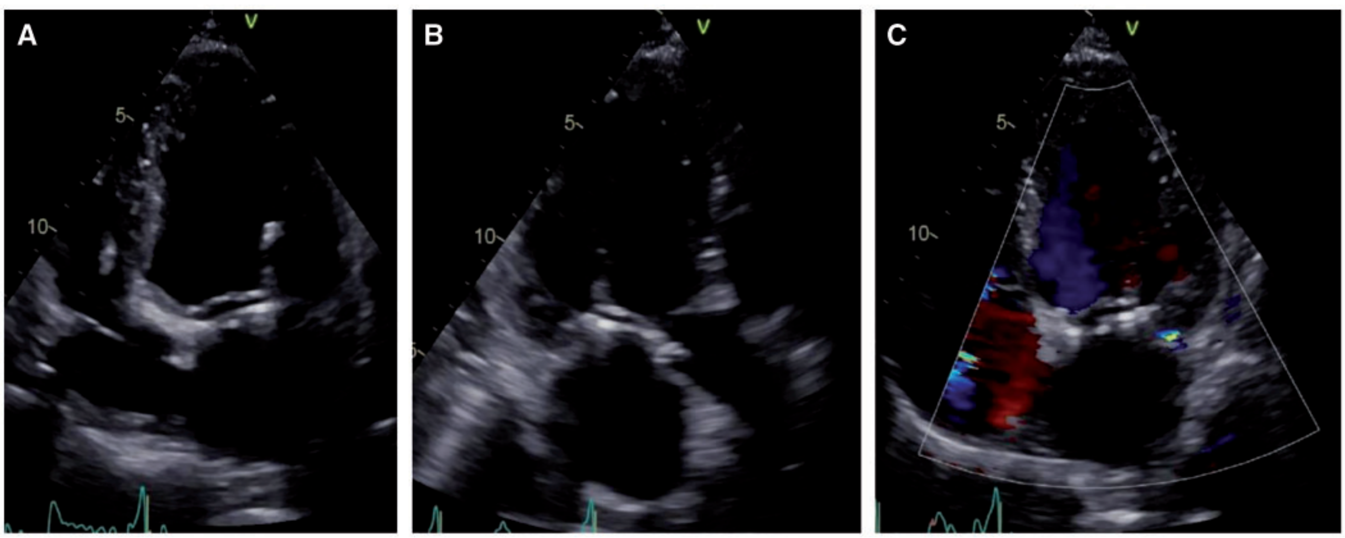

Figure 6: Echocardiographic image after repositioning of the papillary muscle to treat type IIIb functional mitral regurgitation (MR). (**A** and **B**) The coaptation line of the anterior mitral leaflet at the level of the annuloplasty ring in the systole, without residual tenting after repositioning of the papillary muscle (red arrow). (**C**) No residual MR at discharge echocardiography after subannular repair for type IIIb functional MR.

FMR patients who underwent surgical [31] or catheter-based [36] treatment of their secondary MR as compared to the medically treated group. However, all these studies have major methodological flaws which significantly limit their scientific value: (i) none of these studies differentiate between type I and type IIIb FMR and, therefore, represent patient admixture which is difficult to interpret; (ii) include only a historical control group of medically treated patients which is not specified (i.e. the percentage of patients receiving the guideline-directed best medical treatment remains unknown); (iii) ignore the fact that an isolated annuloplasty [31]; and edge-to-edge repair [36] are often not durable in type IIIb FMR during follow-up, and relevant MR reoccurs in 50–70% patients. Therefore, these studies do not differentiate whether progressive heart failure occurs as a sequela of an underlying myocardial disorder or due to reoccurrence of significant MR.

Therefore, we think that we need well-designed prospective cohort studies which would stratify FMR patients into the type I and type IIIb cohorts, include a contemporaneous control group of the best medical treatment and eliminate the confounder of recurrent MR (e.g. by systematic use of subannular techniques). We believe that a prospective multicentre REFORM-MR registry will be the first step to establish the value of standardized subannular repair in type IIIb FMR and to create a solid basis for the future prospective studies addressing the prognostic benefit of FMR treatment.

CONCLUSIONS

In summary, FMR cohort is inhomogeneous and consists of 2 distinct subgroups of patients presenting with a predominantly 'atrial' and 'ventricular' type of secondary MR. These 2 FMR subgroups are different pathophysiological entities and may require tailored surgical treatment to address the primary mechanism of FMR. There is emerging evidence that subannular repair might be beneficial for the long-term outcomes in type IIIb FMR and should probably become a part of the surgical strategy in these patients. To achieve pathophysiological MV correction and to relieve the distortion of subannular MV geometry, papillary muscle repositioning manoeuvres represent the most often used and most promising surgical technique. Minimally invasive techniques in FMR treatment seem to be feasible and safe, when performed in a standardized fashion and in experienced centres. Prognostic benefits of FMR elimination in patients with predominant ventricular disease must still be demonstrated in well-designed prospective studies in the near future.

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