

# FUNCTIONAL MITRAL REGURGITATION: IF THE MYOCARDIUM IS GUILTY DO WE ALSO NEED TO 'REHABILITATE' THE VALVE?

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## ABSTRACT

Mitral regurgitation (MR) is the most frequent valvulopathy in the general population with an incidence that grows with age and is associated with a poor prognosis. Regardless of its primary cause, which can be both ischaemic and non-ischaemic cardiomyopathy, it finally activates a self-feeding process. Due to the complexity of mitral valve (MV) apparatus and its interaction with the myocardium, even the diagnosis could represent a challenge for physicians. Higher technological instruments such as 3D echocardiography and cardiac magnetic resonance could play an important role in the evaluation of MV. In this paper we reviewed the most salient aspects of functional MR pathophysiology as well as the current diagnostic methods. The management of functional mitral regurgitation (FMR) is even more challenging and controversial; the optimal approach, timing, and effectiveness of interventions are still debated. Treatment of FMR begins with optimal medical therapy for left ventricular dysfunction, including cardiac resynchronisation when indicated. While functional improvement after surgery is well established, the benefits in terms of survival are still questionable. Moreover, in patients with high perioperative risk there is a growing interest in emerging percutaneous techniques. Among a variety of medical, surgical, and percutaneous opportunities, authors support an accurate case-by-case evaluation to find a tailored and stepwise treatment according to anatomical features and patient comorbidities.

**Keywords:** Functional mitral regurgitation, cardiomyopathy, heart failure, cardiac resynchronisation therapy, new interventional therapies.

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## DEFINITION AND CLASSIFICATION

Mitral regurgitation (MR) is a common valvular defect with an incidence that grows with age, up to 9.3% in the population over 75 years old; a further worsening of these epidemiologic data can be expected as a consequence of an ageing population. Mitral valve (MV) performance is the result of a complex interaction of many different components: mitral leaflets (ML), mitral annulus (MA), left ventricle (LV), and subvalvular apparatus made of papillary muscles (PM) and chordae tendineae. The MA is a non-planar saddle-shaped

structure that interconnects the other moving elements while being dynamic itself: the MA systolic apical bending allows a sphincter-like shrink with an area reduction of about 30%; this adjustment decreases leaflet tissue stress and maintains coaptation. The failure of this perfect interplay leads to a pathologic retrograde blood flow from the LV to the left atrium (LA) during systole. From the pathophysiological point of view, MR can be defined according to Carpentier Classification: Type 1: normal leaflet motion at the annular plane but annular dilatation or leaflet perforation; Type 2: coaptation beyond the plane secondary to leaflet

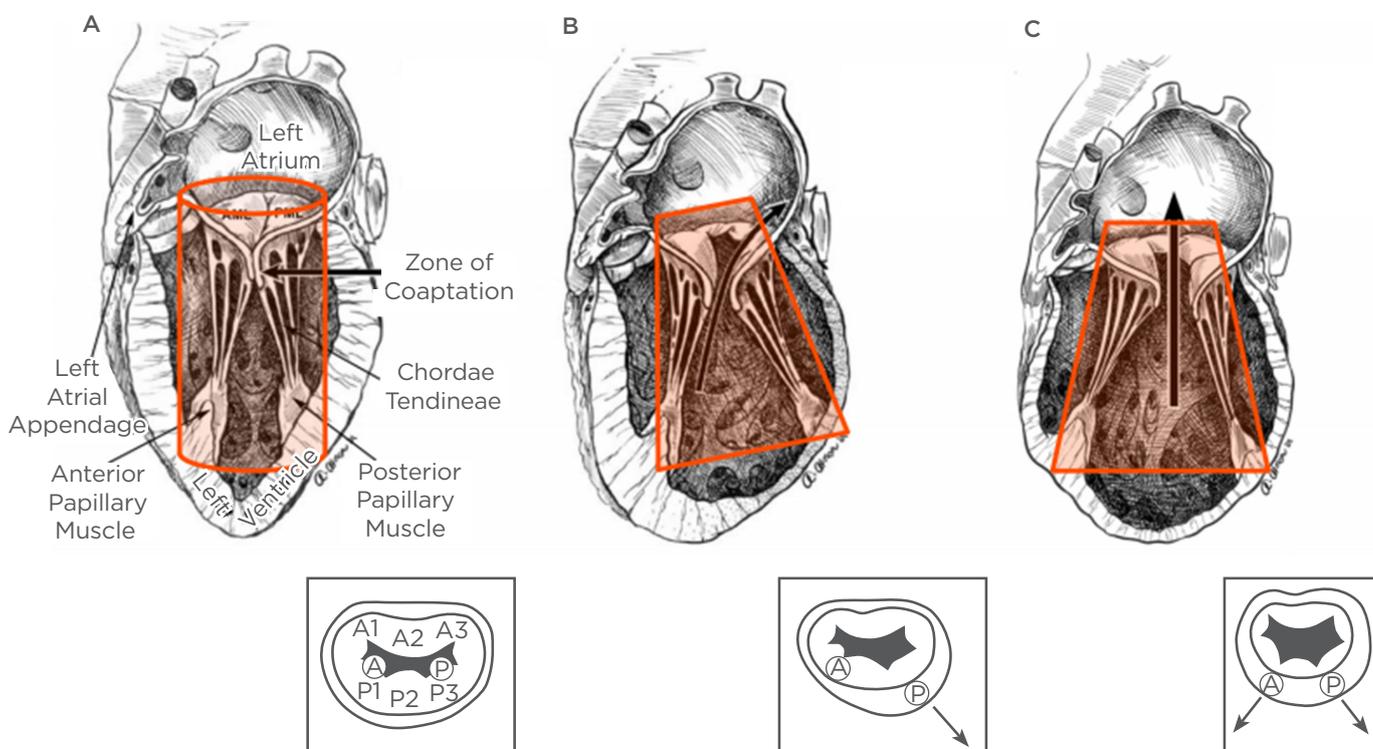
prolapse or PM rupture; Type 3: coaptation proximal to annular plane associated with valvular and subvalvular sclerosis with restrictive leaflet motion (3A: systolic and diastolic, 3B: systolic). Functional mitral regurgitation (FMR) is defined as secondary to myocardial pathology and rules out a primary disease of the valvular tissues; with respect to the Carpentier system, FMR corresponds to a I or III B Class.<sup>1</sup> Moderate-to-severe MR can be diagnosed in about 12% of patients with systolic heart failure (HF) and is associated with poor prognosis; already in 1997, the Survival and Ventricular Enlargement trial demonstrated that FMR detected within the first 16 days after myocardial infarction (MI) is an independent predictor of mortality.<sup>2,3</sup> Recent studies reported similar results in HF patients regardless of the ischaemic or non-ischaemic genesis of the cardiomyopathy.

## PATHOPHYSIOLOGY

MR activates a self-feeding process: LA systolic regurgitant blood returns to the LV during diastole causing volume overload and progressive chamber dilatation, leading to increased LV wall stress, worsening of LV myocardial function, displacement

of PM, and annular dilatation. Regardless of the underlying cardiomyopathy, FMR is driven by several mechanisms: LV chamber dilatation, subvalvular apparatus, dyssynchrony of the LV, and insufficient mitral leaflet adaptation.

LV chamber dilatation causes an enlargement of the annulus and a distortion of its typical 'D' shape with assumption of a circular geometry and a consequent malcoaptation of the leaflets; Yiu et al.<sup>4</sup> demonstrated that ventricle dilatation is also associated with the loss of the systolic annular contraction that worsens regurgitation degree (Figure 1). Subvalvular apparatus is composed of PM and chordae. Under physiological conditions PM stay parallel to the LV long axis and their contraction balances the systolic forces generated on MV leaflets by ventricular pressure. Despite this, it has been a longstanding thought that PM impairment was only due to the ischaemic/infarctual injury of the PM themselves. Recent evidence, in animal models first and in patients afterwards, support the hypothesis that peri-PM myocardium dysfunction (particularly of the lateral wall) is responsible, via PM displacement, for leaflet malapposition.<sup>5</sup>



**Figure 1: Normal mitral valve apparatus (A); mitral regurgitation (MR) with eccentric jet due to lateral left ventricular wall dilatation and posterolateral papillary muscle displacement (B); MR with concentric jet due to global left ventricular wall dilatation, leaflets malcoaptation, and displacement of both papillary muscles (C).**

Dyssynchrony of the LV results in the dyssynchrony of adjacent PM contraction and in leaflet closure; this process has been demonstrated regardless of the dyssynchrony cause: intraventricular conduction defects (very common in dilated ventricles) as well as ischaemic regional contraction defect; in particular LV dyssynchrony in the setting of anterior MI showed to be an independent predictor of FMR.<sup>6</sup> Insufficient mitral leaflet adaptation: 3D echocardiography (3DE) has recently demonstrated, in the setting of LV dilatation, a further compensatory mechanism, as a response to chronic leaflet tethering, which leads to an increase in mitral leaflet tissue and a larger leaflet area; the deficiency of this compensatory system favours MR.<sup>7</sup> The latter described mechanism threatens the definition of FMR itself; it is nowadays accepted that in FMR chronic mechanical stretch stimulates both ML growth and enlargement as a means to prevent regurgitation in the setting of severe LV dilatation.<sup>8</sup> Anatomopathological studies confirmed the reactivation of embryonic processes, partly mediated by transforming growth factor beta expression, with consequent abnormal matrix composition, increased collagen concentration, and activation of valvular interstitial cells.<sup>9</sup> This also represents a challenge during the diagnostic process: to distinguish secondary compensatory modifications from a primary damage of ML that would rule out FMR diagnosis.

## DIAGNOSIS

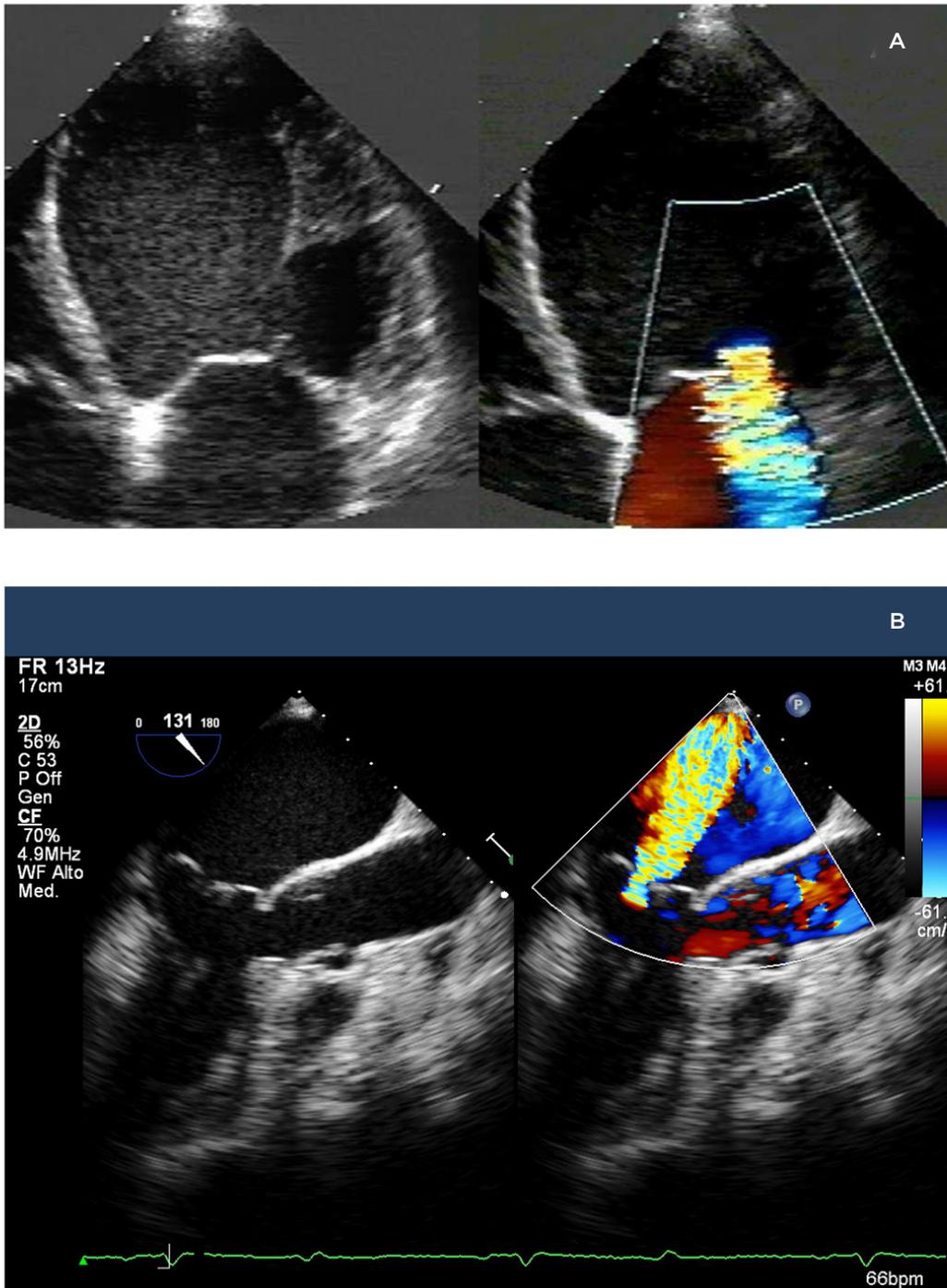
History and physical examination are insensitive for FMR diagnosis; symptoms include effort dyspnoea, asthenia, and reduced exercise capacity but appear to be nonspecific. Physical examination can be misleading as well because the typical systolic murmur related to MR can become low-pitched and soft in the presence of decreased LV pressures. Echocardiography is thus the mainstay for FMR diagnosis and quantification (Figure 2). Assessment of MR severity by echocardiography is complex and requires high accuracy. The 'eyeball' evaluation of the size of the colour Doppler MR jet in the LA is strongly discouraged; current European Association of Echocardiography guidelines support an integrative approach with both quantitative and qualitative parameters.<sup>10</sup> Qualitative parameters include LA size, mitral filling pattern, density of the MR signal on Continuous-Wave Doppler, pulmonary veins (PVs) flow pattern, and pulmonary artery pressure. Despite being

qualitative, some of these parameters are either highly specific or sensitive and help mitigate quantitative method errors: for instance, inverted systolic flow in PVs supports MR severity while conversely, an 'A-wave dominant' mitral inflow pattern excludes severe MR. The most accepted quantitative method is the effective regurgitant orifice area (EROA) calculation that is usually derived by the proximal isovelocity surface area (PISA) method. The assumption of a circular regurgitant orifice is the main limitation of the PISA use in FMR, typically characterised by an elliptical shaped orifice, and leads to an underestimation of the MR grade. Current guidelines indicate the need to consider severe primary MR if the EROA is  $\geq 40$  mm<sup>2</sup>, while the threshold for severity is 20 mm<sup>2</sup> in FMR.<sup>10</sup>

To date, higher technological instruments such as 3DE and cardiac magnetic resonance (CMR) can help physicians in the complex study of MV structures. 3DE allows the calculation of vena contracta sectional area and thus a direct assessment of EROA without any geometric and flow assumptions and the carried bias. 3DE is rapidly developing and correlates with CMR results. Nevertheless, CMR remains the gold standard diagnostic tool for accuracy, reproducibility, and precision in evaluating LV function and LV volumes, and offers an excellent alternative for directly quantifying EROA and LV regurgitant volume; this technique presents some limitations as well (arrhythmias, non-compatible pacemakers or cardioverter defibrillators, claustrophobia) and should be reserved to cases in which echocardiography is technically difficult or equivocal.<sup>11</sup> Further evidences are needed to better define the role of these new methods and to integrate them into a linear and reliable diagnostic process: nowadays, what does one do with a FMR patient with an EROA  $\geq 20$  mm<sup>2</sup> accurately measured by CMR or transesophageal 3DE?

## THERAPY

We described the complexity of FMR pathophysiology and of the diagnostic process (Figure 3). Treatment of FMR is also challenging and controversial: indications, types of intervention ranging from drugs administration to surgery, timing, and interplay among different approaches are still debated. The first enigma physicians need to decipher is about the main target of therapy: the myocardium, or the valve itself?



**Figure 2: Severe functional mitral regurgitation (MR) in transthoracic echocardiography apical four-chamber view (A); severe functional MR in transoesophageal echocardiography long axis view (B).**

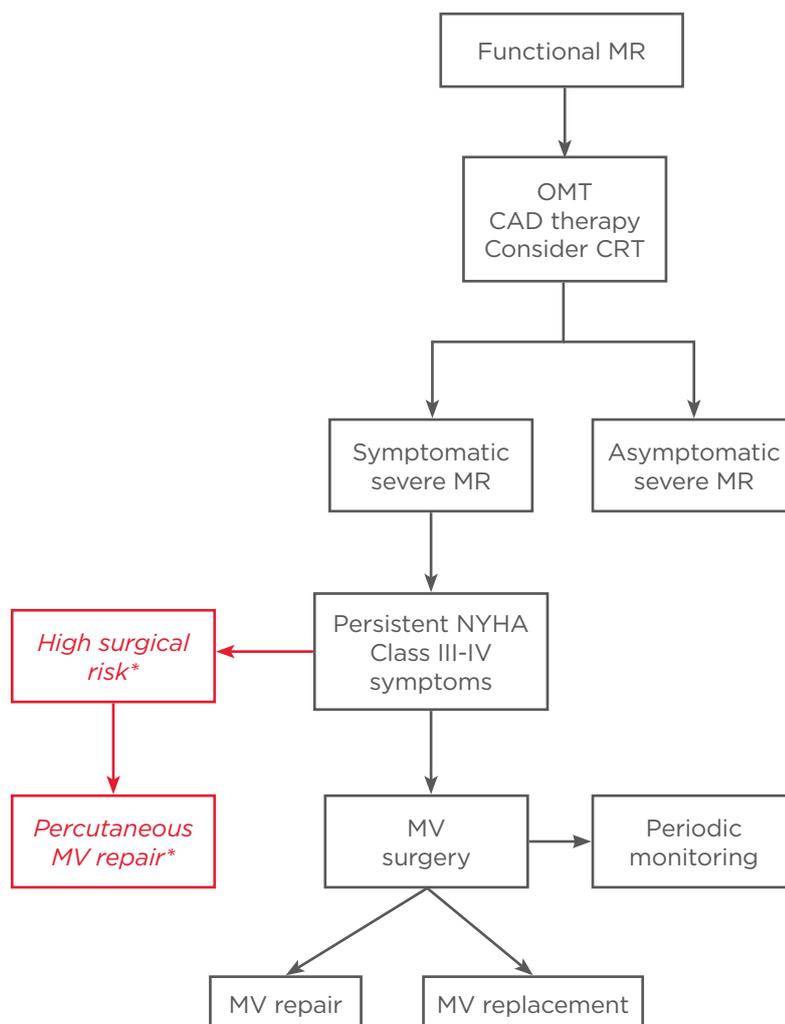
### Optimal Medical Therapy (OMT)

OMT is the mainstay of therapy. The therapy goal is to improve survival, increase cardiac performance, and reduce symptoms. Beta blockers, angiotensin-converting-enzyme inhibitors or angiotensin receptor blockers, and aldosterone antagonists are drugs that are able to address myocardial dysfunction by counteracting apoptosis and fibrosis; the resulting effect is the reduction

of LV remodelling.<sup>12,13</sup> Vasodilators and loop diuretics act in concert to reduce LV pre and post-load, reduce the entity of MR, and finally improve HF symptoms.

### Cardiac Resynchronisation Therapy (CRT)

The rationale for CRT is that approximately 30% of patients with LV dysfunction and chronic HF present not only depressed contractility but also impairment of conduction pathways.



**Figure 3: Algorithm for the management of functional mitral regurgitation.**

MR: mitral regurgitation; OMT: optimal medical therapy; CAD: coronary artery disease; CRT: cardiac resynchronisation therapy; NYHA: New York Heart Association; MV: mitral valve.

It is well known that inter and intra-ventricular conduction delays lead to asynchronous contraction of LV wall segments, impaired LV efficiency, and uncoordinated PM motion. CRT is a mini-invasive technique able to improve ventricular synchrony, which is thus transmitted to valvular and subvalvular apparatuses, by stimulating both ventricles at the same time; in particular, LV is reached by a pacing lead positioned distally into the coronary sinus (CS). FMR reduction is consequently gained by improvement of myocardial contractility, reversal of LV remodelling, PM resynchronisation, and by increasing MA contraction forces. Van Bommel et al.<sup>14</sup> demonstrated a significant reduction of MR in 98 high-surgical risk patients with moderate-to-severe FMR undergoing CRT: 1 Grade or more MR improvement was observed in 49% of patients and was an independent predictor of survival.

The CARE-HF trial<sup>15</sup> enrolled 813 HF patients in III/IV New York Heart Association (NYHA) Class and showed that the incidence of the composite endpoint of death and all-cause rehospitalisation was 39% in the CRT group versus 55% in medical-therapy group. Moreover CRT reduced the mitral regurgitant jet area and increased LV performance, leading to symptom relief and better quality of life.<sup>15</sup> The MADIT-CRT trial<sup>16</sup> confirmed, in patients with severe LV dysfunction, a MR significant reduction: 1 grade or more improvement occurred in 15.3% of the CRT group patients versus 8.3% of the control group. In the same study, the extent of improvement of echocardiographic measures was directly related to 1 year incidence of death or HF hospitalisations.<sup>16</sup> Nevertheless, response to CRT is not always predictable; despite numerous and heterogeneous criteria having been proposed in the literature to define a

positive response to CRT, it appears unquestionable that a quote of about 30% of patients have little or no benefits from CRT. This failure can be attributed to procedural issues (inappropriate LV lead positioning), and to the extent and location of the scar tissue in ischaemic patients, as well as to the natural history of the underlying progressive disease.<sup>17</sup> Current American College of Cardiology/American Heart Association (ACC/AHA) guidelines<sup>18</sup> on valvular disease recommend CRT in symptomatic patients with chronic severe FMR who meet the other criteria for device therapy (Class 1A).

## Surgical Treatment

When symptoms persist despite OMT, patients are often referred to surgery, which may represent the final therapeutic option. As mentioned before, the prognosis of dilated and ischaemic cardiomyopathy worsens when FMR complicates the disease.<sup>19,20</sup> Surgical intervention has been associated with improvement of HF symptoms and LV reverse remodelling; even so, the best surgical technique and the prognostic impact of surgery are still debated. Mihajlevic et al.<sup>21</sup> indeed, in their propensity matched analysis of 390 patients with moderate-to-severe FMR referred to coronary artery bypass graft (CABG), demonstrated that additional MV annuloplasty reduced FMR and improved symptoms but was not associated with longer survival. The same topic has been addressed in a recent randomised trial: RIME investigators<sup>22</sup> evaluated whether MV repair during CABG in patients with moderate FMR may improve functional capacity and LV reverse remodelling. Compared to CABG alone, additional mitral annuloplasty increased peak oxygen consumption, NYHA class, and reduced LV volumes and MR severity; moreover recurrent moderate or greater FMR was observed at 1 year in 4% of treated patients, and in 50% of CABG alone patients. Despite improvement of these clinical and echocardiographic parameters, driven by the higher surgical risk, death incidence at 1 year was higher (9% versus 5%,  $p=0.66$ ) in the annuloplasty group.<sup>22</sup>

In a very recent study Smith et al.<sup>23</sup> demonstrated that the addition of MV repair to CABG resulted in a reduction of MR but found no significant differences in terms of LV reverse remodelling and 1 year survival. These disappointing results on survival after MV surgery during CABG can be explained by both

the predictable increased morbidity in the perioperative time and by the main feature of FMR itself: a myocardial rather than a valvular disease. The benefits of a combined procedure need thus to be carefully balanced against the higher surgical risk. It appears unquestionable that FMR worsens patients outcome but, conversely, there is no clear evidence that FMR correction contributes to better it. Nevertheless, the reported data must be interpreted with caution since most studies are retrospective, observational, single-centre, or underpowered for hard endpoints, and thus suffer from potential referral, selection, and reporting biases. Moreover, the majority of the enrolled patients underwent surgery according to old and nowadays suboptimal approaches: flexible rings, incomplete bands, inadequate size of the annuloplasty rings. Since surgical techniques evolve so rapidly, further studies are certainly needed.

To date, the state of the art of MV repair is restrictive annuloplasty: an undersized, rigid, D-shaped ring implantation able to accomplish leaflet coaptation and valve competency. The major concern of MV repair is the recurrence of significant MR, that ranges from 10-30% at 1 year; echocardiographic predictors of mid-term failure have been proved to be extreme leaflets tethering (posterior leaflet angle  $>45^\circ$ , distal anterior leaflet angle  $>20^\circ$ ) and/or advanced remodelling (end-diastolic diameter  $>65\text{mm}$ , end-systolic volume  $>100\text{ ml/m}^2$ , sphericity index  $>0.7$ ). Whenever the above mentioned conditions are present, undersized annuloplasty should be avoided and chordal-sparing MV replacement should probably be preferred. However, despite higher MR recurrence, MV repair in the past few years has greatly exceeded MV replacement. According to the Society of Thoracic Surgeons between the years 2008 and 2012, about 66% of MV surgeries have been performed using a conservative approach, and this choice was mainly motivated by lower perioperative mortality.<sup>24</sup> Because MR recurrence after repair has been proposed as responsible for surgery failure in reducing mid to long-term mortality, renewed interest in more radical techniques has recently been raised. Acker et al.<sup>25</sup> have very recently published the results of a randomised trial including 251 patients with severe ischaemic MR undergoing MV repair or chordal-sparing replacement. Authors demonstrated, as expected, a higher MR recurrence in the repair group (32.6%

versus 2.3%) but a similar perioperative mortality. Despite the fact that the trial showed no significant difference with respect to the primary endpoint (reduction of the left ventricular end-systolic volume at 12 months) and to major adverse cardiovascular events the study was not powered to show a survival difference at 1 year.<sup>25</sup> Moreover, the above mentioned echocardiographic predictors of repair failure were not considered as exclusion criteria and the high recurrence of MR might have compromised the repair approach potential benefit; therefore it remains debatable as to which one, between repairing and replacing, is the best approach.

Despite the fact that these results are expected to improve on longer term follow-up, doubt about the real target of therapy remains the real challenge for physicians. As a consequence, recent surgical techniques have gone beyond the MV and targeted the subvalvular structures (chordal resection, relocation of PM) and the LV. The latter seems to be the most promising approach: infarct plication, infarct excision and patching, septal reshaping, and external restraint are some of the proposed techniques. Two extracardiac devices have been introduced in the last decade. The CorCap is a LV passive restraint device that was shown in the Acorn trial to provide significant additional benefit in terms of LV reverse remodelling, when added to MV surgery alone in patients with idiopathic dilated cardiomyopathy (IDC).<sup>26,27</sup> Coapsys is the second device and consists of two epicardial pads (anterior and posterior) connected and drawn together by a transventricular chord: the few data available suggest a potential reduction of MR severity and improvement of clinical parameters. Most of the published data pertain predominantly to ischaemic MR, which is the most diffuse form of FMR; fewer data are available about the long-term outcome of surgical MV repair in non-ischaemic LV dysfunction. De Bonis et al.<sup>28</sup> demonstrated that MV repair for FMR in IDC can be performed with a low in-hospital mortality with long-term benefits in terms of NYHA functional class and LV dimensions and function. On the basis of all these evidences, current European Society of Cardiology guidelines<sup>29</sup> recommend surgical treatment for severe FMR in patients with an ejection fraction >30% undergoing CABG (Class I, level of evidence C), while according to the ACC/AHA guidelines<sup>18</sup> in the same subset, MV surgery is reasonable

(Class IIa, level of evidence B). Conversely few evidences support MV surgery in patients not requiring myocardial revascularisation; according to both American and European guidelines, MV surgery “may be considered” (Class IIb) only for severely symptomatic patients despite OMT.

## Percutaneous Options

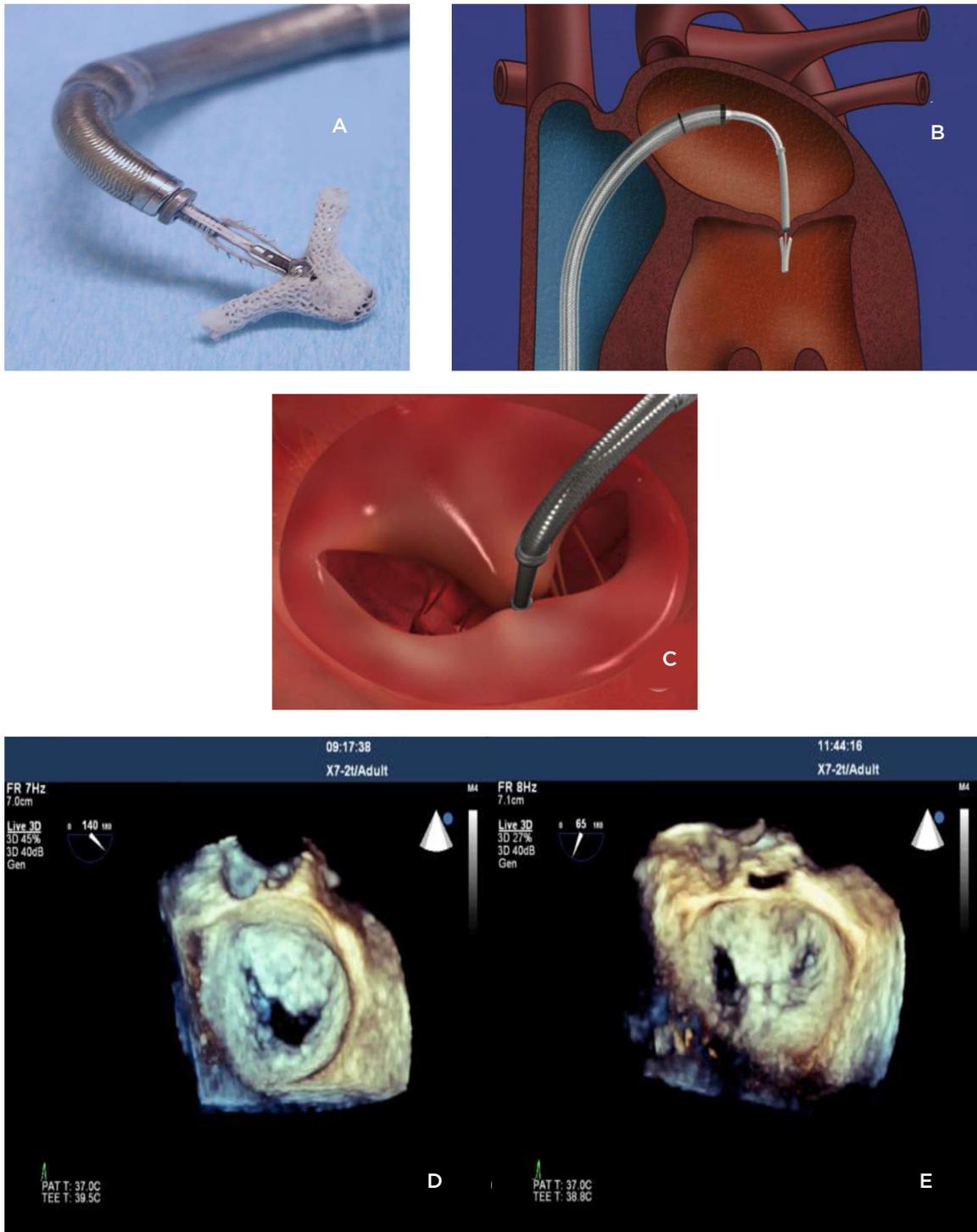
In recent years percutaneous valve therapy greatly advanced: the complexity of the mitral apparatus makes the conception and the evaluation of mitral devices as compared to aortic ones more challenging. Nevertheless, the need for percutaneous techniques is motivated by the population ageing phenomenon which carries higher comorbidities in older patients: about 70% of these patients are either not referred or denied MV surgery.<sup>30</sup> Several transcatheter MV therapies have been adapted from surgical techniques and are being applied in patients at high operative risk. Even though the percutaneous approach has not received approval according to AHA/ACC guidelines, MitraClip technology proved to be safe and effective and rapidly reached a widespread diffusion with over 10,000 patients treated<sup>31</sup> (Figure 4).

Based on the edge-to-edge surgical technique, it is a percutaneous device able to deliver on anterior and posterior leaflets one or more clips via transeptal access and to restore coaptation. The EVEREST II randomised trial<sup>32,33</sup> compared MitraClip to MV surgery in a cohort of 279 patients with severe MR, including a quote of FMR of almost 30%. Although surgery was more effective at reducing MR, both groups showed a similar degree of LV reverse remodelling and NYHA class improvement. Moreover, the rates of primary efficacy endpoint at 12 months (a composite of freedom from death, from surgery for valve dysfunction, from Grade 3+ or 4+ MR) was lower in percutaneous-repair group as compared to surgery group (55% versus 73%); the same advantage was kept at 4 years follow-up.<sup>32,33</sup> These findings were confirmed by the ACCESS-EU<sup>34</sup> - the largest real-world database on MitraClip therapy, which included a larger quote of FMR patients (70%). Despite these promising results, a challenge lies ahead: mortality represents the hardest endpoint and it will require years or even decades to be unquestionably defined.

Devices and techniques are continuously evolving: a recently proposed alternative technique is the

indirect annuloplasty. Based on the anatomical proximity of the CS to the posterior mitral annulus, the devices inserted into the CS are meant to create tension that is transmitted to the annulus and reduces annular circumference. The CARILLON is the only device currently approved for use in Europe but its penetration in clinical practice is limited by several issues: increased distance between CS and mitral

apparatus in dilated hearts, left circumflex artery proximity and the correlated risk of compression, and preclusion of future CRT.<sup>31</sup> New devices for transvascular direct annuloplasty, such as Mitralign, Accucinch, and Valtech systems are already showing up in the FMR skyline; all these promising techniques will drive physicians to less invasive approaches and will widen the therapeutic opportunities for very high risk patients.



**Figure 4: MitraClip device (A); MitraClip deployment (B and C); 3D echocardiographic view before (D) and after MitraClip deployment (E).**

## CONCLUSION

FMR is a complex disease presenting both diagnostic and therapeutic challenges. It is the author's opinion that FMR has to be considered as a LV pathology and that the LV needs to be the first target of therapy. Medical therapy, and revascularisation therapy for ischaemic FMR as well as CRT indeed showed the best results in

terms of hard clinical endpoints. The valve itself, meant in the complexity of its anatomical interactive structures, has to be addressed as a second-line approach; the variety of both surgical and percutaneous techniques available suggests the need for an accurate case by case evaluation and a tailored strategy driven by valve and ventricle anatomy as well as patients' characteristics and comorbidities.

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