Surgical Treatment of Functional Ischemic Mitral Regurgitation

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THE 8 ORIGINAL PAPERS ARE

Bjerre M, Jensen H, Andersen JD, Ringgaard S, Smerup M, Wierup P, Hasenkam JM, Nielsen SL. Chronic Ischemic Mitral Regurgitation Induced in Pigs by Catheter-Based Coronary Artery Occlusion. J Heart Valve Dis 2008; 17:283-289.

Jensen H, Jensen MO, Ringgaard S, Smerup MH, Sorensen TS, Kim WY, Sloth E, Wierup P, Hasenkam JM, Nielsen SL. Geometric determinants of chronic functional ischemic mitral regurgitation: insights from three-dimensional cardiac magnetic resonance imaging. J Heart Valve Dis 2008; 17(1):16-22.

Henrik Jensen, Morten O. Jensen, Morten H. Smerup, Steffen Ringgaard, Thomas S. Sørensen, Niels T. Andersen, Per Wierup, J. Michael Hasenkam, Sten L. Nielsen; Three-Dimensional Assessment of Papillary Muscle Displacement in Ischemic Mitral Regurgitation. J Thorac Cardiovasc Surg 2010;140,6:1312-1318.

Henrik Jensen, Morten O. Jensen, Morten H. Smerup, Stefan Vind-Kezunovic, Steffen Ringgaard, Niels T. Andersen, Rikke Vestergaard, Per Wierup, J. Michael Hasenkam, Sten L. Nielsen: Impact of Papillary Muscle Relocation as Adjunct Procedure to Mitral Ring Annuloplasty in Functional Ischemic Mitral Regurgitation. Circulation 2009;120[suppl 1]:S92–S98.

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INTRODUCTION

FUNCTIONAL ISCHEMIC MITRAL REGURGITATION – AN UNSOLVED CHALLENGE!

Improved and available health care in the present era has successfully increased the life expectancy of many patients, since we now treat a wide range of diseases, which would have shortened the longevity only one or two decades ago. Accordingly, in cardiovascular disease, the heart team of cardiologists and cardiac surgeons is now able to offer very effective treatment modalities for most cardiovascular conditions, and often more than one qualified treatment modality is available, e.g. the choice in aortic stenosis between transcatheter and conventional valves, and the choice in ischemic heart disease between coronary artery bypass surgery (CABG) and percutaneous coronary intervention. Meanwhile, there are cardiovascular diseases for which we as physicians have not been able to produce a sufficiently effective treatment, and the topic of the present thesis, functional ischemic mitral regurgitation (FIMR), belongs to this category.

FIMR has been defined as mitral regurgitation secondary to myocardial infarction or coronary artery disease in patients with anatomically normal mitral valve leaflets and chordae tendineae. Bursi et al. (1), reviewed the prevalence of FIMR after myocardial infarction, and reported that any FIMR is present in 21% of patients, and 3-13% have at least moderate FIMR. A similar prevalence is observed in a Scandinavian population, with any FIMR in

28% of patients referred for CABG surgery, and with at least moderate FIMR in 2.7% (2). It has clearly been demonstrated by Grigioni et al. (3, 4), that FIMR aggravates prognosis after myocardial infarction corresponding with severity, and thus there is an absolute need for an effective treatment. Currently, the "gold-standard" treatment of FIMR is concomitant down-sized ring annuloplasty at the time of CABG surgery. However, this procedure has a failure rate around 20-30% in terms of recurrent FIMR after the first 2 - 4 years, and there are few, if any, other disciplines in cardiac surgery where we consider such a result a "gold standard". This underscores that we still have not identified a truly effective and lasting treatment of FIMR, that relieves patient suffering and improves survival. Therefore, FIMR is very much an unsolved challenge.

As a response to this challenge, investigators have become aware of the neccessity to fundamentally readdress FIMR to optimize treatment, and this resulted in new insights into the pathogenesis of FIMR. As a result, focus was shifted to include the importance of remodeling of the left ventricular (LV) subvalvular apparatus, which consists of the chordae tendineae and papillary muscles, because these structures were identified to play a pivotal role in the pathogenesis of FIMR. Also, mechanistic insights into the forces acting to balance the complex mitral valve apparatus has been done in vitro and in vivo, producing new knowledge of how to most physiologically address the mitral valve. Accordingly, where surgical therapy of FIMR previously was addressing only the mitral annulus dilatation, specific surgical techniques were introduced addressing the many different aspects of the subvalvular mitral valve apparatus.

In many ways we are at a cross road in terms of what constitutes optimal FIMR treatment: is CABG combined with mitral valve ring annuloplasty better than CABG alone in moderate FIMR? Does mitral valve repair really produce better outcome than mitral valve replacement? And does adding an adjunct valvular repair or subvalvular LV reverse remodeling procedure shift that balance? In the present thesis, to shed further light on these questions and help identify potential cornerstones in improving the "gold standard", the current status and future perspectives of the surgical treatment of FIMR is addressed.

Historical note on mitral valve surgery

As early as in the fifteenth century, Leonardo Da Vinci sketched the mitral valve with great accuracy and precision, but five hundred years were to pass before the birth of mitral valve surgery was seen in the early twentieth century. Initially, efforts were directed to treat mitral valve stenosis due to rheumatic fever, and a theoretical consideration of this was published by Sir Lauder Brunton in 1902. Twentyone years later in 1923, Cutler and Levine reported the first actual mitral valve operation, using a median sternotomy and insertion of a curved knife through the left ventricular apex to cut a stenotic mitral valve. In 1925 Souttar digitally opened a stenotic mitral valve and thereby introduced the "closed commissurotomy". Meanwhile, another 32 years were to pass before open mitral valve surgery was introduced in 1957 by Lillehei, utilizing cardiopulmonary bypass. From that point development picked up the pace and only four years later in 1961 Starr and Edwards published a paper describing the first human implantation of a mechanical mitral valve prosthesis. The concept of mitral valve repair and mitral valve ring annuloplasty emerged in the late 1960's, inspired by the pioneering work of Dr. Alain Carpentier, and continuing this day, substantial efforts are being made to optimize the design of mitral annuloplasty rings.

PATHOPHYSIOLOGY OF FIMR

CLASSIFICATION OF MITRAL VALVE REGURGITATION

Dr. Carpentier classified mitral regurgitation (MR) into three main patho-anatomic types (figure 1) (5):

Type I; Normal leaflet motion. Seen in a dilated mitral annulus in dilated or ischemic cardiomyopathy or due to leaflet perforation from endocarditis

Type II; Leaflet prolapse. Seen in patients with myxomatous degeneration or fibroelastic defeciency, causing a floppy mitral valve with chordal elongation and/or rupture. Rarely seen in ischemic cardiomyopathy patients with papillary muscle elongation or rupture

Type III; Restricted leaflet motion (IIIa : diastole, IIIb : systole). Both types can be caused by rheumatic valve disease. IIIb can also be caused by papillary muscle displacement in dilated or ischemic cardiomyopathy

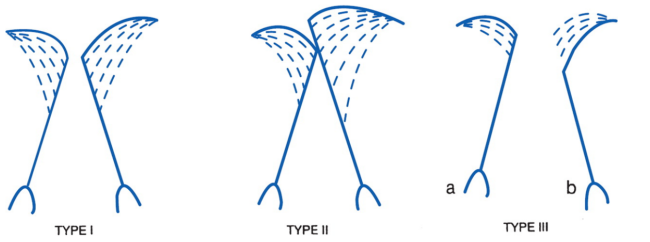


Figure 1. Classification of mitral valve regurgitation. Leaflet motion during the heart cycle is shown by the dotted lines. Type I mitral regurgitation is due to annular dilatation with normal leaflet motion. Type II mitral regurgitation is due to leaflet prolapse. Type III is subdivided into restriction during diastole ("a") or systole ("b"). Type IIIb is typically seen in patients with ischemic mitral regurgitation. From Carpentier A: Cardiac valve surgery: The "French correction." J Thorac Cardiovasc Surg 1983; 86: 323.) Reproduced with permission from Elsevier.

THE NORMAL MITRAL VALVE

In the normal heart (6-9) in diastole, the maximum mitral valve circumferences is approximately 10 cm, and the mitral valve area approximately 8 cm2, with a linear variation with the body surface area for an indexed value of 5 cm2/m2. The mitral annular area is reduced up to 40% during systole. The normal human mitral annulus is roughly elliptical and is saddle-shaped in systole, and flat in diastole. The mitral annulus moves upward into the left atrium in diastole, facilitating atrial filling, and toward the LV apex during systole. The annulus has two major collagenous structures: the right fibrous trigone, a part of the central fibrous body, and the left fibrous trigone. Collagen bundles extend circumferentially around the posterior annuls from each fibrous trigone, but the posterior two-thirds of the annulus is primarily muscular. The mitral valve has two major leaflets, the anterior and posterior, each covering ½ of the mitral annulus. The anterior mitral leaflet spans the distance between the commissures and covers one third of the annular circumference and is in fibrous continuity with the aortic annulus. The posterior leaflet spans 2/3 of the circumference and usually contains three scallops, P1-P3. The anterior leaflet has no scallops, but for nomenclature it is labelled accordingly A1-A3 (figure 2). The leaflet surface near the free

margin on the atrial side, where leaflet coaptation occurs, is called the rough zone, with the remainder of the leaflet surface called the smooth zone. The two leaflets are separated by the postero-medial and antero-lateral commissures, where small commissural leaflets can be identified. The leaflets include three histological layers: the solid collagenous core continuous with the chordae tendineae, the spongiosa on the atrial surface and forming the leaflet leading edge, and a thin fibroelastic covering of most of the leaflets. On the atrial aspect of both leaflets, this fibroelastic surface is rich in elastin. In addition, the leaflets contain contractile tissue, blood vessels and both afferent and efferent nerves. The combined surface area of the two leaflets is up to two times the surface area of the mitral orifice, while in systole the anterior leaflet alone can cover the mitral annular orifice.
The chordae tendineae, which connect the mitral leaflets with the papillary muscles, are divided into three groups. Marginal (primary) chordae insert on the leading edge of the leaflets to prevent valve-edge prolapse during systole (figure 2). The second-order chordae, including two larger “strut" chordae on the anterior leaflet, insert on the ventricular surface of the leaflets at the junction of the rough and clear zones and are important for optimal annular-ventricular continuity and systolic function. The strut chordae remain taut throughout the cardiac cycle as demonstrated by Rijk- zwikker (8), facilitated by coordinated contractions of the papillary muscles. On the posterior leaflet the second order chordae are also named intermediate chordae. Basal or tertiary chordae originate directly from the trabeculae carneae of the ventricular wall and attach to the posterior leaflet near the annulus. Also, commissural chordae exist, also known as “fan” chordae due to their anatomical presentation. Chordae can contain nerve fibers, blood vessels and muscle tissue. Humans have a total of about twenty-five chordae tendineae. In humans the chordae tendineae vary in length from approximately 0.25 to 2.25 cm from the valvular towards the LV insertion, and vary in diameter from 0.24 to 1.75 mm.

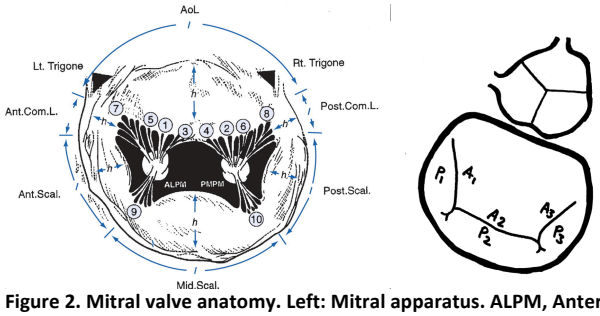


Figure 2. Mitral valve anatomy. Left: Mitral apparatus. ALPM, Anterolateral papillary muscle; PMPM, posteromedial papillary muscle; AoL, aortic leaflet; Ant.Com.L, anterior commissural leaflet; Post.Com.L., posterior commissural leaflet; Ant.Scal., anterior scallop; Mid.Scal., middle scallop. Right: Surgeons view of the mitral valve, leaflet coaptation segments A1-P1, A2-P2 and A3-P3 and the aorta is outlined. Left image from: Sakai T. et al: Distance between mitral annulus and papillary muscles: anatomic study in normal human hearts. J Thorac Cardiovasc Surg 1999; 118: 636. Reproduced with permission from Elsevier.

There are two papillary muscles, the antero-lateral (APM) and postero-medial (PPM). The PPM often has multiple seperated heads, while the APM is less divided. The papillary muscles are sitting in parallel with the commissural regions and, accordingly, each of the APM and PPM send chordae tendineae to both the anterior and posterior mitral valve leaflet and the adjacent commissure. The APM is supplied by branches of the left coronary artery, most often a diagonal branch from the left anterior descending artery, but it may also be supplied by an obtuse marginal branch from the circumflex artery. The main blood supply to the PPM follows the dominant coronary artery, and thus it is supplied by the posterior descending coronary artery in 85%, and the circumflex coronary artery in 15 %. The PPM has two-vessel perfusion in 37% while the APM has two-vessel perfusion in 71% of normal individuals. This leaves the PPM more vulnerable to ischemia. The supply of blood to the papillary muscles comes from large penetrating branches originating from epicardial vessels. The tip, mid-portion, and base generally receive their vascular supply from separate tributaries (10). When addressing the “inter-papillary muscle distance” it is pivotal to define if it is the distance between the papillary muscle tips or papillary muscle bases, that is being described. The normal inter-papillary muscle distance is 2.1 cm from tip to tip, but naturally the distance between the bases is smaller than that. The normal distance from each papillary muscle tip to the anterior annulus fibrosa is 2.6 – 2.8 cm (11).

THE MITRAL VALVE APPARATUS IN FIMR

Ischemic heart disease will cause compensatory dilatation of the LV. First, the regions affected by the ischemia will dilate and cause local remodeling. Later, as the disease progresses, global LV remodeling and dilatation will occur. FIMR is a result of this LV remodeling, and the different myocardial regions affected will impact different parts of the mitral valve apparatus.

The mitral valve force balance

During systole, the LV pressure pushes the leaflets towards the left atrium and thereby exerts a closing force. This closing force is counterbalanced by tethering forces in the chordae tendineae, which are fixated on the papillary muscles, and the leaflet attachment to the mitral valve annulus. In the physiological state, the mitral valve apparatus exists in a perfect force-balance during systole between opposing forces to secure a competent valve. Geometric as well as hemodynamic changes will affect this force balance. As described by Levine et al. (12), inotropic vasopressors will increase closing forces and reduce tethering forces due to less papillary muscle displacement, resulting in less FIMR. In contrast, non-inotropic vasopressors will increase FIMR by increasing tethering forces more than closing forces. The impact on the force balance from changing the geometrical position of the papillary muscle tips has been extensively investigated by Nielsen et al. utilizing strain gauge technology; Using in vitro porcine valves, they demonstrated that distorting papillary muscle geometry causes functinal MR due to mitral valve malalignment and a redistribution of the tethering forces (13, 14). Also, they used a porcine model of acute FIMR (15) to demonstrate, that tethering forces are different between ischemic (reduced forces) and non-ischemic (increased forces) regions. This underscores the role of a disturbed mitral valve force balance in the pathogenesis of FIMR.

Do the leaflets change in FIMR?

FIMR has often been defined as MR in patients with a normal mitral valve leaflets, that are simply distorted due to annular dilatation and papillary muscle displacement. In 2009 Dal-Bianco et al. (16) used an experimental ovine model to demonstrate that mitral leaflets can adapt and increase mitral valve leaflet area and thickness due to mechanical stresses imposed by papillary muscle tethering. Meanwhile, in the clinical setting as early as in 1983, Boltwood et al. (17) postulated that mitral leaflet tissue can stretch somewhat to accommodate dilatation of the mitral com-

plex. This was further proven by Grande-Allen et al. in 2006 (18), who reported that explanted hearts from transplant recipients (dilated or ischemic cardiomyopathy) had stiffened valves with reduced distensibility, compared with normal autopsy valves. Furthermore, Chaput et al. (19) showed, that FIMR patients have an adaptation to chronic tethering by a 35% increase in mitral valve leaflet area, compared with normal controls. Also, Beaudoin et al. (20) recently demonstrated mitral valve enlargement in chronic aortic regurgitation, probably as a compensatory mechanism to prevent functional MR in the dilated LV.

Annulus and leaflets

LV dilatation causes mitral annular dilatation and requires the mitral valve leaflets to cover more area during closure. Eventually, the demand of leaflet tissue exceeds the normal redundancy, causing Carpentier type I mitral valve dysfunction.

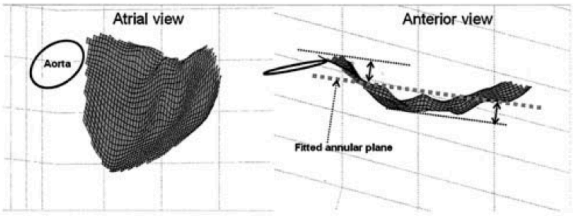


Figure 3. 3D cardiac MRI reconstruction of the occlusional leaflet area. Left: anterior view of the mitral valve from the atrial view. Right: anterior view of the mitral valve revealing the saddle-shaped annulus. From Jensen et al.(21) Geometric Determinants of Chronic Functional Ischemic Mitral Regurgitation: Insights from Three-Dimensional Cardiac Magnetic Resonance Imaging. The Journal of Heart Valve Disease 2008;17:16-23. Reproduced with permission from J. Heart Val. Dis.

Using an ovine chronic FIMR model, Tibayan et al. (22) showed that after inferior myocardial infarction, animals with FIMR had greater septal-lateral annular dilatation compared with non-FIMR animals. In a porcine chronic FIMR model, Jensen et al. (21) used two-dimensional cardiac magnetic resonance imaging (MRI) to reconstruct three-dimensional (3D) geometry and address concomitant mitral annular and leaflet coaptation geometry (figure 3). They revealed increased annular area, septo-lateral distance, inter commisural distance, tenting height, tenting volume and occlusional leaflet area compared with healthy controls (please see figure 4 for nomenclature). Clinical studies have confirmed these experimental results. Using 3D echocardiography, Watanabe et al. (23) showed that in FIMR patients compared with healthy controls, the mitral annulus flattens and dilates. Ahmad et al. (24) used 3D echocardiography to show that FIMR patients, compared with healthy controls, have annular dilatation with both an increase in the intertrigonal distance and posterior annular perimeters. The question whether or not isolated annular dilatation will cause FIMR was addressed by Otsuji et al. (25). They compared patients with annular dilatation due to either lone trial fibrillation or ischemic cardiomyopathy, demonstrating that isolated mitral annular dilatation does not cause important mitral regurgitation. This indicates that further insult to the LV wall underlying the papillary muscles is needed before valvular incompetence occurs.

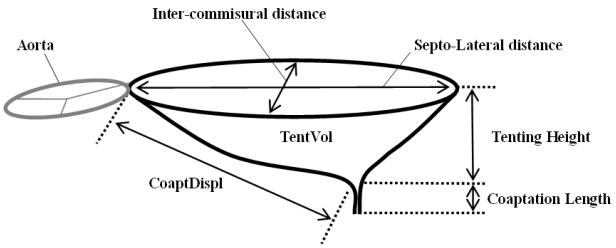


Figure 4. Mitral valve coaptation geometry . Mitral valve annular and leaflet geometric parameters based on 3D surface plot from 12 cardiac MRI cine images rotated around the mitral annular center. CoaptDispl indicates lateral displacement of coaptation; TentVol, tenting volume. From Jensen H. et al. (26) Impact of Papillary Muscle Relocation as Adjunct Procedure to Mitral Ring Annuloplasty in Functional Ischemic Mitral Regurgitation Circulation 2009;120;S92-S98. Reproduced with permission from Wolters Kluwer Health.

Papillary muscles and the LV

Initially, the concept of papillary muscle dysfunction was suggested as a causative factor in FIMR. Meanwhile, the role of papillary muscle dysfunction has been assessed by Uemura et al. (27), concluding that the papillary muscle longitudinal systolic strain had no significant relationships with FIMR, and that papillary muscle displacement from the anterior annulus was the only independent predictor of mitral regurgitation fraction. Also, in the early phase after myocardial infarction, Chinitz et al. used cardiac MRI in FIMR to demonstrate, that the presenece of lateral wall infarction, rather than presence or extent of papillary muscle infarction, was associated with increased MR grade (28).

Since dysfunction of the papillary muscle themselves could not be identified as the cause of FIMR, focus was shifted to papillary muscle displacement and leaflet tethering as causal factor. Otsuji et al. (29), using 3D echocardiography to examine a chronic FIMR ovine model, identified the increase in papillary muscle tethering distances from baseline as the only independent predictor of FIMR volume. In patients with functional MR (ischemic or dilated), Yiu et al. (30) showed that systolic valvular tenting area and PPM displacement were strongest predictors of effective regurgitation orifice. Also recently, Hsuan et al. (31) identified mitral valvular tenting and inter-papillary muscle distance as independent predictors of significant FIMR in patients. These and other reports have facilitated the current concensus in the litterature, identifying papillary muscle displacement from the anterior mitral annulus to cause tethering and tenting of the leaflets (figure 5). This causes FIMR due to restricted systolic leaflet motion, i.e. Carpentier type IIIb dysfunction. Moreover, Nakai et al. (32) showed that, in patients with LV ejection fraction < 50%, increased LV sphericity augments tethering of both anterior and posterior mitral valve leaflets, but with greatest influence from on the posterior leaflet tethering.

While there is no doubt that the papillary muscles in FIMR are displaced away from the anterior mitral annulus, it is not trivial to determine the 3D direction in which they are displaced. The distance from the anterior mitral annulus fibrosa is to the papillary muscle tip has been used as a measure of apical papillary muscle displacement (30, 33). Meanwhile, this is not neccesarily correct, since the anterior mitral annulus to papillary muscle tip distance will also increase from papillary muscle displacement in lateral and antero/posterior direction. Only a Carthesian “internal” coodinate system will allow definition of the apical, lateral

and antero/posterior directions and accordingly the precise geometry of the papillary muscle displacement.

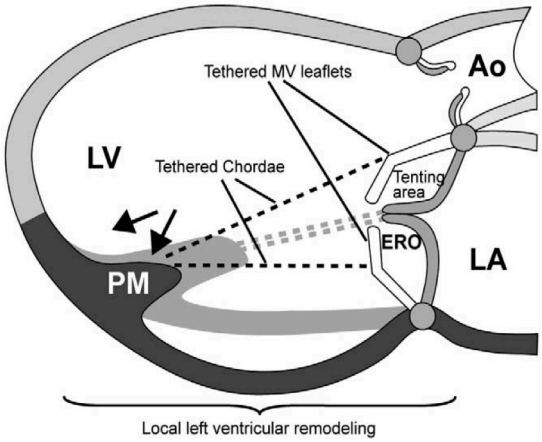


Figure 5. Local left ventricular remodeling in FIMR. The apical and posterior papillary muscle displacement (arrows) produces mitral valve tenting. The shaded image represents the normal ventricle with normal mitral valve closure. The dark area represents the local left ventricular remodeling. LV, left ventricle ; Ao , aorta ; LA, left atrium ; PM, papillary muscle; MV, mitral valve ; ERO, effective regurgitant orifice. From Bursi et al. Mitral Regurgitation After Myocardial Infarction: A Review. The American Journal of Medicine (2006) 119, 103-112. Reproduced with permission from elsevier.

Using tantalum markers and cinefluoroscopy, Tibayan et al. (22) used an ovine chronic FIMR model and to define a 3D coordinate system in the LV. They showed the APM was displaced in lateral and apical direction, and the PPM was displaced in lateral and posterior direction, while the PPM was not apically displaced. On the contrary, the PPM was acutally closer to the annulus compared with baseline. The tantalum marker technique is a very precise method to obtain such 3D geometric insight, but also pizoelectric crystals, used for sonomicrometry analysis, can be implanted in the heart to provide geometric data. Meanwhile, both the tantalum marker and pizoeletric crystal methods are invasive and therefore lack clinical applicability. A non-invasive method to obtain similar geometric insight was provided by Jensen et al. (II, III). They used 3D morphology cardiac MRI to define Cartesian coordinates for papillary muscle position, the anterior and posterior trigones and the posterior mitral annulus (figure 6). This allowed calculation of APM and PPM distances to trigone points, the annular plane, antero-posterior plane and septo-lateral plane. In this model, relative to controls, animals with FIMR had higher displacements of the PPM from both trigones in postero-lateral directions, and of APM from both trigones in apical direction. It is noteworthy, that this FIMR model confirmed the aforementioned result from Tibayan et al., with no apical PPM displacement. Relative to animals without FIMR, there was significantly higher PPM displacement from the posterior trigone in lateral direction. Inter-papillary muscle distance was the strongest predictor of regurgitant volume.

Despite the many advantages of "internal" reference planes, there are also theoretical drawbacks due to differences in mitral annular anatomy among animals, which will result in different coordinate systems. Furthermore, a coordinate system that is based on annular points changes through the heart cycle because of the physiologic changes in mitral annular shape. To address this, Dagum et al. (34) proposed the used of coordinate free analysis using relatively constant intracardiac distances that describe the 3D geometry and dynamics of the papillary muscle tips.

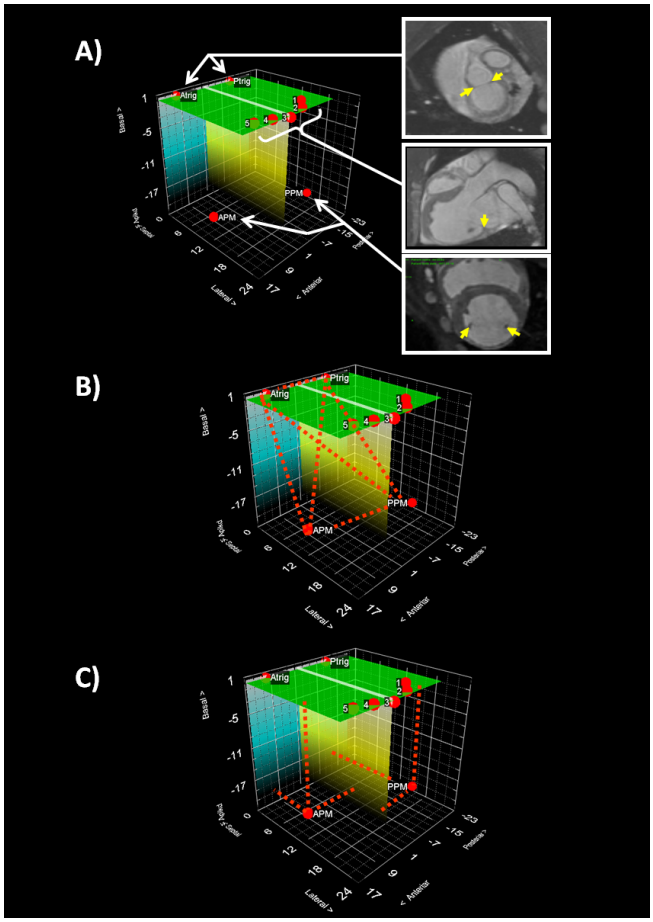


Figure 6. 3D morphology cardiac magnetic resonance imaging. A) Magnetic resonance imaging coordinates for trigone, annulus, and papillary muscle positions (yellow arrows) were transferred to dedicated mathematic analysis software. Annular plane (green) was defined by trigones and least squares fit to annular hinge points. Anteroposterior plane (blue) was defined perpendicular to annular plane and passing through both trigones. Septolateral plane (yellow) was defined perpendicular to annular and anteroposterior planes and passing through point midway between trigones. Distances from papillary muscle tips to B) Atrig and Ptrig and C) reference planes were calculated. Ptrig, Posterior trigone; Atrig, anterior trigone; PPM, posterior papillary muscle; APM, anterior papillary muscle. From Jensen et al. Three-dimensional assessment of papillary muscle displacement in a porcine model of ischemic mitral regurgitation. J Thorac Cardiovasc Surg 2010;140: 1312-18. Reproduced with permission from Elsevier.

Anterior vs. Inferior LV myocardial infarction

Rausch et al. (35), using an ovine FIMR model, demonstrated that after inferior myocardial infarction the mitral annulus dilates asymmetrically with larger distortions toward the lateral-posterior segment, and that annular dilation and peak strains were closely correlated to the degree of FIMR. Komanuhoso et al. (36) compared FIMR patients with anterior or inferior myocardial infarctions. Anterior infarctions caused greater LV dilatation, while there was no difference in annular dilatation or APM displacement from the annulus. Meanwhile, PPM displacement and FIMR grade was significantly higher in inferior infarction patients, indicating that inferior myocardial infarctions produce more

severe geometric changes in the mitral valve apparatus. Agricola et al. (33) showed that anterior LV wall myocarcial infarctions cause predominantly global dilatation and symmetric mitral valve tethering, while inferior LV wall infarctions cause less global remodeling and predominantly asymmetric tethering (figure 7).

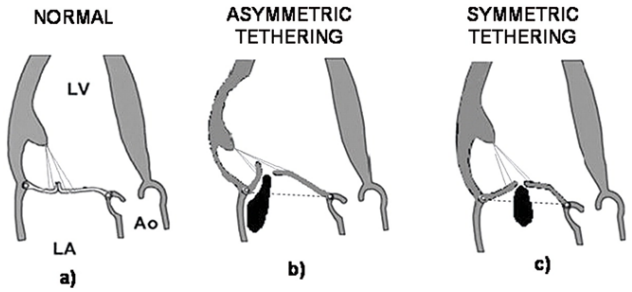


Figure 7. Tethering patterins in FIMR. (a) is reported a normal coaptation of mitral leaflets. (b) shows the predominant posterior displacement of both leaflets, resulting in the appearance of prevalent restriction of posterior leaflet. The basal anterior leaflet is also tethered, but distal to the strut chordae is less restricted than the posterior one. (c) shows the predominant apical displacement of both leaflets. LA: left atrium, LV: left ventricle; Ao: aorta. Modified from Agricola et al. Echocardiographic classification of chronic ischemic mitral regurgitation caused by restricted motion according to tethering pattern. Eur J Echocardiography (2004) 5, 326e334. Reproduced with permission from Oxford University Press.

PROGNOSTIC IMPACT OF FIMR

The prognostic impact on long-term outcome of FIMR according to MR grade was addressed by Grigioni et al. (3, 4), who evaluated five year follow-up after myocardial infarction, reporting that, independently of baseline characteristics and degree of LV dysfunction, FIMR presence was associated with excess mortality and risk congestive heart failure, and the increased risk was directly related to the size of the ERO (figure 8).

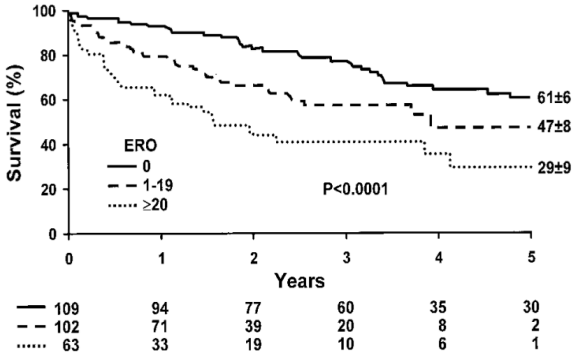


Figure 8. Survival after diagnosis according to effective regrugitation orifice area (ERO). Numbers at bottom indicate patients at risk for each interval. From Grigioni et al. Ischemic Mitral Regurgitation : Long-Term Outcome and Prognostic Implications With Quantitative Doppler Assessment. Circulation. 2001;103:1759-1764. Reproduced with permission from Wolters Kluwer Health

FIMR GRADING

What is severe FIMR?

MR in organic mitral disease is considered severe when the effective regurgitant orifice area (ERO), measured by the proximal isovelocity surface area method, is greater than 40 mm2 (37). In FIMR, a regurgitant orifice ERO >20 mm2, or an exercise induced increase in ERO of 13 mm2, has been identified as predictive of increased mortality by Grigioni et al. (3) and Lancelotti et al. (38), respectively. Accordingly, a lower threshold of severe secondary FIMR compared with primary organic mitral regurgitation has been adopted in the 2012 ESC/EACTS guidelines (39), since an ERO of 20 mm2 and regurgitant volume of 30 ml is now considered severe secondary (functional) MR. In the 2008 AHA/ACC guidelines (40), which did not distinguish between primary and secondary MR, this only qualifies as moderate (grade 2+) MR. Fattouch et al. (41) suggested that a new scale of FIMR grading; mild: ERO < 10 mm^2, moderate: ERO = 10 – 19 mm^2, severe: ERO ≥ 20 mm^2. Also, there are inherent problems with the PISA method to assess ERO in FIMR. In FIMR the ERO is often not circular, but elongated along the line of coaptation. The proximal isovelocity surface area method assumes a circular ERO, and when calculated from a long axis view in the A2-P2 segments, this will cause underestimation of the ERO and FIMR severity. In FIMR multiple jets are often seen and each of these have to be assessed and the sum of ERO's must be used. Also, a number of other limitations to the proximal isovelocity surface area method must be kept in mind (42).

FIMR variability

The mitral valve is an integrated part of the LV and as such it is very much affected by the myocardial contractility, heart rate and pre- and afterload conditions. As a consequence FIMR grade may change when these parameters change, e.g. during exercise. This question was addressed in clinical stuides in which FIMR patients were subjected to different types of exercise and concomitant echocardiography. Lapu-Bula et al. (43) concluded, that exercise induced increase in FIMR severity will limit the LV stroke volume adaptation and exercise capacity. Lancellotti et al. (44) showed, that FIMR severity at rest is unrelated to exercise-induced changes in ERO and the FIMR grade may increase, remain relatively constant or decrease. Also, Lancelotti et al. (38) showed, that an exercise induced increase in ERO of 13 mm2 predicted poor survival. Another important issue regarding the variability of FIMR is, that sometimes the decision whether or not to address the mitral valve surgically is taken preoperatively in the operating room with the patient anesthesized. Meanwhile, intraoperative transesophageal echocardiography may underestimate FIMR as a result of the unloading effect of general anesthesia on the LV. This was demonstrated by Shiran et al. (45), who subjected anesthesized patients to increased preload using fluids, and increased afterload using phenylephrine. In 72% of patients with preoperative grade 2+, this test increased FIMR grade to 3+ or 4+. Patients with preoperative grade 1+ or 3+ were less likely to change FIMR grade after pre- and afterload increase.

CHRONIC FIMR EXPERIMENTAL MODEL

To test the efficacy and safety of new surgical procedures to relieve chronic FIMR, preclinical experimental large animal testing must be done using a human compatible animal model, in which the pathophysiologic entity of chronic FIMR is reproducible. Porcine, ovine and canine LV failure and chronic FIMR models have been established to improve surgical therapy. Animal models of chronic FIMR (46-52), acute FIMR (15, 34, 53-57), ischemic LV failure (58-60) and tachycardia induced LV failure (61-63) have been established.

General physiologic, anatomic, coagulation and inflammatory properties are very similar in pigs and humans (64, 65). Porcine mitral valve anatomy is very similar to humans with anterior and posterior leaflets, primary and secondary chordae tendineae and distinct anterior and posterior papillary muscles (8). Moreover, Weaver et al. (66) used domestic and mini-pig hearts to make coronary artery casts, showing that coronary anatomy and the distribution of blood supply to the papillary muscles is very similar in humans and pigs. The APM in pigs was always supplied by branches of the left coronary artery in swine hearts, the same as reported for humans. The blood supply to the PPM was mostly from the right coronary artery in accordance with the dominant supply to the posterior wall of the heart, but occasionally by branches from the circumflex or left anterior descending coronary artery.

Different approaches have been used to induce myocardial infarction in the experimental setting. Circumflex coronary artery ligation through a thoracotomy to induce chronic FIMR in sheep was introduced by Llaneras et al. at the University of Pennsylvania in 1993 (51, 67), who have used the model extensively since then. Also, the technique was adopted by research groups at Harvard Medical School (49) and Stanford University (50). The ovine model has produced valuable insight into the pathofysiology and geometry of chronic FIMR. Meanwhile, to avoid thoracotomy, less invasive techniques based on coronary artery catheterisation have been employed. Infusion of microspheres was used to induce chronic FIMR in dogs by Sabbah et al. (68), and acute FIMR in pigs by Nielsen et al. (15). Also, deployment of sponge like material was used by Sakaguchi et al. (59) to induce LV failure in pigs. Induction of tachycardia was used by Shen et al. (58) to aggravate heart failure in pigs in a study which revealed, that tachycardia induced LV dilatation is reversible unless pacing is accompanied by myocardial ischemia. On the other hand, tachycardial stress may aggravate the deletorious effect of ischemia and increase mortality, as it has been shown that infarction size increases if myocardial oxygen consumption is high (69). Thus, a balanced approach to the use of tachycardial stress in animal models of ischemic heart failure is mandatory to avoid excessive mortality rates. Based on these reports, Bjerre, Jensen et al. in 2008 (46) at Aarhus University in Denmark reported the first porcine closed-chest model of FIMR induced by postero-lateral wall myocardial infarction. They used catheterbased occlusion of the circumflex coronary artery using a balloon and subsequently coils, followed by three times seven days of tachycardial stress using an internal pacemaker. In this model the mitral valve regurgitation correlated with infarct size (figure 9). This is in accordance with the findings of Chinits et al. (28), who used delayed-enhancement cardiac MRI and to identify infarct size as predictor of FIMR grade by multivariate analysis. Interestingly, in this model the papillary muscles themselves were not infarcted (figure 10), so the pathogenesis was due to secondary LV and annular dilatation with concomitant papillary muscle displacement.

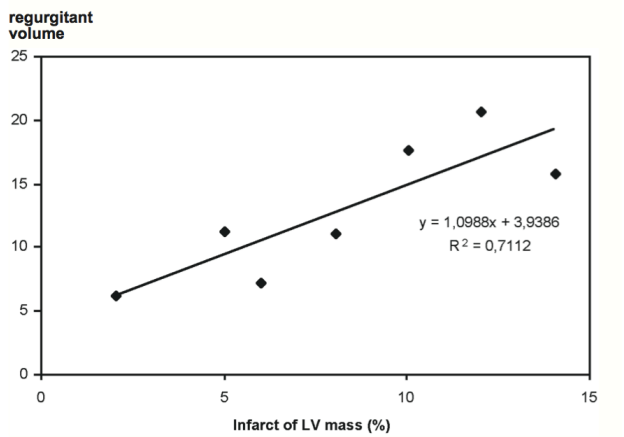


Figure 9. Relation between myocardial infarct size and mitral regurgutation volume. From Bjerre et al. Chronic Ischemic Mitral Regurgitation Induced in Pigs by Catheter-Based Coronary Artery Occlusion. The Journal of Heart Valve Disease 2008;17:283-289. Reproduced with permission from the Journal of Heart Valve Disease.

In a later series of animals Jensen et al. (26) in 2009 optimized the coronary artery occlusion technique, which allowed the ballon occlusion to be omitted. Also, in an effort to reduce early mortality due to tachycardial stress, the pacing intervals were reduced to two times seven days, and with a later onset of the pacing regime. Meanwhile, no improved survival rate was observed; six weeks survival was 39%, with 77% of animals developing mild-moderate FIMR.

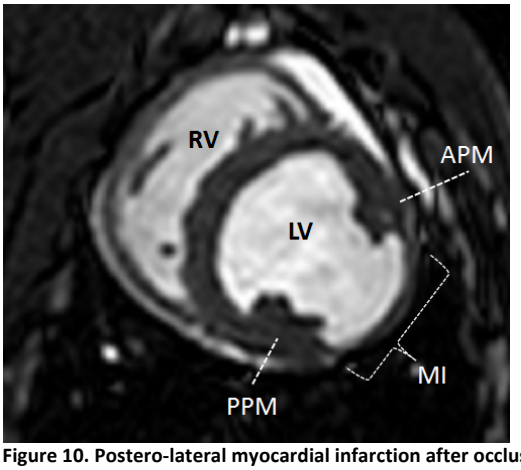


Figure 10. Postero-lateral myocardial infarction after occlusion of the circumflex coronary artery. RV, right ventricle ; LV, left ventricle ; PPM, posterior papillary muscle ; APM, anterior papillary muscle. MI, myocardial infarction. From Jensen et al. Surgical relocation fo the papillry muscles: what are the forces of the relocation stiches acting on the myocardium. J Heart Val. Dis. 2013 Jul;22(4):524-31. Reproduced with permission from the Journal of Heart Valve Disease.

FORCES IN THE MITRAL VALVE APPARATUS

When trying to understand the function and mechanics of the mitral valve apparatus it can be helpful to consider the force balance present during systole, when the mitral valve is closed. In systole, both during isovolumetric contraction and the ejection phase, the mitral valve is being pushed towards the left atrium. To prevent the valve leaflets from being ejected into the left atrium, the leaflet attachment points, i.e. the mitral valve annulus and chordae tendineae, resist the forces imposed on them by the blood pressure. Knowing the physiological forces in the mitral valve apparatus and LV is essential when assessing whether new

surgical techniques induce a non-physiologically high load on these structures.

CHORDAE TENDINEAE / NEO-CHORDAE

In vitro, using a left heart simulator, the magnitude of forces in the cordae tendineae has been examined using different variations of strain gauge technology (70). Jimenes et al. (71-73) measured forces chordae tendineae in explanted human hearts. Tension was in the range of 0.18-0.41 N in anterior leaflet marginal chordae, 0.03-0.25 N in posterior leaflet marginal chordae, 0.95-1.16 N in anterior leaflet strut chordae and 0.25-0.30 N in posterior leaflet intermediate chordae. Using in vitro porcine valves, Nielsen et al. (74) and Jimenes et al. (72), measured tension in marginal chordae tendineae in the range of 0.26-0.5 N and tension in strut chordae to 1.02 N.

In vivo, using a porcine experimental model, Nielsen et al. (15) and Lomholt et al. (75) measured tension in marginal chordae in the range of 0.15-0.34 N, but found up to three times higher tension i anterior leaflet strut chordae, in the range of 0.72-0.73 N.

Recently, transapical chorda tendineae replacement was introduced (76) as a new and promising, minimally invasive surgical approach to mitral leaflet prolapse. Using this technique, Bajona et al. observed peak tension in transapically implanted ePTFE neo-chordae from the anterior mitral leaflet free margin in a porcine model in range from 0.6 –1.1 Newtons (N) in vitro (77) and 0.7-1.1 N in vivo (78), which is higher than tension observed in native chordae. These results were indicative of higher forces in transapically fixated neo-chordae compared with neo-chordae fixated on the papillary muscles, which theoretically impairs repair durability. To further address this question in vivo using a control group, Jensen et al. (79) compared tension in artificial ePTFE neo-chordae fixated transapically or on the APM (figure 11). This was done using an acute porcine model of anterior leaflet prolapse. The authors observed no difference between peak (0.41 vs 0.46 N, P = 0.22) or mid-systolic (0.28 vs 0.19 N, P = 0.12) tension in artificial neo-chordae fixated on the APMs or transapically. These values were inside the range of tension reported for native primary chordae of normal porcine hearts, indicating that chordal insertion site had little influence on tension in the artificial neo-chordae. Meanwhile, the peak rise of tension, i.e. the dF/dtmax, which reflects the tension fluctuations in the neo-chordae, was 40% higher after transapical fixation compared with papillary muscle fixation. Such abnormal tension fluctuations in the transapically fixated neo-chordae may reflect absence of a potential shock absorbing effect of the papillary muscles in the LV myocardium during the cardiac cycle (80). Theoretically, these abnormal tension fluctuations would induce higher leaflet stresses, that may predispose to leaflet tears and early repair failure.

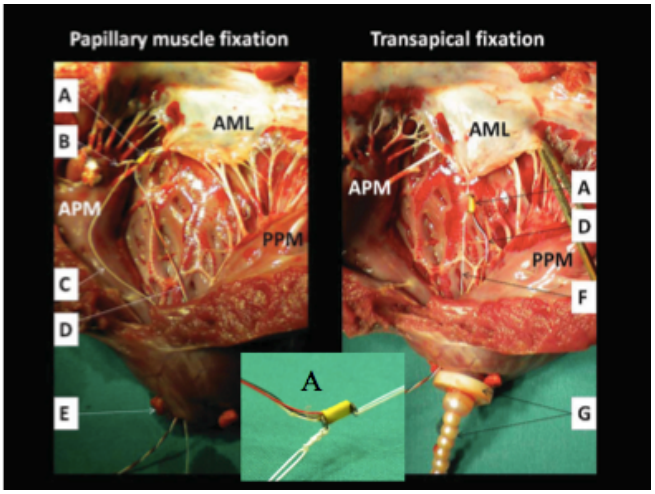


Figure 11. Strain gauge. The strain gauge is mounted in line with ePTFE sutures attached to the mitral leaflet and left ventricular fixation point . AML, Anterior mitral leaflet; APM, Anterior papillary muscle; PPM, Posterior papillary muscle; A, Strain gauge; B, Neo-chord attached to APM with felt pledget; C, slack transapical neo-chord; D, strain gauge wire; E, Left ventricle apex closed with felt pledgets; F, Tight transapically fixated neo-chord; G, neo-chord lead through disc and string of pearls. Reproduced with permission from Elsevier.

MITRAL VALVE LEAFLETS

Leaflet enlargement was proposed as a solution to compensate for anterior leaflet tethering. In vitro, using freshly explanted porcine hearts, Granier et al. (81) showed that after implanting a patch in the anterior leaflet, strut chordal forces were reduced from 0.69-0.83 N to 0.49-0.54 N, indicating reduced stress on the belly of the implanted patch. Also, Rahmani et al. (82), also using explanted porcine heart in vitro, showed that displacing the PPM induced tethering and 39.8% increase in the forces of intermediate chordae tendineae to the posterior leaflet, whereas subsequent posterior leaflet patch augmentation decreases forces by 31%.

In vitro, Rabbah et al. (83) assessed alfieri stich tension in porcine leaflets mounted on a rigid annulus with both intact and flail leaflets, producing maximum tension in systole, up to 0.2 N. Meanwhile, Nielsen et al. (84) used an ovine experimental model to show that maximum Alfieri stich tension was 0.26 N, which was seen in diastole during LV filling. After inducing acute FIMR, maximum tension increased to 0.46 N, still observed in diastole, and the increase in tension correlated with increasing septo-lateral mitral annular diameter. The difference between the in vivo and in vitro results may be explained by the limitations of in vitro settings, which did not allow evaluation of the effect of annular dynamics on leaflet approximation and thereby force magnitude.

MITRAL VALVE ANNULUS / RING ANNULOPLASTY

The impact on forces in the mitral valve apparatus from different annuloplasty ring designs has been addressed. In a porcine in vivo experiment, Nielsen et al. (85) showed that down-sized ring annuloplasty reduces tension in anterior leaflet strut chordae, but not on the anterior leaflet marginal chordae. Therefore, a flat down-sized ring annuloplasty may protect mitral repairs on the central portion of anterior leaflet but may not protect repairs that solely involve the anterior leaflet's leading edge. In vitro, using explanted human mitral valves, Jimenes et al. (73) compared a saddle shaped and flat annulus, revealing statistically significant reduced tensions with the saddle shaped annulus in strut and

commisural chordae, but increased tension in marginal, intermediate and basal chordae. Meanwhile, Askov et al. (86), using a porcine in vivo model, compared rigid saddle shaped with completely flexible rings; The saddle shaped rings reduced tension in all marginal, strut and intermediate chordae, but the flexible ring only reduced posterior marginal chordae. The obvious inherent limitations of in vitro experiments, where the normal physiological role of mitral annular and papillary muscle contraction is not present, is the plausible explanation of these differences between in vitro an in vivo results.

Also, forces acting on rings implanted in the mitral valve annulus were addressed; Hasenkam et al in 1994 (87) showed that the maximum force generated on a mechanical mitral valve from the myocardium is 6-8 N. Jensen MO et al. (88), used a porcine experimental model to observe that flat rings are subjected to bending forces of 1.3-1.59 N in the commissural area, 0.64 N in the anterior annulus, and 0.15 N in the posterior annulus, whereas the saddle shaped ring was not subjected to significant bending forces. Recently, Siefert et al. 2012 (89) in an ovine experimental model used strain gauges mounted on a device implanted in the mitral annulus, revealing that at increasing LV pressures from 90 to 200 mmHg, the cyclic change in forces increased from 3.9 to 6.7 N in the septal-lateral direction, and from 2.6 to 3.5 N in the inter-commissural direction. Higher forces were measured in the septo-lateral direction at all LV pressures. Also, in an ovine chronic FIMR model, Siefert et al. (90) demonstrated, that an inferior LV infarction significantly decreased cyclic septo–lateral forces while modestly lowering forces in the transverse direction. Recently, in a porcine model using healthy pigs, Jensen MO et al. (91) measured forces in three stiches, placed from the posterior trigone to the posterior annulus, used to down-size the annulus. They revealed, that at 32% down-sizing, a total force increase of 3.5 N was observed in the stiches.

PAPILLARY MUSCLES / PAPILLARY MUSCLE RELOCATION

The forces developed in each papillary muscle was measured to 4.1 N in vitro by Jensen MO et al. (92), using a setup with each papillary muscle mounted on a force measuring rod. Askov et al. (93) confirmed this general level of forces in the papillary muscles, using a custom made strain gauge mounted in-line in the papillary muscle myocardium to measure 5.8 N in the APM and 5.9 N in the PPM.

Also, papillary muscle forces after mitral valve replacement was addressed. It is now common surgical practice to preserve and resuspend the mitral valve leaflets in the valve prosthesis sewing ring when performing mitral valve replacement. This has been seen as a mean to preserve the annular-ventricular continuity to improve postoperative LV function. Further insight into this matter was provided by Askov et al. (94). They showed that after chordal sparing mitral valve replacement, papillary muscle forces increased significantly from 5.9 to 7.5 N in the APM, and from 5.8 to 7.5 N in the PPM, while also lifting the papillary muscle tips closer to the annulus.

The forces in artificial expanded polytetrafluoroethylene (ePTFE) sutures used for papillary muscle relocation (figure 12) was assessed using a porcine chronic FIMR experimental model by Jensen et al. (95). For this purpose a dedicated device using strain gauge technology was developed to measure the tension in line with the papillary muscle relocation sutures (96) (figure 11). At 5 mm anterior papillary muscle relocation and 15 mm posterior papillary muscle relocation, cyclic change in tension was 1.4 ± 0.3 N in the anterior papillary muscle stich and 1.1 ± 0.3 N in the posterior papillary muscle stich. These values are in range with normal tension in the mitral valve apparatus, and equivalent to only 19-24% of total papillary muscle forces. Therefore, this technique apparently does not induce a non-physiologically high cyclic load on the mitral valve complex that could potentially jeopardize the applicability of this procedure. If chordal tension in diastole was zero, then the cyclic tension reported would be equal to the absolute forces in the papillary muscle relocation stiches. Meanwhile, although previous studies on chorda tendineae tension has shown forces close to zero in diastole, this cannot automatically be assumed to be the case in this study due to the suspension of the LV myocardium.

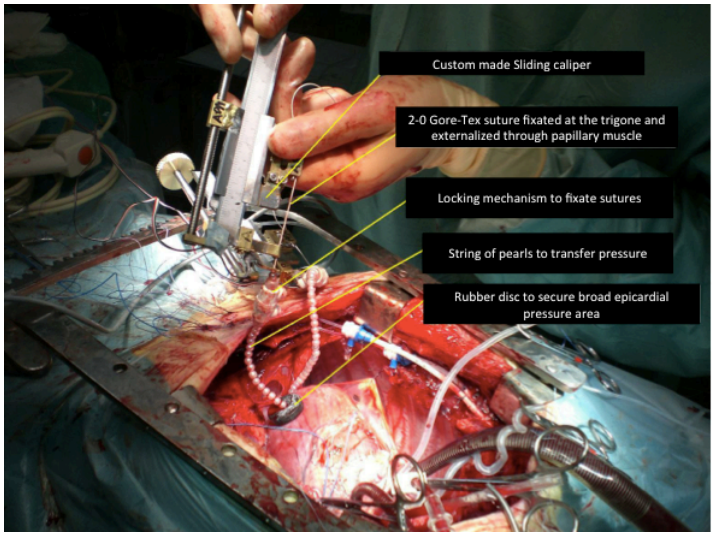


Figure 12. Papillary muscle relocation device. The heart is seen with epicardial pressure plate over the myocardium adjacent to the anterior papillary muslce. A string of pearls transfers forces to the strain gauge monted on the device. An identical device was used for the stich to relocate the posterior papillary muscle.

CURRENT STANDARD TREATMENT FOR FIMR

The proper combination of the current treatment modalities is a constant source of debate in the surgicial and cardiology communitites dealing with FIMR patients.

Standard treatment options

CABG attempts to improve LV function and mitral valve coaptation geometry by increasing myocardial blood supply to restore proper contraction and reverse LV remodeling.

Mitral valve ring annuloplasty +/- down-sizing, aiming to correct annular dilatation and Carpentier type I dysfunction. Current ring annuloplasty designs vary over a wide range of flexibility/rigidity properties and 3D shapes.

Mitral valve replacement

Adjunct procedures

Direct mitral valve repair using different techniqies, e.g. cordal cutting and posterior leaflet augmentation, aims to restore proper coaptation length by alleviating leaflet tethering.

Subalvular approaches cover a wide range of surgical approaches aiming to reduce LV volume, reverse papillary muscle displacement and relieve leaflet tethering. Some of these techniques have been succesfully introduced in the clinical setting.

Guidelines

Controversy prevails as to what constitutes optimal treatment in patients with chronic FIMR. The most recent CABG guidelines from the American College of Cardiology Foundation/ American Heart Association from 2011 (97) recommend that in patients undergoing CABG who have ≥ moderate ischemic mitral valve regurgitation not likely to resolve with revascularization, concomitant mitral valve repair or replacement at the time of CABG is reasonable. The 2012 guidelines from the European Society for Cardiology / European Society for Cardio-Thoracic Surgery (98) are shown in table 1. These guidelines recommend, that when mitral valve surgery is indicated, valve repair using an undersized, rigid ring annuloplasty is favourable. Also, in patients with pre-operative predictors of increased FIMR recurrence, subvalvular techniques adresseing leaflet tethering may be considered in addition to mitral valve ring annuloplasty.

	Class of recommendation	Level of evidence
Surgery is indicated in patients with severe FIMR undergoing CABG, and LVEF >30%.	I	C
Surgery should be considered in patients with moderate FIMR undergoing CABG.	IIa	C
Surgery should be considered in symptomatic patients with severe FIMR, LVEF <30%, option for revascularization, and evidence of viability.	IIa	C
Surgery may be considered in patients with severe FIMR, LVEF >30%, who remain symptomatic despite optimal medical management (including cardiac resynchronization if indicated) and have low comorbidity, when revascularization is not indicated.	IIb	C

Table 1. Indications for mitral valve surgery in chronic secondary mitral regurgitation. ESC/EACTS guidelines 2012 (table 13). From Vahanian et al. Guidelines on the management of valvular heart disease (version 2012). European Heart Journal 2012, (1873-734X (Electronic)).

The exact combination of surgical methods depends on FIMR severity, and although no formal consensus exists, the overall impression from published litterature, guidelines and ongoing randomised studies indicate the following treatment according to FIMR severity options (table 2).

Table 2. Surgical treatment modalities according to severity in chronic FIMR.

CABG ALONE TO TREAT FIMR

"STICH" trial

The impact on survival in FIMR patients from CABG vs. medical treatment was addressed by, Deja et al. (99), who in 2012 reported the FIMR subgroup analysis from the STICH trial (CABG in patients with LVEF of 35% or less randomized to CABG or medical treatment). In mild FIMR, mortality hazard ratio for CABG vs. medical treament was 0.77 (statistically significant in per-protocol analysis), while there was no significant mortality difference between CABG and medical treatment in none-trace or moderate-severe FIMR. Meanwhile it should be noticed, that in patients randomized to CABG, the decision to perform mitral valve surgery was made by the surgeon. Subgroup analysis in the moderate-severe FIMR patients revealed, that CABG combined with mitral valve surgery showed a clear trend towards improved long term survival compared with both CABG alone, and medical therapy alone. However, probably due to the relatively small number of patients in the moderate-severe FIMR subgroup (n = 91), this difference did not reach statistical significance.

Does CABG correct FIMR?

To address whether CABG surgery actually relieves FIMR fourteen studies (100-113) published between 1988 and 2012 addressing outcome after isolated CABG for FIMR have been published. Follow-up was from 30 days to 15 years, and 5 year survival rates ranged from 50-85%. Nine studies reported late FIMR grade. Mustonen et al.(100), Lam et al. (102) , Fukoshima et al. (103), Hwang et al. (111), Christenson et al. (109), Penicka et al. (113) and Fattouch et al. (112) reported 33%, 60%, 46%, 10%, 8%, 53% and 70% respectively with ≥ grade 2+ recurrent FIMR. Aklog et al. (106) and Campavala et al. (104) reported 40% and 47%, respectively, with grade 3-4 recurrent FIMR. Tolis et al. (105) reported a mean postoperative FIMR grade of 0.54. Overall, this indicates that CABG does not sufficiently correct FIMR. However, some authors reported a low incidence of postoperative FIMR after isolated CABG. Further insight to help explain why some FIMR patient cohorts benefit from CABG, while others do not, was offered by Penicka et al. (113) in 2009. They reported 12 month outcome in patients with moderate FIMR undergoing isolated CABG, and revealed that improvement in FIMR grade was observed only in patients with concomitant presence of viable myocardium (at least five viable segments) and absence of dyssynchrony between papillary muscles (< 60 ms).

MITRAL VALVE RING ANNULOPLASTY

In 1957, Lillehei et al. (114) reported the first procedure of surgical correction of pure mitral insufficiency by suture plication of leaflets under direct vision. Several different techniques for reducing the mitral anulus have been reported since then, utilizing sutures to reduce the length of the commisural regions (115, 116) or the mural posterior annulus (117-119). Carpentier et al. in 1969 published the first paper introducing the concept of mitral valve annuloplasty using a ring later known as the Carpentier Edwards Classic Ring (120). Down-sized ring annuloplasty in FIMR in patients undergoing CABG, currently constitutes the "golden standard" treatment modality.

Annuloplasty ring design

It is not a trivial task to decide which ring to choose. Dozens of different annuloplasty rings are commercially available, each claiming to have a specific advantage for a specific pathology. Therefore, it is helpful to divide the rings into categories according to their shape and physical properties. Annuloplasty rings are divided into; a) complete rings or partial posterior annular bands, and b) rigid, semi-rigid or flexible. Also, pericardial strips and simple steel wires have been used in the same way as posterior annular bands. The complete rings are available in a number of 3D designs that aim to facilitate optimal annular support depending on pathology, e.g. Ischemic; IMR Etlogix (121), Degenerative; Myxo dEtlogix ring (122), Duran Ancore Ring and Band (123), Cosgrove Edwards band (124), Dilated cardiomyopathy; Geoform (125). Meanwhile, the choice of ring is very surgeon dependent and some surgeons will use the same ring over a wide variety of valve pathologies. One example of a 3D ring designed to address a specific pathology is the Carpentier-McCarthy-Adams IMR Etlogix ring, designed specifically to treat FIMR (126). This ring is complete and rigid, offering down-sizing of the septo-lateral distance to counteract type I Carpentier leaflet dysfunction. The most notable part of the design is an indentation in the P3 area to emphasize remodeling of the annulus in the region often severely dilated in FIMR due to infero-lateral myocardial infarction. Also,

the physiological anatomical saddle-shaped configuration has been adopted in the rigid St. Jude Saddle Ring (127), and the semi-rigid Physio II ring (128), among others.

Down-sized ring annuloplasty

In 1995, Bolling et al. (129) introduced the undersized (or restrictive) annuloplasty for the treatment of ischemic or dilated functional MR by implanting rings one size smaller than the measured intertrigonal length. The undersizing is meant to compensate for at dilated annulus and improve mitral leaflet coaptation. The necessity of performing complete ring annuloplasty was underscored by Onorati et al. (130), who reported that using flexible posterior bands produced inferior results in FIMR compared with complete rigid remodeling rings. Accordingly, many surgeons consider annular down-sizing as mandatory when performing ring annuloplasty for FIMR.

Currently, the actual undersizing is done by chosing an annuloplasty ring with smaller dimensions than the patients valve in terms of inter-trigonal distance, inter-commisural distance, septo-lateral distance and anterior leaflet height and area. Each ring manufacturer supplies a sizing kit, that uses som of these parameters to define the amount of down-sizing. I.e, if the sizing kit determines that the patients anterior leaflet is a size 30, then chosing a size 28 is equivalent to down-sizing one size, since there is no size 29, because the manufacturers only use even or odd numbers. Meanwhile, there is a great variation between manufacturers in terms of the dimensions of a given ring size (131). Also, the risk of ring dehiscence after too rigorous down-sizing must be kept in mind (132).

Does ring annuloplasty induce papillary muscle relocation?

Since papillary muscle displacement was identified as a pivotal geometric change in FIMR, and down-sized ring annuloplasty produced suboptimal results, it was investigated wheter the ring annuloplasty itself had an impact on 3D papillary muscle position? In a porcine chronic FIMR model, Jensen et al. (133) analyzed 3D papillary muscle position before and six weeks after down-sized ring annuloplasty. Data analysis revealed, that the ring annuloplasty attenuated LV basal torsion patterns, which changed papillary muscle position relative to the annular points. Meanwhile, no overall pattern of a direct papillary muscle relocation effect was observed, indicating that further adjunct procedure is necessary to obtain direct papillary muscle relocation (figure 13).

Mitral stenosis after down-sized mitral valve ring annuloplasty

Naturally, there is a limit to how much down-sizing kan be done, before the valve opening becomes too small to allow unobstructed blood flow. A valve area less than 1.5 cm2 and a mean gradient of > 5 mmHg is considered moderate mitral valve stenosis. Magne et al. in 2008 showed increased mitral valve gradients and increased pulmonary pressure with concomitant reduced functional capacity after down-sized mitral valve ring annuloplasty (134), Walls et al. in 2008 (135) reported a mean postoperative transmitral gradient of 5.5 mmHg after mitral valve ring annuloplasty. Martin et al. in 2013 (136) reported increased transmitral gradients after implantation of the IMR Etlogix ring; the gradient increased from 3.3 mmHg at rest to 7.8 mmHg during exercise.

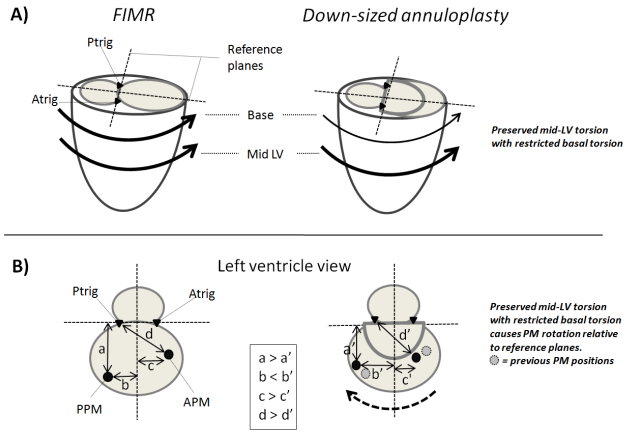


Figure 13. Attenuated Basal LV Torsion Changes Reference Planes. A) Torsional directions indicated by curved arrows; Reduced torsion at the left ventricle base after ring annuloplasty with preserved torsion at the mid left ventricle. B) Observed changes in papillary muscle distances to reference planes (left ventricle view). FIMR, Functional ischemic mitral regurgitation; Atrig, Anterior trigone ; Ptrig, Posterior trigone ; APM, Anterior papillary muscle ; PPM, Posterior papillary muscle. The mitral and aortic annulus and annuloplasty ring are delineated. a/a', lateral PPM displacement ; b/b', posterior PPM displacement ; c/c', anterior APM displacement ; d/d', APM displacement from posterior trigone. From Jensen et al. Does Down-Sized Ring Annuloplasty Induce Papillary Muscle Relocation in Ischemic Mitral Regurgitation? The Journal of Heart Valve Disease 2010;19:692-700. Reproduced with permission from J. Heart Val. Dis.

Furthermore, Kubota et al. (137) demonstrated, that postsurgical exercise induced mitral stenosis results from restricted anterior leaflet opening at the leaflet tip level because of subvalvular tethering in the presence of surgical annular size reduction. This study showed, that ring size itself was not the sole determinator for the occurence of mitral stenosis, since a Physio ring size 24 with an opening area of 2.7 cm2, could produce a functional area of less than 1.5 cm2. Meanwhile, recent studies indicate that mitral stenosis after mitral valve ring annuloplasty may not have an impact on clinical outcome. Williams et al. in 2009 (138) demonstrated that increasing mitral gradient after down-sized mitral valve ring annuloplasty does not appear to adversely impact survival or heart failure hospitalization. Also, and Rubino et al. in 2012 (139) in a series of 125 patients undergoing CABG and down-sized mitral valve ring annuloplasty reported, that the induction of mild mitral stenosis did not affect clinical, functional and echocardiographic outcomes.

4.3 CABG COMBINED WITH MITRAL VALVE RING ANNULOPLASTY

Adding ring annuloplasty to CABG to treat moderate, moderate to severe or severe FIMR (grade 2-4+) has been addressed thoroughly. Thirty-five studies (48, 140-173) published between 2001 and 2012 address this topic, with follow-up from 13 months to 8.6 years. Figure 14 shows the prevalence of recurrent FIMR ≥ grade 2+ in the studies that define recurrent FIMR, revealing a bulk of reports with 20-30% of patients with recurrent FIMR 2-4 years after combined CABG and ring annuloplasty. It is noteworthy, that almost half the studies report using down-sizing of the annulus by 2 sizes, mostly using rigid or semi-rigid rings, but the patients still have a high frequency of recurrent FIMR.

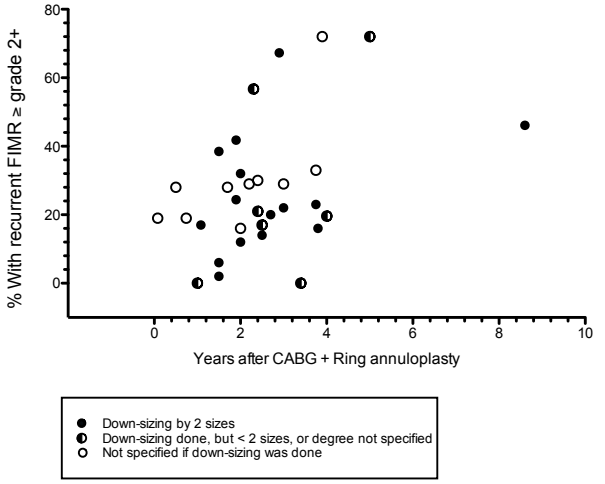


Figure 14. Recurrent FIMR ≥ grade 2+ after mitral valve ring annuloplasty is seen in 20-30% of patients at 2-4 years follow-up despite down-sized ring annuloplasty.

This high rate of FIMR recurrence after ring annuloplasty may be due to restricted leaflet mobility (174, 175), augmented posterior leaflet tethering (154), papillary muscle displacement outside of the mitral annulus (176), continued LV remodelling (48) and reduced coaptation forces (13), among others. These parameters all indicate LV dilatation, and accordingly it is pivotal to address whether mitral valve ring annuloplasty induces LV volume reduction. The pre-to-postoperative change in LV end diastolic diameter (LVEDD) was available in twelve studies (48, 143, 145, 150, 153, 155-157, 163, 170, 171) (figure 15), clearly revealing that combined ring annuloplasty and CABG induces LVEDD volume reduction.

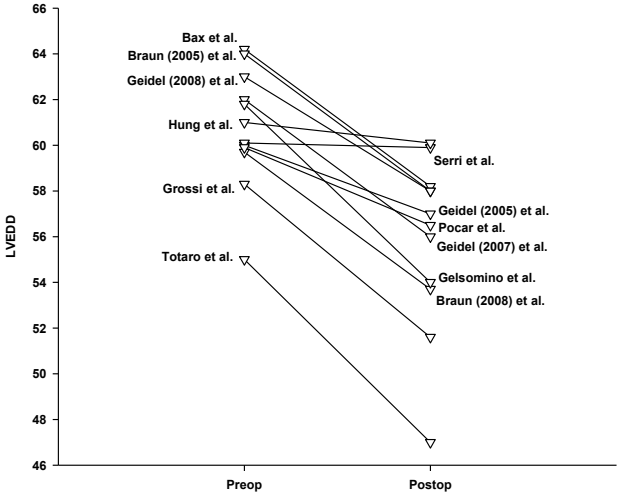
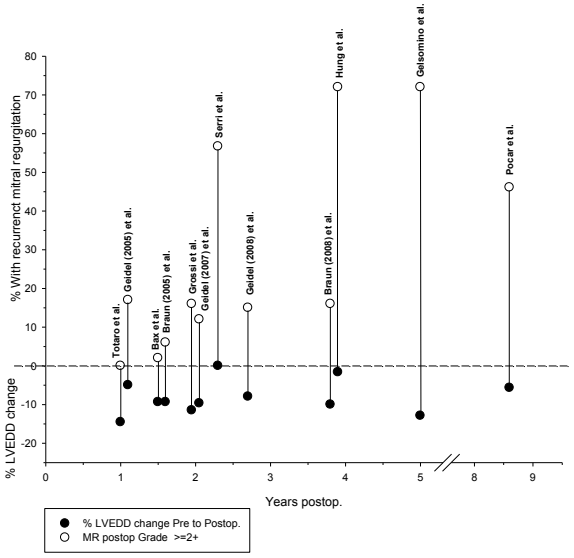


Figure 15. Left ventricular end diastolic diameter (LVEDD) is reduced after mitral ring annuloplasty. Follow up in these studies is from one to nine years.

Responers vs. Non-responders

The overall pattern of reverse LV remodeling and LV volume reduction after combined CABG and ring annuloplasty offers no explanation to why 20-30 % of patients develop recurrent FIMR. To further address this, figure 16 shows the LVEDD data displayed in figure 15, with FIMR recurrence rates displayed concomitantly to reveal if the patients with recurrent FIMR have less change in LVEDD compared with patients without recurrent FIMR.



igure 16. Change in left ventricular end diastolic diameter (LVEDD) shown concomitant with recurrent FIMR rate, recurrent FIMR ≥ grade 2+.

The surprising overall pattern is, that recurrent FIMR is present despite reverse LV remodeling and reduced LVEDD at postoperative follow-up. This could be interpreted in many ways. These results suggest, that LV dilatation has nothing to do with recurrent FIMR, but this would be in sharp contrast to what has previously been reported by Hung et al. (48), among others. Also, it could be argued that LVEDD is only a surrogate marker for LV volume, and because coaptation occurs is systole, systolic geometric parameters should be used. However, the results may be explained by looking a bit more detailed at the populations we are addressing. It may be a mistake to consider the groups of patients with FIMR as a homogenous entity who all behave the same way in terms of LV reverse remodeling and recurrent FIMR. More insight to this was offered by six studies (147, 148, 151, 154, 165, 167) who looked at responders vs. non-responders in terms of recurrent FIMR after combined CABG and ring annuloplasty (figure 17). In these six studies, non-responders were defined as having recurrent FIMR grade ≥ 2+ (moderate). Three studies assessed LVEDD and three studies assessed LV end diastolic volume. In all studies, pre- and postoperative dimensions were higher in the non-responders, and in three studies, there was continued LV remodeling/dilatation in the non-responders group. The logical consequence of this is, that somewhere between the preoperative values of responders and non-responders, a cut-off value to predict recurrent FIMR can be identified.

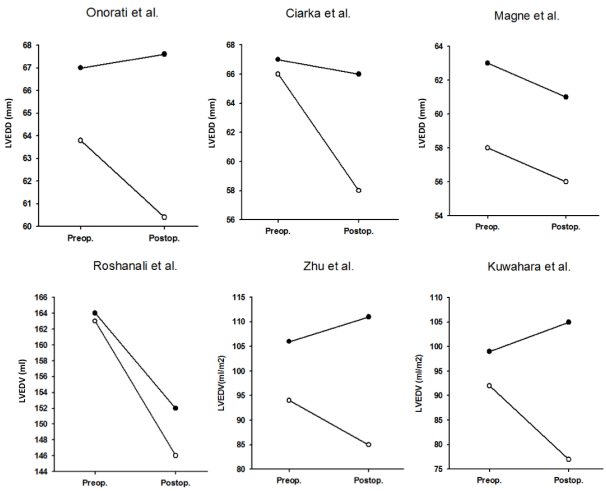


Figure 17. Responders vs. Non-responders after mitral ring annuloplasty. Responders (white dots) and non-responders (black dots) to mitral valve ring annuloplasty and CABG. Non-responders were defined as postoperative recurrent FIMR grade ≥ 2+. LVEDD, left ventricular end diastolic diameter ; LVEDV, left ventricular end diastolic volume.

Cut-off values predicting recurrent FIMR

Cut-off values to predict recurrent FIMR after combined CABG and ring annuloplasty was first suggested by Calafiore et al. (177, 178) who in 2001 identified a preoperative coaptation depth > 10 mm as cut-off to choose valve replacement over repair. Since then, a number of investigators identified preoperative parameters to predict recurrent FIMR after ring annuloplasty (table 3).

Author	Preoperative predictor of recurrent FIMR
Calafiore et al. (172, 173)	Coaptation depth > 10 mm
Magne et al. (143)	Posterior leaflet angle ≥ 45°
Gelsomino et al., and van Garsse et al. (174, 175)	Anterior mitral leaflet angle ≥ 39.5°
Troubil et al. (168)	Anterior mitral leaflet angle ≥ 27°
van Garsse et al. (176)	Anterior/posterior tethering angle ratio > 0.76
Braun et al. (164)	LVEDD > 65 mm
Onorati et al. (177)	LVEDD ≥ 70 mm
Lee et al. (167)	LVEDD > 3.5 cm/m²
Gelsomino et al. (140)	LV end-systolic volume ≥145 mL
	LV systolic sphericity index ≥ 0.7
	LV myocardial performance index < 0.9
	LV wall motion score index < 1.5
Roshanali et al. (142)	End-systolic inter-papillary muscle distance of 20 mm (NB! papillary muscle base-to-base diastance)
Onorati et al. (177)	Coaptation depth ≥ 0.5 cm after surgery (NB! Postop.)

Table 3. Preoperative parameters to predict recurrent FIMR after ring annuloplasty.

Also, Ciarka (165) reported that patients with recurrent FIMR had had increased preoperative posterior and anterior leaflet angles, tenting height, tenting area, and LV sphericity index compared with patients without recurrent FIMR. Kongsaeropong et al. (152) identified mitral annular diameter, tethering area, and FIMR severity as independent predictors for failure of combined CABG and ring annuloplasty. Matsunaga et al. (141) concluded that ring annuloplasty does not protect against recurrent FIMR in patients with severe outward displacement of the PPM. Also, van Garsse et al. (179) identified papillary muscle dyssynchrony as the strongest predictor of recurrent FIMR. These predictors of recurrent FIMR after combined CABG and ring annuloplasty all tell the same story about dilated LVs with displaced papillary muscles causing leaflet tethering, increased leaflet angles and tenting height (coaptation depth) and reduced coaptation length. Thereby the parameters listed above give an indication of when this LV remodeling has crossed the "point of no return".

Does persistent FIMR affect outcome?

In light of these risk factors of recurrent FIMR, it is important to note, that Crabtree et al. (146) (figure 18) and Hausmann et al. (180) demonstrated, that recurrent FIMR after CABG and down-sized mitral valve ring annuloplasty predicts worse outcome.

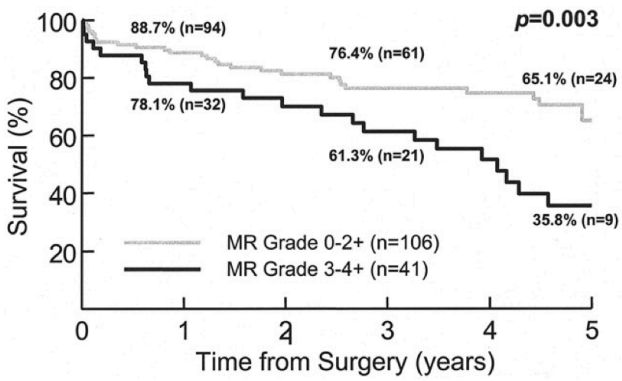


Figure 18. Kaplan-Meier survival estimates for patients undergoing mitral valve repair for functional ischemic mitral regurgitation (MR) stratified by degree of postop. FIMR. From Crabtree et al. Recurrent Mitral Regurgitation and Risk Factors for Early and Late Mortality After Mitral Valve Repair for Ischemic Mitral Regurgitation Ann Thorac Surg 2008;85:1537–43. Reproduced with permission from Elsevier

However, the decision between CABG and CABG combined with a ring annuloplasty is not completely straight forward, since on one side CABG alone does not always sufficiently correct FIMR. On the other side, however, adding the risk of a concomitant mitral valve procedure also has a 20-30% risk of recurrent FIMR. A direct comparison between CABG and CABG combined with mitral valve ring annuloplasty sheds further light on this question.

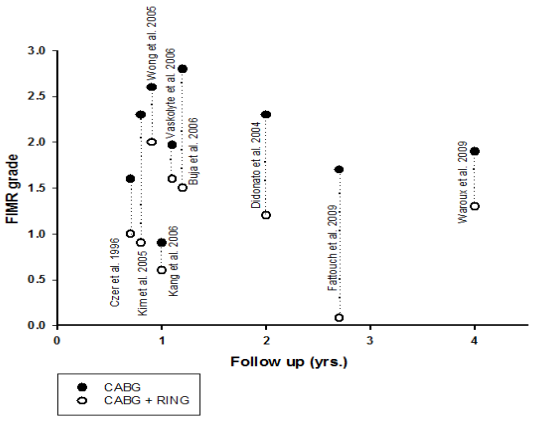
CABG ALONE VS. COMBINED CABG AND RING ANNULOPLASTY

General litterature review

Twenty-two studies (99, 181-201) published between 1996 and 2013 comparing CABG alone with combined CABG and ring annuloplasty to treat FIMR. Eight papers stated that down-sizing of the mitral annuloplasty ring was done. Early mortality (reported as in hospital, 30-day or operative) was in range from 0 - 18% after CABG alone, and 3 - 21% after combined CABG and ring annuloplasty. Four studies reported significantly higher early mortality in the combined CABG and ring annuloplasty group, while one study (STICH subgroup) reported the opposite. Follow-up was 1-10 years, and five year survival was in the range from 52 - 95% after CABG alone, and from 44-94% after combined CABG and ring annuloplasty. Two studies (99, 186) observed a late survival advantage from CABG combined with ring annuloplasty.

Both were studies on patients with low LV ejection fractions of 28% and < 35%, respectively, and it should, be emphasized that the data are observational since the decision to treat the mitral valve during CABG was left to the surgeon. All remaining studies showed no impact on long term survival from combined CABG and ring annuloplasty.

a)



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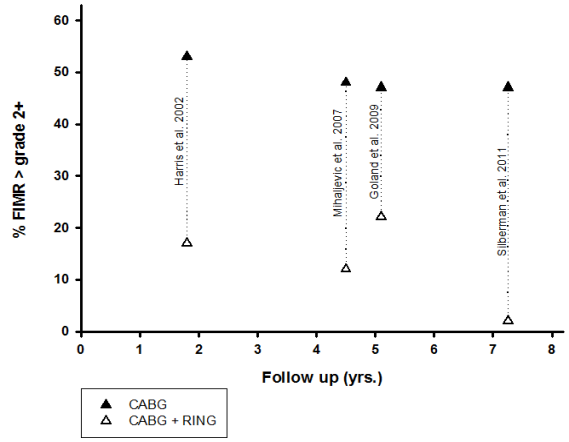

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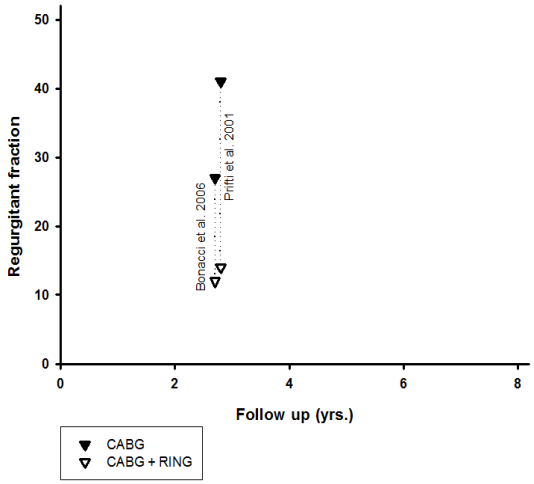

Figure 19. Recurrent FIMR after CABG alone vs. combined CABG and RING, shown as; a) FIMR grade, b) % with recurrent FIMR, c) regurgitant fraction. FIMR, functional ischemic mitral regurgitation ; CABG, coronary artery bypass grafting ; RING, mitral valve ring annuloplasty.

Preoperative New York Heart Association (NYHA) functional class was reported in seventeen studies, and in 71% of the studies NYHA class was higher in the combined CABG and ring annuloplasty group. In ten studies, postoperative NYHA class was reported, and despite the higher preoperative NYHA class, combined CABG and ring annuloplasty showed the same or lower NYHA class compared with CABG alone in all studies. In seventeen of the studies postoperative MR grade was available, and in all studies combined CABG and ring annuloplasty had lower postoperative MR grade (figure 19).

Randomized trials / meta analysis

Most of the papers addressed above are retrospective with the inherent limitations that entails. Meanwhile, three randomized studies and a meta analysis merit further presentation; Benedetto et al. (183) in 2009 published a meta analysis of nine retrospective studies including a total of 2479 patients with FIMR grade 2.2 - 3.9 undergoing a CABG (n=1515) or CABG combined with mitral valve surgery, predominantly mitral valve ring annuloplasty (n=964). They found no benefit on long-term survival, however mitral valve surgery did reduce FIMR grade more than CABG only, and also resulted in a non-significant tendency of improved NYHA functional class. The first randomized study comparing CABG alone (n = 54) combined CABG and ring annuloplasty (n = 48) in patients with grade 2+ FIMR was published in 2009 by Fattouch et al. (182). In this study in a residual FIMR grade of only 0.08 after combined CABG and mitral valve ring annuloplasty compared with 1.7 in the CABG groups was observed at a mean follow-up of 32 months. Furthermore, LV dimensions and NYHA class also improved compared with CABG alone, although no difference in five-year survival was observed (89% vs. 94%, NS). The second randomized trial ("RIME-trial") comparing CABG (n = 39) with combined CABG and mitral valve ring annuloplasty (n = 34) was published by Chan et al. (199) in 2012. At one year follow-up, they reported significantly greater reduction in LV volumes, LV sphericity and FIMR grade, and improved peak oxygen consumption in patients receiving combined CABG combined with ring annuloplasty. Meanwhile, no survival difference was observed (95% vs. 91%, NS). The third randomized study comparing CABG (n = 16) with CABG combined with ring annuloplasty (n = 15) was published by Bouchard et al. (201) in 2013. Again, no survival difference was observed between groups, however, in contrast with the former studies, no difference in NYHA class or FIMR grade between groups was observed. No explanation is obvious why CABG was more efficient, and CABG combined with ring annuloplasty less efficient in this study compared with the former two at relieving FIMR and improving functional status, but the low samle size and relative short follow-up should be taken into account.
A number of randomized trials are underway to compare CABG alone vs. combined CABG and ring annuloplasty in moderate FIMR in North America (NCT00806988), Russia (NCT01368575) and Israel (NCT00394797, identified using clinicaltrials.gov).

MITRAL VALVE RING ANNULOPLASTY VS. MITRAL VALVE REPLACEMENT

An essential question when touching the subject of risk of recurrent FIMR after ring annuloplasty is why not just replace the valve with concomitant preservation of the subvalvular apparatus, thus effectively reducing the risk of recurrent FIMR? The obvious drawbacks of risking valve degeneration with bioprostheses and need for anticoagulation therapy and of bleeding with mechanical valves must be balanced against the poor prognosis associated

with recurrent FIMR. Twenty-one papers (168, 180, 187, 190, 202-217), including a Cochrane review and a meta analysis, comparing combined CABG and ring annuloplasty vs. CABG and mitral valve replacement in moderate or severe FIMR, have been published. The early mortality rate was in the range from 3-20% after ring annuloplasty and 5-21% after replacement. In 8/20 studies early mortality was significantly higher after replacement, including 5/8 of the most recent studies, and in 12/20 studies there was no significant difference. The overall impression is that early mortality rates may be lower after mitral valve ring annuloplasty compared with replacement.

Five year survival ranged from 51-84% in the annuloplasty ring group, and from 50-91% in the replacement group. A meta analysis by by Vassileva et al. in 2011 (210), a cochrane review by Rao et al. in 2011 (209) and a restrospective study by Milano et al. in 2008 (187) favoured ring annuloplasty in terms of long term survival. Meanwhile, in five other recent retropective studies Lorusso et al. in 2013 (212), Chan et al. in 2011 (211), Maltais et al. in 2011 (208), Magne et al. in 2008 (207), and Micovic et al. in 2008 (206) concluded no survival difference between groups. Overall, in terms of long term survival, 6/20 studies favoured ring annuloplasty, 12/20 found no difference and 1/20 favoured mitral valve replacement.

Eight studies (168, 180, 190, 203, 207, 211, 212, 215, 217) reported postoperative FIMR grade in the ring annuloplasty groups, revealing from 9-59% of patients with ≥ grade 2+. Recurrent FIMR after replacement was addressed by Lorusso et al. (212) Magne et al. (207) and Chan et al. (211), reporting 6%, 4% and 14% with recurrent FIMR (≥ moderate) after mitral valve replacement, compared with 25%, 18% and 59% after ring annuloplasty, respectively. The freedom from reoperation was addressed in ten studies (190, 204, 206, 211-214, 217) and ranged from 42-100% after ring annuloplasty, and from 93-100% after mitral valve replacement, with an overall tendency of slightly higher incidence of reoperations after ring annuloplasty.

Twelve studies (168, 187, 202-208, 214, 215, 217) reported preoperative NYHA functional class. In seven of these studies, approximately 90% of patients preoperatively were in NYHA class III-IV, with lower preoperative NYHA class in the remaining five studies. Two studies reported postoperative NYHA class, and in both cases ring annuloplasty produced lower NYHA class compared with mitral valve replacement (203, 206).

To shed further light on the optimal treatment for patients with severe FIMR, a randomised study is currently being conducted by the National Heart, Lung, and Blood Institute in the United States. This study compares ring annuloplasty vs. mitral valve replacement with preservation of the subvalvular apparatus in patients with severe chronic FIMR (NCT00807040). In this study, CABG is a possibility, but not mandatory. The study is expected to enroll 250 patients with completion in February 2014.

CARDIAC RESYNCHRONIZATION THERAPY

Cardiac resynchronization therapy is obtained using a biventricular pacemaker, with a right ventricular apical lead and an LV pacing electrode through the coronary sinus in an LV epicardial vein. The technique is used in patients with low LV ejection fraction and left bundle branch block due to ischemic or dilated cardiomyopathy. In 2012 van Garsse et al. (179) identified papillary muscle dyssynchrony as the strongest predictor of recurrent FIMR after CABG and down-sized ring annuloplasty, which underscores the importance of electro-mechanical synchronization during mitral valve closure. Accordingly, a number of investigators have shown the beneficial effect of cardiac resynchronization therapy in functional MR and FIMR as a result of increased transmitral pressure gradients, reversal of LV remodeling and reduced leaflet tethering (218-222).

ADJUNCT PROCEDURES IN FIMR

In the present chapter new experimental technologies and techniques in FIMR will be addressed. Also, existing techniques, which have been used in the context of FIMR, but do not yet constitute a standardized and widespread available treatment modality, are addressed. Many of the devices described were developed to treat heart failure, and not specifically FIMR, but due to the close interplay between the failing LV and functional MR, they have been included as potential future therapies for FIMR.

5.1 The mitral valve annulus: Innovations in mitral valve ring annuloplasty

Adjustable rings

The latest innovation in mitral valve ring annuloplasty design includes adjustable rings, allowing changes of the septo-lateral dimension after implantatin. The MiCardia DYANA annuloplasty system (223, 224) is a nitinol-based complete rigid ring that allows modification of the septal-lateral diameter by activating radio-frequency wires attached to the ring and externalized to the pericardium. The ring is activated under transesophageal echocardiography guidance in the loaded beating heart and proof of concept has been demonstrated in patients by correct both early and late residual FIMR. In 2013, Maisano et al (225) published the one year follow-up of the Cardinal adjustable ring annuloplasty in a mixed cohort of Carpentier type I, II and III MR. The ring allowed intraoperative increase or reduction of ring size, thereby they successfully corrected residual MR, systolic anterior motion and high transvalvular pressure gradient. The corrections could be done both according to water testing or post cardiopulmonary bypass.

Minimally invasive ring annuloplasty

The latest innovations in mitral valve annulolasty rings support the concept of minimally invasive implantation. Indirect mitral valve ring annuloplasty using percutaneus techniques was introduced by implanting an annuloplasty device in the coronary sinus, which is located parallel with the posterior mitral annulus. Even though the coronary sinus is located more towards the left atrial side compared with the mitral annulus, it is possible to reduce annular size by compressing the coronary sinus. The obvious appeal of the coronary sinus approach is simplicity and ease of use. Meanwhile, the litterature reports than in 45-95% of patients the coronary sinus crosses over the circumflex coronary artery or an obtuse marginal branch with risk of compression and myocardial ischemia, thereby limiting the use of this method (226). A number of percutaneous coronary sinus annuloplasty devices have undergone initial clinical testing. Harnek et al. in 2011 reported the 12 moths results of the Edwards Monarch System (227) (EVOLUTION trial), emphazising the need for preoperative imaging to detect when the coronary sinus crosses the circumflex coronary artery. Siminiak et al. (228) in 2012 published the one year outcome of the Carillon device (TITAN trial) in heart failure patients, showing reduced MR grade and reverse LV remodeling compared with a control group without device implantation. However, mortality in the implantation group was 23%. Machalaany et al. in 2013 (229) published the 12 months follow-up of

the with the Viacor PTMA device (PTOLEMY-2 trial), revealing only a mild impact on MR reduction, and during follow-up, the risk/benefit ratio remained suboptimal. Overall, the coronary sinus devices so far have produced suboptimal results in terms of safety and efficacy.
Direct percutaneous catheter based mitral annuloplasty techniqeus have been introduced. These techinques utilize retrograde transarterial placement of of a guide catheter over the aortic valve to access the mitral valve annulus. The annuloplasty is obtained using nitinol clips (Guided Delivery Systems) or by pledgets placed using radiofrequency catheters to penetrate the mitral annulus (Mitralign system), to facilitate anchoring and down-sizing of the mitral annulus. These two devices are still under development, but have undergone first in man testing (230). Also, the CardioBand system, utilizing device based placement of a posterior annuloplasty dacron band fixated by metallic helices, has been tested in a porcine model (231).
The Medtentia double helix mitral annuloplasty ring was developed to further facilitate faster and easier surgical minimally invasive mitral valve ring annuloplasty implantation (figure 20).

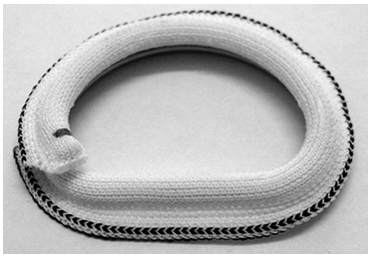

Figure 20. Medtentia annuloplasty ring. Medtentia ring prototype. The Medtentia ring prototype was fitted with a polyester cloth-sewing ring. Only the "atrial" helix arm is seen, whereas the "ventricular" helix arm is hidden below the sewing cloth. From Jensen et al. Medtentia Double Helix Mitral Annuloplasty System Evaluated in a Porcine Experimental Model. Innovations 2010;5:114–117. Reproduced with permission from Wolters Kluwer Health.

This ring consists of a double helix similar to a key ring and is implanted by rotating it around the mitral valve leaflets to place one helix arm in the left atrium and one arm in the left ventricle. The ring is thereby fixated by squeezing the mitral annulus, establishing a potential for sutureless implantation. The Medtentia ring underwent initial evaluation in a chronic porcine experimental model by Jensen et al. (232) showing no sign of mitral valve dysfunction or tissue damage 10 weeks postoperatively. Also, in 2013 Konderding et al. (233), using a tachycardia induced ovine model of functional MR, the Medtentia ring was compared with the Carpentier-Edwards Classic ring, and at up to 12 months follow-up, the two rings showed comparable functional outcome. The first five cases of successful implantation in patients has been done, and a multicenter clinical trial is being prepared (personal communication).

Transcatheter mitral valve implantation
When addressing recurrent FIMR in patients with a previous ring annuloplasty, an interesting new possiblity was introduced by de Weger et al. (234), who in 2011 demonstrated first in man experience with transcatheter "valve-in-ring" mitral valve implantation after previous ring annuloplasty, and recently Descoutures et al. (235) in 2013 published a series of seventeen patients undergoing transcatheter implantation of a valve after failed mitral valve ring annuloplasty. Also, Cullen et al. in 2013 (236) published a series of ten patients undergoing "valve-in-valve" transcatheter mitral valve implantation after previous bioprosthetic mitral valve replacement. Furthermore, the concept of a pure transcatheter mitral valve implantation is in the preclinical development phase (237).

LEAFLETS AND CHORDAE: DIRECT REPAIR TECHNIQUES

Alfieri stich
In 1995 Alfieri et al. (238) introduced the edge-to-edge repair technique for degenerative mitral valve regurgitation, i.e. mitral valve prolapse. This "Alfieri stich" is a suture that attaches the anterior leaflet to the posterior leaflet, typically the A2 to P2 region, to use the non-prolapsing leaflet to fixate the prolapsing leaflet and correct MR. Although developed for degenerative MR, the Alfieri stich has also been used combined with ring annuloplasty in FIMR. Bhudia et al. in 2004 reported the Cleveland clinic results with the Alfieri technique, revealing that > 30 % of patients had recurrent grade 3-4+ FIMR 18 moths after posterior band flexible ring annulplasty and Alfieri stich (239). Meanwhile, De Bonis et al. (240) in 2005 obtained better results with the Alfieri stich combined with complete ring annuloplasty, reporting recurrent FIMR ≥ grade 3+ in 3.7% and ≥ grade 2+ in 14.8% at 18 months follow-up.

Mitraclip
Inspired by the Alfieri stich, Fann et al. (241) in 2004 introduced a percutaneous device which would later be known as the "MitraClip" (figure 21). This is device is implanted using a femoral venous access and the left atrium and mitral valve is accessed through the atrial septum. A clip is then placed to attach and fixate the anterior and posterior mitral valve leaflets, using the same principle as the Alfieri stich. Feldman et al. in 2009 published the "Everest I" safety and efficacy trial of the MitraClip (242), reporting a reduction in MR grade to < 2+ in the majority of patients. In 2013, Foster et al. (243) reported the 12 months follow-up of the EVEREST I and the EVEREST II roll-in phase patients with acute procedural success (74%) (defined as a reduction in MR grade to ≤ 2 at discharge), revealing that patients with recurrent MR at 12 months have a worse development in LV volumes and wall stresses. The EVEREST II randomized trial was done to compare the Mitraclip with conventional mitral valve repair using ring annuloplasty, and the 12 months follow-up was published by Feldman et al. (244) in 2011. They demonstrated that percutaneous repair was less effective at reducing MR than conventional surgery, and that both procedures were associated with similar improvements in clinical outcomes. The MitraClip showed a better safety profile due to a higher rate of blood transfusion in the surgery group.

Figure 21. The mitraclip device. The device i s covered with polyester fabric to facilitate tissue in-growth. The distal gripping element helps with leaflet fixation. The clip delivery system exits through a guide catheter. From Feldman et al. Percutaneous Mitral Repair With the MitraClip System Safety and Midterm Durability in the Initial EVEREST

(Endovascular Valve Edge-to-Edge REpair Study) Cohort. J Am Coll Cardiol 2009;54:686–94. Reproduced with permission from Elsevier.

Recently, Mauri et al. in 2013 (245) reported the four years follow-up of the EVEREST II trial, showing that percutaneous repair, compared with surgery, is associated with similar mortality and symptomatic improvement, but has a higher rate of MR requiring repeat procedures, and less improvement in LV dimensions. The authors concluded that surgery remains the standard of care for treatment of MR among eligible patients. Clinical implementation of the MitraClip is ongoing and it has been added to the ESC/EACTS 2012 guidelines (98) as a possibility in both functional and degenerative MR for the inoperable or high risk patients. Currently, a randomized study (RESHAPE-HF) is being conducted, comparing optimal medical treatment with and without the MitraClip in grade 3-4+ functional MR patients with LV ejection fraction < 40%, who are not candidates for conventional mitral valve surgery.

Leaflet augmentation

The pathogenesis of FIMR is caused by type I and IIIb leaflet dysfunction, both acting to pull the mitral leaflets apart and reduce coaptation area. Initially the ”physiological reserve” of mitral valve leaflet area can compensate for the lacking leaflet tissue, but eventually coaptation becomes insufficient and MR occurs. To compensate for this lack of sufficient mitral leaflet area, Dobre et al. (246) in 2000 introduced the concept of posterior leaflet augmentation (figure 22), presenting two cases of successful mitral valve repair the restricted P2-P3 region using a bovine pericardial patch and ring annuloplasty, and another two successful cases were published by Rendon et al. in 2002 (247). In 2009 de Varennes et al. (248) published a series of fourty four patients with severe FIMR undergoing ring annuloplasty and posterior leaflet augmentation, showing a 90% freedom from moderate or severe FIMR at 38 months follow-up and significantly improved NYHA functional class. Moreover, Jassar et al. (249) in 2012, using an ovine FIMR model, showed that posterior leaflet augmentation combined with normo-sized ring annuloplasty enhanced leaflet coaptation more effectively compared with down-sized or normo-sized ring annuloplasty alone.

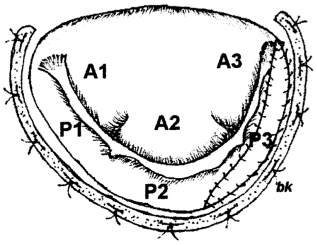

Figure 22. Posterior leaflet augmentation. The mitral valve, showing pericardial patch enlargement of the medial half of P2, the entirety of P3, and the posteromedial commissure of the PML and posterior mitral ring annuloplasty. A1 to A3 and P1 to P3 represent anatomic regions of the anterior and posterior leaflets. From Dobre et al. anatomic and physiologic correction of the restricted posterior mitral leaflet motion in chronic ischemic mitral regurgitation. J Thorac Cardiovasc Surg 2000;120:409-11. Reproduced with permission from Elsevier.

Also, augmentation of the anterior leaflet to correct tethering was introduced by Kincaid et al. (250) in 2004; Twenty five patints with grade 3-4+ FIMR received posterior band annuloplasty and patch enlargement of the anterior leaflet using a bovine patch, reporting a 2 year freedom from moderate or severe FIMR of 81%. Meanwhile, the scarceness of published reports using the anterior leaflet augmentation indicates that this technique has not gained footing in clinical practise. Also, in vitro (81, 82), the impact from leaflet augmentation on chordae tendineae forces have been addressed.

Chordal cutting

Cutting second order “strut” chordae tendineae to relieve anterior leaflet tethering and correct FIMR (figure 23) was introduced by Messas et al. in 2001 (251) using an acute FIMR ovine model, and further evaluated in 2003 (252), using a chronic ovine FIMR model. In this context it is note worthy, that the strut chordae of the anterior leaflet are load-bearing structures, and Lomholt et al. (75) in 2002 demonstrated, that strut chordae support more than three times the tension compared with primary chordae tendineae. He et al. (253) in 2008 used an in vitro setup to demonstrate that cutting anterior leaflet strut chordae increased tension in marginal chordae tendineae to the anterior leaflet by four fold. Also, Padala et al. (254) in 2011, analysing tethered porcine leaflets in vitro, reported 3.4 fold increased marginal chordal tension compared with baseline, and this ratio increased to 5.5 fold after strut-chordal cutting. Therefore, concern has been raised that chordal cutting would remove the valvular-ventricular continuity, which is established by the load-bearing second order chordae tendineae between the belly of the anterior and posterior leaflets and the papillary muscles. A number of papers on the subject of cutting anterior leaflet strut chordae have been published, and these reports point in different directions regarding whether or not chordal cutting has adverse effects on FIMR grade, LV volumes and LV function. Using helthy sheep, Nielsen et al. (255) in 2003 showed regional LV systolic dysfunction near insertion sites of strut chordae. Rodriguez et al. (256, 257) in 2004 and 2005 published their results with chordal cutting in healthy and acute FIMR sheep, concluding that chordal cutting did not prevent or decrease acute FIMR, but caused increased anterior leaflet stresses, global LV dysfunction and altered global LV geometry after chordal cutting. Meanwhile, using an ovine chronic FIMR model, Messas et al. in 2003 (47) used chordal cutting to successfully treat FIMR with no impairment of LV ejection fraction, and in 2010 (258), still using the chronic FIMR ovine model, they used chordal cutting to decrease progression of post myocardial infarct LV remodeling with sustained reduction of FIMR during chronic follow-up.

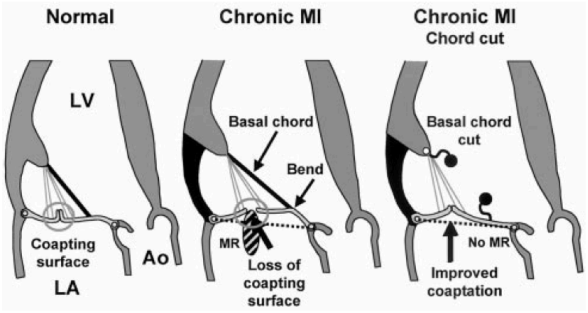

Figure 23. Chordal cutting. Left, at baseline, leaflet area exceeds that needed to cover the annulus, creating a coapting leaflet surface to prevent MR. Center, inferior infarction most distorts the base of the anterior leaflet, which is tethered by basal chordae to form a bend, reducing the coapting surface and causing MR. Right, basal chordal cutting can eliminate this bend, improve coaptation, and reduce MR; the marginal chordae prevent prolapse. Circulation 2003;108;II-111-II-115.

From Messas et al. Efficacy of Chordal Cutting to Relieve Chronic Persistent Ischemic Mitral Regurgitation. Reproduced with permission from Wolters Kluwer Health.

Also, Messas et al. (259) reported that that chordal cutting in healthy sheep did not cause any adverse effect on global or segmental LV contractility and no change in LV volumes.
From the clinical setting, a retrospective analysis was published by Borger et al. (260) in 2007. They reported a series of ninety two FIMR patients undergoing undersized flexible incomplete ring annuloplasty ring with (n=43) or without (n=49, controls) chordal cutting. Although the chordal-cutting group had an increased risk profile, including worse LV function and more mitral leaflet tenting, perioperative outcomes were similar. Compared with controls, chordal cutting resulted in decreased leaflet tenting, increased leaflet mobility, and decreased recurrence of FIMR at two years follow-up.
Future persepectives of chordal cutting includes efforts to invent minimally invasive catheterbased techniques. Along these lines, Slocum et al. (261) 2009 used radio frequency ablation in vitro to cut chordae tendineae, and Abe et al. (262) in 2008 demonstrated in vitro that high intensity focused ultrasound can be used to divide chordae tendineae. Also, as an alternative approach to avoid left atriotomy, Fayad et al. (263) in 2005 desribed the chordal cutting using an aortotomy access.

THE MITRAL SUBVALVULAR APPARATUS

A vast number of suggestions how to address LV dilatation and papillary muscle displacement in functional MR have been suggested in the past decade. The main categories include surgically addressing the LV myocardium, passive LV constraint, direct papillary muscle relocation, transventricular devices and papillary muscle approximation. The techniques have been developed and used for dilated as well as ischemic cardiomyopathy, and therefore many of the techniques described in the following sections apply to both patient categories.

SURGICALLY ADDRESSING THE LV MYOCARDIUM

The Dor procedure / Surgical LV restoration

In 1944 Beck et al. (264) reinforced an LV aneurysm with a piece of fascia lata, but the first actual resection of an LV aneurysm was reported in 1955 by Likoff et al. (265). Since then a vast number of techniques have been introduced to treat LV aneurysms, scarring and dilatation. A pivotal advance was done in 1984, when Dor et al. introduced the endoventricular patch plasty, which consists of an incision in the anterior wall, a circular suture in healthy tissue to narrow down the scar tissue region, a patch covering the area encircled by this suture and finally closure of the LV incision by adapting/approximating or overlapping the infarcted myocardium using felt pledgetted sutures (figure 24). Other surgeons have adopted different variations of the Dor procedure, and the label "surgical ventricular restoration" (SVR) is used for this category. In later series, to control the amount of volume reduction obtained from tightening the stich that narrows the aneurysm, a balloon was inflated to a desired volume in the LV during stich tightening. In 1998 Dor et al. (266) published a series of 269 patients undergoing SVR. In hospital mortality varied from 0-12.5% depending on the degree of dyskinetic LV myocardium. Overall, LV ejection fraction and pulmonary pressures improved. In this study, MR postoperatively was not addressed.

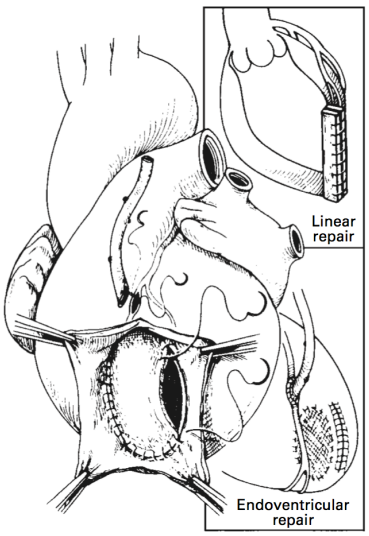

Figure 24. The Dor procedure / Surgical ventricular restoration. Left ventricular restoration by endoventricular patch repair (the Dor procedure) as opposed to simple linear aneurysmectomy. From Westaby et al. Non-transplant surgery for heart failure. Heart 2000;83:603-610. Reproduced with permission from BMJ Publishing Group Ltd.

A number of studies addressed FIMR in the context of SVR; Menicanti et al. in 2002 (267) reported 46 patients with ≥ grade 2+ FIMR, undergoing suture mitral annuloplasty, SVR and CABG. Early postoperatively 84% had ≤ grade 1+ FIMR, no change in LV ejection fraction was observed and survival at 30 months was 63%. Di Donato et al. in 2007 (268), based on a series of 55 patients with grade 2+ FIMR receiving SVR and CABG, concluded that FIMR was significantly reduced a three years postoperatively, and that it was not neccesary to add mitral valve repair. The authors specifically demonstrated SVR significantly reduced inter-papillary muscle distance. Also, in 2008 Prucz et al. (269) showed improved survival and better freedom from recurrent FIMR from adding SVR to CABG. Meanwhile, Klein et al. in 2012 (270) revealed, that SVR could potentially lead to distortion of the subvalvular mitral apparatus, causing an increase in FIMR. In their study, 33% of patients with FIMR grade < 2+ preoperatively experienced increased FIMR after SVR to grade ≥ 2+ immediately postoperatively, neccesitating implantation of a ring annuloplasty.
In 2009 Jones et al. (271) published the "STICH" trial (hypothesis 2), in which 1000 patients were randomised to CABG with or without concomitant SVR. At four years postoperatively, there was no difference in symptoms, mortality or hospitalization for cardiac causes, and preoperative FIMR grade did not affect outcome (postoperative MR grade not reported). In 2012 Jae et al. (272), in a subgroup analysis of the STICH trial, showed that patients with less dilated LVs and better ejection fraction may have improved clinical outcome from adding SVR, indicating that SVR continues to have a role in the treatment of patients with ischemic cardiomyopathy. In patients for whom SVR is planned, survival improved in those achieving a postoperative LV end systolic volume index of 60 mL/m2 or less. The very large, extensively remodeled, LV at baseline might limit the ability of SVR to achieve a sufficient volume reduction and derive a clinical benefit.

Infarct plication / Inferior wall restoration

LV plication of scar tissued following myocardial infarction was described decades ago, meanwhile, specifically plicating the myocardium overlying the papillary muscles has a much shorter history. In 2000 Liel-Cohen et al. (49), using an ovine chronic FIMR

model, showed that infarct plication significantly reduced FIMR, relocated the papillary muscles towards the mitral annulus, and reduced inter-papillary muscle distance and leaflet tethering. Inspired by the SVR techniques, Menicanti et al. in 2001 (273) described three surgical methods (direct linear closure, insertion of patch and triangulation suture) of inferior wall restoration to exclude nonfunctional myocardium and address FIMR. Guy et al. in 2004 (274) showed that a polyester fiber mesh covering the infarction zone, prevented infarct expansion and development of FIMR. In 2005, Ramadan et al. (275) reported three cases using plication of infero-basal LV scar tissue to relocate the PPM combined with CABG without using ring annuloplasty in three patients with grade 3-4+ FIMR. Echocardiography seven months postoperatively showed trivial or no FIMR in all patients and reduced LV volumes. Also, Tanaka et al. in 2007 described two cases of successful using SVR techniques in two patients with FIMR and postero-basal aneurysms to significantly reduce FIMR (276).
To facilitate a minimally invasive off-pump procedure Hung et al. in 2009 (277), using an ovine experimental model, reported that papillary muscle relocation could be obtained by injecting polyvinyl-alcohol polymer into the myocardium adjacent to the papillary muscles, thereby reducing FIMR grade.

The Batista procedure

In 1996 Batista et al. published their initial ovine experimental and clinical case report using the "Bastista" procedure, which is a partial left ventriculectomy, in which a slice of LV myocardium is excised to reduce LV volume (278) (figure 25). In 1997 McCarthy et al. (279) published the Cleveland Clinic initial experience with the the Batista procedure in 53 patients with dilated cardiomyopathy and a mean of grade 2.8 mitral regurgitation. At short term follow-up LV volume was reduced, ejection fraction improved and no MR was present. The authors concluded that the procedure "may become a biologic bridge, or even alternative, to transplantation". Meanwhile, in 2001 Franco-Cereceda (280) published the Cleveland Clinic three year follow-up, revealing only 60% survival and only 26% freedom from heart failure, and concluded that "Early and late failures preclude the widespread use of partial left ventriculectomy". In 2003 Kawaguchi et al. (281) showed that patients with significant functional MR did have reduced MR grade 90 days postoperative, but they did not benefit more from the Batista procedure compared with patients without MR in terms of survival, LV diameters or functional class.
Epicardial approaches

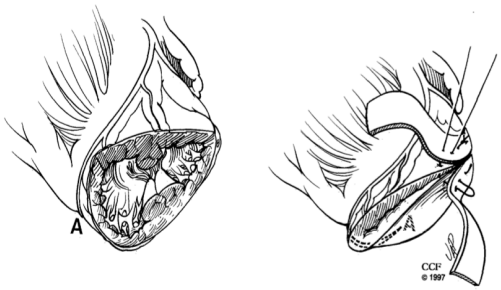

Figure 25. The Batista procedure. Partial left ventriculectomy (left) with the lateral wall and lateral branch of the circumflex coronary artery excised. After closure (right) the LAD artery at the apex (point A) wraps around the reconstructed apex. The wall between the papillary muscles was sutured together. From McCarthy et al. Early Results With Partial Left Ventriculectomy. J Thorac Cardiovasc Surg 1997;114:755-65. Reproduced with permission from Elsevier.

In 1999 an epicardial device providing passive ventricular constraint was introduced, using what would be known as the Acorn's cardiac support device (figure 26). The Acorn device is a biocompatible polyester mesh fabric jacket shaped to cup the ventricular apex with a longitudinal opening for size adjustment.
It is placed around both ventricles, covering the LV starting at the apex and attached above the atrio-ventricular junction. It is then wrapped firmly around the heart after which the cut edge is sutured. In 1999, feasibility of the passive ventricular constraint was proven by Power et al. (63) using an ovine experimental model of tachycardia induced heart failure to show improved LV function and less functional MR in animals receiving passive ventricular constraint.

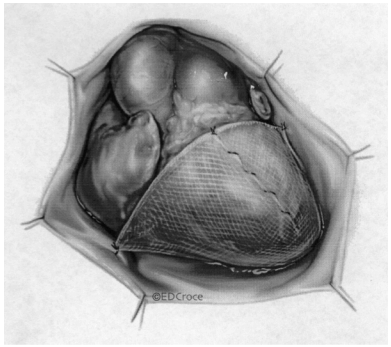

Figure 26. Acorn device. Position and attachment of the jacket on the epicardial surface of the two ventricles. The Ligaclips are on the undersurface of the heart and therefore not visible. From Power et al. Passive ventricular constraint amends the course of heart failure: a study in an ovine model of dilated cardiomyopathy. Cardiovascular Research 44 (1999) 549–555. Reproduced with permission from Oxford University Press.

Konertz et al. in 2001 (282) published the Acorn device clinical safety and feasibility study, in which 27 idiopatic cardiomyopathy patients had improved LV ejection fraction and NYHA class, and reduced MR grade and LV volumes six months postoperatively. Further scientific basis of the Acorn device in the treatment of functional MR was provided by the prospective controlled randomized multicenter Acorn Clinical trial, which included 193 patients with significant functional MR due to dilated cardiomyopathy. Patients were randomised to mitral valve surgery (84% ring annuloplasty) with or without the Acorn device. The five-year follow-up was published by Acker et al. in 2011 (283), revealing greater decreases in LV volume in the Acorn group, but no difference in survival or the frequency of recurrent MR between groups.
In 2002, using a chronic ovine FIMR model, Hung et al. (57) obtained papillary muscle relocation and removed FIMR using an inflatable ballon overlying the infarcted myocardium under the PPM. Also, in 2007, Hung et al. (284) published the eight weeks follow-up of this procedure, revealing no recurrent FIMR and improved mitral valve coaptation geometry.
A number of other epicardial devices are being tested experimentally, e.g. the BACE device and the Mitral Touch device; Raman et al. in 2011 (285) described the BACE device, which is a silicone band with inflatable chambers to support the underlying LV myocardium. The device wrapped around the base of the LV and fixated using sutures. The device was tested in an ovine model and in five FIMR patients undergoing CABG and proved effective in removing FIMR up to six months postoperatively. The Mitral Touch device is a C-shaped clamp with one arm placed in the transverse sinus and the posterior arm just apical to the atrioven

tricular groove on the LV posterolateral wall. The device was introduced and tested by Takasaya et al. in 2010 (286), using a canine model of tachycardia induced LV failure. The Mitral Touch device was effective in significantly reducing MR by reduced the septo-lateral mitral annuluar dimension on the beating heart.

Direct papillary muscle relocation

The "Kron technique"

The first clinical experience with papillary muscle relocation was published in 2002 by Kron et al. (287) (figure 27). In this paper, 18 patients with grade 2-3+ FIMR due to previous transmural infarctions of the inferior LV wall received concomitant CABG and size 26-28 semi-rigid ring annuloplasty.

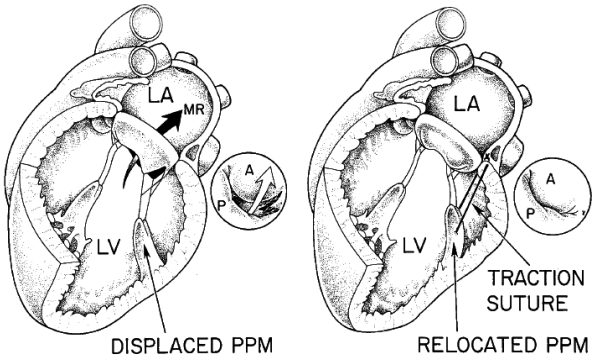

Figure 27. Papillary muscle relocation. A = anterior mitral leaflet; LA = left atrium; LV = left ventricle; MR = mitral regurgitation; P = posterior mitral leaflet. From Kron et al. Surgical Relocation of the Posterior Papillary Muscle in Chronic Ischemic Mitral Regurgitation. Ann Thorac Surg 2002;74:600–1. Reproduced with permission from Elsevier.

Papillary muscle relocation was done using a single prolene throw placed in the PPM tip and fixated at the posterior annulus, thereby enabling relocation of the papillary muscle closer to the posterior annulus. In this series, follow-up at 2 months showed trace residual FIMR in 3 patients and none in the remainder. Recently, Rabbah et al. (288) verified the beneficial effect on mitral valve coaptation geometry from adding the "Kron technique" in an in vitro model of continued LV dilatation after mitral valve ring annuloplasty.

RING + STRING

The Kron technique inspired a number of surgeons to adopt and further develop the concept of direct papillary muscle relocation. Most notably, in 2005 Langer et al. (289), using an ovine model of acute FIMR, showed that relocating the PPM alone reduced FIMR. Two years later in 2007, the same group published the "RING + STRING" paper (290) inspired by the Kron technique. In this study, an ePTFE suture was placed on the PPM tip and then the suture was placed under the aortic valve commisure between the non-coronary and left coronary aortic sinus cusps, through the mids-eptal fibrous mitral annulus (saddle horn) and through the aortic wall to the epicardial side. This allowed adjustment of the papillary muscle relocation STRING on the partially loaded beating heart, (though still on exctracorporal circulation), guided by transesofageal echocardiography (figure 28). In 2009 Langer et al. (291) reported their results on 30 patients with moderate to severe FIMR and severe mitral valve tethering (tenting height ≥ 10 mm) undergoing CABG, down-sized mitral annuloplasty (flexible posterior band) and STRING. Compared with a historical matched control group, the STRING group had significantly less residual FIMR at 26 months postoperatively.

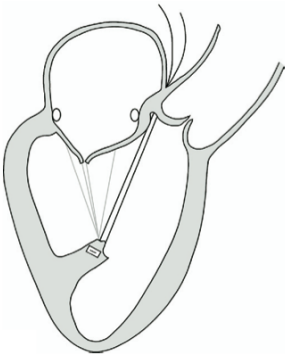

Figure 28. Schematic representation of the trans- ventricular suture technique (STRING). The suture is tied under echocardiographic guidance in the loaded beating heart to reposition the displaced posterior papillary muscle toward the fibrosa. From Langer et al. RING plus STRING: Papillary muscle repositioning as an adjunctive repair technique for ischemic mitral regurgitation. J Thorac Cardiovasc Surg 2007;133:247-9. Reproduced with permission from Elsevier.

Further developments of papillary muscle relocation

A number of investigators have further developed the papillary muscle relocation techniques. Marasco et al. in 2007 (292) published their results using the technique in 6 patients, and, using a canine acute FIMR model (293), they further attempted to optimize the PPM relocation using two sutures to direct relocate the PPM towards the antero-lateral commisure. In 2008, in three patients, Arai et al. (294) combined down-sized mitral valve ring annuloplasty with relocation of both papillary muscles towards the posterior annulus and cutting secondary chordae to the anterior leaflet. In 2008 Masuyama et al. (295) showed that, compared with chordal cutting alone, chordal translocation, using taut stiches from each papillary muscle to the saddle-horn, improved both the LV function and mitral geometry in a canine model of acute FIMR. In 2009 Shingu et al. (296), using a mixed group of 22 functional ischemic and non-ischemic patients, showed that anterior directed papillary muscle suspension is better than posterior directed suspension of approximated papillary muscles in terms of mitral valve diastolic filling. In 2011, Fattouch et al. (297) published their series of 55 patients undergoing relocation of both papillary muscles towards the adjacent annulus, combined with CABG and ring annuloplasty. This group was compared with a propensity macthed control group of patients treated with down-sized ring annuloplasty and CABG. At 32 months postoperatively, recurrent FIMR ≥ moderate was present in 3.7% of papillary muscle relocation patients compared with 11.5% of controls, and the papillary muscle relocation group had superior mitral valve coaptation geometry and experienced fewer cardiac-related events. Also, in 2012 Fattouch et al. (298) published a series of 25 patients, in which intraoperative 3D echocardiography was used to guide the extent of papillary muscle relocation.

Epicardial pressure discs to obtain papillary muscle relocation

On the theoretical level, both the Kron and RING+STRING techniques have potential limitations, that might impair long term durability. Only the papillary muscle tips are pulled toward the annulus, which transfers tension to a single geometric point to relieve mitral leaflet tethering, thereby inducing high papillary muscle myocardial tissue stresses. Second, only PPM relocation was performed, although APM displacement intuitively also carries the potential to induce additional leaflet tethering. Third, the

impact on mitral valve leaflet and subvalvular geometry from papillary muscle relocation was not addressed. To address these topics, Jensen et al. in 2009 (26),using a porcine model of chronic FIMR, compared rigid down-sized ring annuloplasty with and without relocation of both papillary muscle towards the respective trigone. To optimize reverse LV remodeling and support the LV wall, relocation was done using epicardial pressure discs attached to ePTFE stiches (figure 29). The papillary muscle relocation was done guided by preoperative 3D cardiac MRI which, compared with a control group of healthy pigs, indicated the need for 5 mm APM relocation and 15 mm PPM relocation to restore normal papillary muscle tip to trigone distances. Strain gauge technology was used to measure the tension in the papillary muscle relocation stiches, and allow detection of the exact moment when a force was exerted on the LV myocardium. One week postoeratively cardiac MRI was repeated, revealing reduced mitral valve tethering and a general tendency of improved mitral valve coaptation geometry in the papillary muscle relocation group.

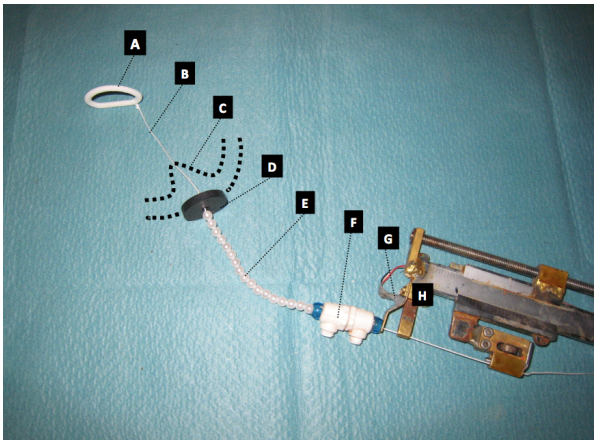

Figure 29. Papillary muscle relocation setup. A, Ring annuloplasty; B, Gore-Tex suture; C, papillary muscle outline; D, rubber disc; E, string of pearls; F, suture locking device; G, strain gauge; H, sliding caliper. Only the posterior papillary muscle stitch is displayed, but an identical setup was used for the anterior papillary muscle. From Jensen H. et al. Impact of Papillary Muscle Relocation as Adjunct Procedure to Mitral Ring Annuloplasty in Functional Ischemic Mitral Regurgitation Circulation 2009;120;S92-S98. Reproduced with permission from Wolters Kluwer Health.

Transventricular devices

To facilitate less invasive "off-pump" surgical approaches to treat ischemic and dilated LV cardiomyopathy, transventricular devices to be implanted on the beating heart were developed. These devices are fixated by epicardial pressure discs that offer a broad pressure bearing surface on the epicardium. The transventricular devices essentially reduce one big chamber to two smaller chambers by bisecting the LV cavity. According to the law of Laplace for cylindrical chambers, circumferential wall stress is directly proportional to LV radius. Therefore, the transventricular devices hypothetically reduces LV wall stress, and this was confirmed by finite element modeling (299).

In 2001 McCarthy et al. (300), using a canine tachycardia induced model of functional MR, introduced the Myosplint device (figure 30), which consists of an implantable transventricular splint and two epicardial pads that are adjusted to draw the walls of the LV together and reduce the radius. The Myosplint reduced LV volumes and improved ejection fraction, but did not change MR grade. Schenk et al. in 2001 (301) published the first 5 cases of myosplint implantation in patients, also concluding that MR was not corrected by the device. Furthermore, Fukamachi et al. (302) published the safety and efficacy trial of the Myosplint device in 2005, reporting improved NYHA class and LV ejection fraction, and reduced LV volumes, but again it was concluded that the device did not correct functional MR.

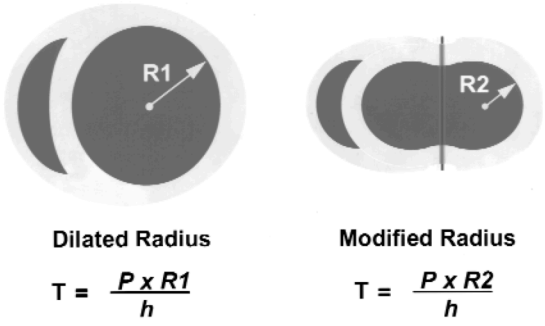

Figure 30. Theoretical concept of the Myosplint device. The law of Laplace explains the increased wall stress (T) in the dilated heart that is directly related to the radius (R1) and intraventricular pressure (P) and, inversely by wall thickness (h). The splinted chamber creates a modified bilobular shape. Wall stress now is directly proportional to the reduced radius of each lobe (R2). From McCarthy et al. Device-based change in left ventricular shape: A new concept for the treatment of dilated cardiomyopathy. J Thorac Cardiovasc Surg 2001;122:482-90. Reproduced with permission from Elsevier.

In 2004 Fukamachi et al. (303) and Inoue et al. (304) introduced the Coapsys device in a canine model of tachycardia induced functional MR to successfully reduce MR. The Coapsys device consists of two epicardial pads and an ePTFE-coated, braided polyethylene subvalvular chord. The two pads are located on the surface of the heart, with the load-bearing subvalvular chord passing through the LV. The device is designed to address both papillary muscle displacement and annular dilatation (figure 31). A multicenter prospective randomized RESTOR-MV clinical trial was conducted, which compared the Coapsys device with ring annuloplasty in FIMR patients undergoing CABG. The intraoperative results of the patients receiving the Coapsys device were published by Grossi et al. in 2005 (305), showing relocation of the anterior papillary muscle towards the anterior annulus, improved mitral valve coaptation geometry and reduced FIMR grade.

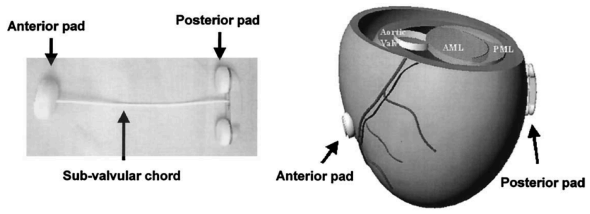

Figure 31. The Coapsys device consists of an epicardial anterior pad, an epicardial posterior pad, and a subvalvular chord (left). The 2 pads are located on the surface of the heart with the load-bearing subvalvular chord passing through the ventricle (right). AML, Anterior mitral leaflet; PML, posterior mitral leaflet. From Inoue et al. The Coapsys device to treat functional mitral regurgitation: in vivo long-term canine study. J Thorac Cardiovasc Surg. 2004;127(4):1068-76. Reproduced with permission from Elsevier.

In 2006 (306) Grossi et al. published the intraoperative comparison between Coapsys and ring annuloplasty, reporting that both

techniques successfully treated FIMR, but also that LV volume was reduced signifiantly more in the Coapsys group. In 2010, the RESTOR-MV trial two year follow-up was published by Grossi et al. (307).Coapsys provided a greater decrease in LV end-diastolic dimension and showed both a survival advantage and better complication free survival (including death, stroke, myocardial infarction, and valve reoperation). Meanwhile, the ring annuloplasty was more effective in reducing FIMR grade. Unfortunately, the study was terminated when the sponsor failed to secure ongoing funding.

A common denominator for the epicardial transventricular devices is the broad epicardial pressure disc, which transfers pressure to a larger area and pushes/supports the LV myocardium in which intuitively is a more physiological and stress relieveing method, compared with putting stiches in a single point on the endocardial myocardium. Meanwhile, none of these devices are able to attach the stiches at the mitral annulus to relocate the papillary muscles in the optimal direction. This is obtained by the papillary muscle relocation technique used by Jensen et al. (26),which combines the two concepts of stiches fixated to the mitral annulus to relocate the papillary muscles and the broad epicardial pressure plates to avoid putting all the tension on a single point of myocardium which theoretically entails risk of elongation or tearing (figure 32).

Papillary muscle approximation

In FIMR the papillary muscles are displaced away from the mitral annulus, which is addressed by the papillary muscle relocation techniques described previously. Meanwhile, the papillary muscles also move away from each other in lateral direction, augmenting leaflet tethering and counteracting proper alignment of the leaflets.

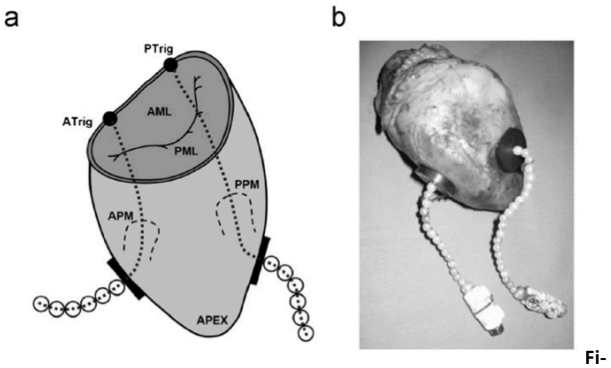

Figure 32. Epicardial pressure plates for papillary muscle relocation. Papillary muscle relocation and traction suture force transmission system. (a) Schematic displaying the suture attached to the anterior and posterior fibrous trigones and exteriorized. ATrig: Anterior Trigone, PTrig: Posterior Trigone, AML: Anterior Mitral Leaflet, PML: Posterior Mitral Leaflet, APM: Anterior Papillary Muscle, PPM: Posterior Papillary Muscle. (b) Picture of a porcine heart with the attached force transmission system. From Jensen MO et al. External approach to in vivo force measurement on mitral valve traction suture. Journal of Biomechanics 45 (2012) 908–912. Reproduced with permission from Elsevier.

The importance of inter- papillary muscle distance was adressed by Jensen et al. in 2010 (308) who, using a chronic porcine FIMR model, showed that the only independent predictor of FIMR grade by mulitivariate regression analysis was inter-papillary muscle distance (figure 33). Recently, in a study of 435 chronic FIMR patients undergoing CABG and down-sized mitral valve ring annuloplasty, van Garsse in 2012 (160) identified preoperative inter- papillary muscle distance to be associated with severity of anterior leaflet tethering, which was a strongly associated with recurrent FIMR. Meanwhile, long before these papers were published to offer this insight, researchers had begun addressing the problem surgically. In 2002, Timek et al. (309), using an acute ovine FIMR model, used a papillary muscle approximation ”PAPS” suture to reduce the inter-papillary muscle distance and mitral valve tethering, but did not remove MR. The first clinical paper to introduce papillary muscle approximation using the ”papillary muscle sling” was publised by Hvass et al. in 2003 (310). Ten patients with dilated LVs and an inter-papillary muscle distance of 3.8 mm had a 4 mm Gore-Tex tube placed through the trabeculations beneath the posterior and anterior papillary muscles, which were then approximated and fixated using sutures (figure 34). The procedure was combined with down-sized mitral valve ring annuloplasty (Physio ring) and CABG.

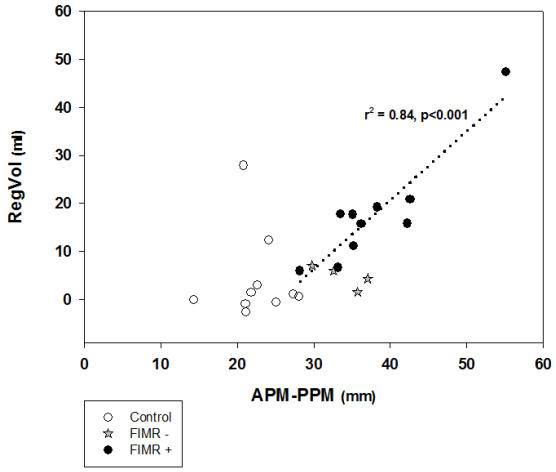

Figure 33. Correlation between anterior to posterior papillary muscle (APM–PPM) distance and regurgitant volume (RegVol). Of all end-systolic papillary muscle position parameters, anterior to posterior papillary muscle distance showed strongest correlation with regurgitant volume. -FIMR, Functional ischemic mitral regurgitation less than grade II; +FIMR, functional ischemic mitral regurgitation of at least grade II. From Jensen et al. (308)Three-dimensional assessment of papillary muscle displacement in a porcine model of ischemic mitral regurgitation. J Thorac Cardiovasc Surg 2010;140:1312-18. Reproduced with permission from Elsevier.

In 2010 Hvass et al. (311) published 55 months follow-up of thirty-seven patients using this technique concomitantly with CABG and mitral valve ring annuloplasty. There were thirty-five late survivors, thirty-one patients had none/trace FIMR, two patients had mild FIMR and two patients required reoparation for moderate-severe FIMR. Also reverse LV remodeling and improved NYHA class was observed. Matsui et al. in 2005 (312) described a modified version of the papillary muscle sling, using pledgeted sutures to pull the papillary muscles together.

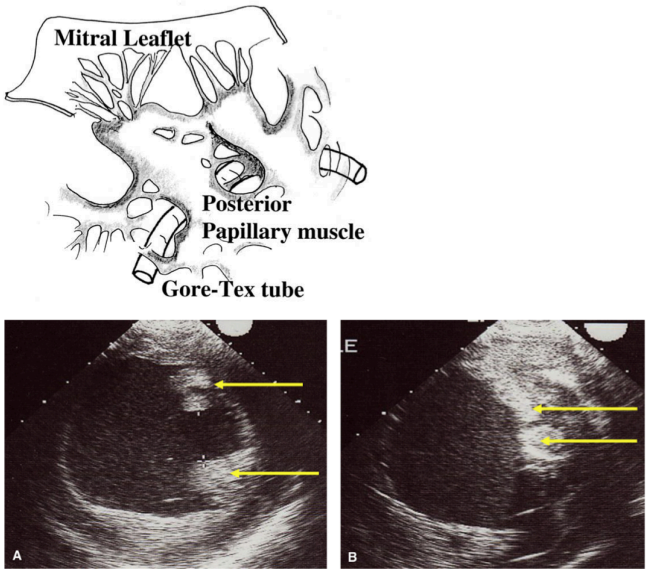

Figure 34. Papillary muscle proximation. Top: The Gore-Tex tube encircles the trabecular base of the posterior papillary muscle, then that of the anterior papillary muscle. The tube is then tightened and secured with sutures, creating a complete sling that brings both papillary muscles in close contact. Bottom: the papillary muscles (arrows) before (A) and after (B) placement of the intra- ventricular sling encircling both papillary muscles. From (left) Hvass et al. Papillary Muscle Sling: A New Functional Approach to Mitral Repair in Patients With Ischemic Left Ventricular Dysfunction and Functional Mitral Regurgitation. Ann Thorac Surg 2003;75:809–11, (right) The papillary muscle sling for ischemic mitral regurgitation. J Thorac Cardiovasc Surg 2010;139:418-23. Reproduced with permission Elsevier.

Also, Ishikawa et al. in 2008 (313) introduced the "sandwich plasty", which brings together the sometimes numerous heads of each papillary muscle using felt pledgeted sutures. This brings the chordae to the anterior and posterior leaflet together, facilitating coaptation. The papillary muscle approximation techniques have been adopted by a number of centers producing good results in terms of avoiding recurrent FIMR and obtaining LV reverse remodeling and reduced leaflet tethering (314-320). Among these, Manabe et al. in 2012 (320) showed, that the augmented posterior leaflet tethering observed after down-sized ring annuloplasty is attenuated by papillary muscle approximation at short term follow-up. The relative wide acceptance of the procedure is most likely facilitated by the relative simplicity of the procedure that allows the surgeon to do the procedure with only little risk and added cross-clamp time. Also, papillary muscle approximation done during minimally invasive valve surgery has been introduced (321).

DISCUSSION

FIMR is caused by LV remodeling and dilatation as a compensatory mechanism in the pathogenesis of ischemic heart failure. LV dilatation at the annular and mid-cavity level induces Carpentier type I and IIIb dysfunction, respectively. It has been established that chronic FIMR aggravates prognosis according to severity. CABG effectively treats myocardial ischemia, but it does not induce sufficient reverse LV remodeling to correct FIMR. Accordingly mitral valve ring annuloplasty has been adopted to correct the FIMR by addressing Carpentier type I dysfunction, i.e. annular dilatation. Treatment of FIMR depends on severity. Currently consensus in the litterature is, that down-sizing the annulus by 1-2 sizes is recommended to treat moderate FIMR. The litterature, including randomized studies demonstrate, that CABG combined with mitral valve ring annuloplasty is more effective in removing FIMR compared with CABG alone. Also, intuitively as a result of less FIMR, adding a mitral valve ring annuloplasty also improves NYHA functional class more than CABG alone. Crabtree et al. (146) showed, that postoperative FIMR reduces survival. Therefore, in chronic FIMR patients, the reduced postoperative FIMR after CABG combined with mitral valve ring annuloplasty would be expected to produce better survival than CABG alone. However, there is no late survival benefit from adding a ring annuloplasty. This can be explained by a tendency of higher early mortality due to the addition of the mitral valve procedure. Also, although less frequent than after CABG alone, significant recurrent FIMR is also present after CABG and mitral valve ring annuloplasty in 20-30% of patients. This calls for an effort to reduce the added operative risk form mitral valve repair, and also for a more effective mitral valve repair to reduce the incidence of recurrent FIMR. The former may theoretically be obtained by pursuing minimally invasive mitral valve repair techniques, e.g. catheter based techniques. Meanwhile, effectiveness of these devices in removing FIMR cannot be expected to be better (or even equal) to open surgery. Moreover, the long-term effectiveness of these devices are still to be seen and they do not yet play a significant role in clinical practice. To reduce the incidence of recurrent FIMR, direct mitral valve repair, e.g. leaflet augmentation and chordal cutting, were introduced with good clinical outcome in terms of freedom from recurrent FIMR. Furthermore, a vast number of subvalvular approaches were introduced, including SVR, papillary muscle relocation and approximation, epicardial and transventricular devices. SVR directly addresses the geometrical shape of the LV and accordingly improves FIMR, but the procedure is not trivial in terms of technical difficulty, risk of bleeding and added cross-clamp time. Therefore it may not be ideal if CABG and mitral valve ring annuloplasty is to be done concomitantly. Also, the lack of survival benefit from adding SVR to CABG in the STICH trial must be taken into account. Many device based subvalvular procedures are still under clinical evaluation. The Acorn, Coapsys and Myosplint devices are among the devices that have been most thoroughly investigated, but none of the devices can match the effect of ring annuloplasty in avoiding recurrent FIMR. Meanwhile, they produce good results in terms of reverse LV remodeling and they can be implanted without cardioplegic arrest, and as such they may play a role as adjunct procedure to CABG and mitral valve ring annuloplasty to stabilise the LV and avoid aggravation of the Carpentier type IIIb dysfunction.

Currently, two direct surgical subvalvular procedures show the potential to improve outcome after CABG and mitral valve ring annuloplasty with minimum of added cross-clamp time; the papillary muscle relocation technique introduced by Kron et al. and further developed by Langer, Schaefers et al., and the papillary muscle approximation technique introduced by Hvass et al. These techniques improve late freedom from recurrent FIMR compared with CABG combined with mitral valve ring annuloplasty. Furthermore, the techniques are relatively simple to add to a mitral valve ring annuloplasty procedure and therefore do not prolong cross-clamp time significantly. In this context, the papillary muscle relocation method used in the experimental setting by Jensen et al. (26) is noteworthy, because it adds the epicardial pressure plates to the Kron technique, and also addresses both papillary muscles. Due to the epicardial support, this technique hypothetically adds more to the LV reverse remodeling effect compared with a stich on a single myocardial point on the papillary muscle tips.

Meanwhile, before embarking on new surgical techniques, what about simply replacing the valve? In that way there will certainly be less recurrent FIMR, and with preservation of the subvalvular apparatus the annular-ventricular continuity is preserved. The discussion between mitral valve ring annuloplasty and mitral valve replacement is currently most relevant in grade 3-4+ FIMR. Although it is often stated in scientific publications that repair is superior to replacement, the most recent papers published do not agree on whether or not a survival advantage is gained with repair over replacement. Again, the problem of recurrent FIMR after mitral valve ring annuloplasty may aggravate progonsis after repair despite a clear tendency of less perioperative mortality. In the subset of patients considered potential candidates for mitral valve replacement, the higher FIMR grades of 3-4+ indicate more dilated LV's with more tethered valves, predicting recurrence of FIMR. This raises the question of whether adding a subvalvular procedure to mitral valve ring annuloplasty would produce better outcome. To further elucidate this question, a randomized study comparing valve replacement with mitral valve ring annuloplasty in patients with grade 3-4+ FIMR is being conducted. In this study it is allowed to add an adjunctive subvalvular procedure if the surgeon finds it neccessary, but it is not mandatory. Patient enrollment is expected to be completed in 2014.

SUMMARY

INTRODUCTION

In many ways we are at a cross road in terms of what constitutes optimal FIMR treatment: is CABG combined with mitral valve ring annuloplasty better than CABG alone in moderate FIMR? Is mitral valve repair really better than replacement? And does adding a valvular repair or subvalvular reverse remodeling procedure shift that balance? In the present thesis I aim to shed further light on these questions by addressing the current status and future perspectives of the surgical treatment of FIMR.

CURRENT SURGICAL TREATMENT FOR FIMR

CABG alone

The overall impression from the litterature is that patients are left with a high grade of persistent/recurrent FIMR from isolated CABG. CABG is most effective to treat FIMR in patients with viable myocardium (at least five viable segments) and absence of dyssynchrony between papillary muscles (< 60 ms).

Mitral valve ring annuloplasty.

A vast number of different designs are available to perform mitral valve ring annuloplasty with variations over the theme of complete/partial and rigid/semi-rigid/flexible. Also, the three-dimensional shape of the rigid and semi-rigid rings is the subject of great variation. A rigid or semi-rigid down-sized mitral valve ring annuloplasty is the most advocated treatment in chronic FIMR grade 2+ or higher.

Combined CABG and mitral valve ring annuloplasty.

CABG combined with mitral valve ring annuloplasty leads to reverse LV remodeling and reduced volumes. Despite this, the recurrence rate after combined CABG and mitral valve ring annuloplasty is 20-30% at 2-4 years follow-up. This is also true for studies strictly using down-sized mitral valve ring annuloplasty by two sizes. A number of preoperative risk factors to develop recurrent FIMR were identified, e.g. LVEDD > 65-70 mm, coaptation depth > 10 mm, anterior leaflet angle > 27-39.5°, posterior leaflet angle > 45° and inter-papillary muscle distance > 20 mm.

CABG alone vs. combined CABG and mitral valve ring annuloplasty.

The current available litterature, including three randomized studies and a meta analysis, indicate that combined CABG and mitral valve ring annuloplasty has no late survival difference compared with CABG alone, and early mortality might even be higher. Meanwhile, adding a mitral valve ring annuloplasty results in a lower NYHA functional class, most likely as a consequence of a lower incidence of persistent or recurrent FIMR. More randomized studies are being conducted to further address this topic.

Mitral valve ring annuloplasty vs. Mitral valve replacement.

The early survival may be higher after repair compared with replacement, meanwhile, the litterature is more ambiguous in terms of late survival advantages, and recent reports find no late survival advantage from repair over replacement. The recurrence rates after ring annuloplasty addressed above were also present in this subset of patients, whereas the incidence of recurrent FIMR after valve replacement is scarcely reported. There was an overall tendency of slightly higher incidence of reoperations after ring annuloplasty.

The mitral valve annulus: Innovations in mitral valve ring annuloplasty

The latest innovation in mitral valve ring annuloplasty design includes adjustable rings, allowing adjustment of septo-lateral dimensions intra- or postoperatively. Minimally invasive ring annuloplasty using indirect coronary sinus devices, has been introduced, but so far have produced suboptimal results in terms of safety and efficacy. Also, first in man testing of direct percutaneous catheter based mitral annuloplasty techniqeus have been conducted.

Leaflets and chordae: Direct repair techniques

Surgical methods have been developed to directly address the mitral valve leaflets and chordae tendineae to correct leaflet tethering in FIMR. Both the Alfieri stich and the minimally invasive MitraClip attaches the anterior and posterior leaflets, typically the A2-P2 region, to correct incomplete leaflet coaptation. Patch augmentation of the posterior leaflet in the P2-P3 region increases coaptation in the area most prone to cause FIMR. Chordal cutting of the secondary "strut" chordae releases the anterior leaflet from the tethering due to papillary muscle displacement and improves mitral valve geometry.

The mitral subvalvular apparatus

Numerous subvalvular approaches to improve outcome in patients with FIMR have been introduced. They include very invasive techniqeus such as surgical ventricular restoration procedure, surgical techniques directly addressing the papillary muscle displacement, and beating heart procedures using transventricular and epicardial devices applied in a few minutes.

The role of the transventricular and epicardial devices still remains to be defined and many of these devices seem to have a hard time ganing their footing in the clinical practise and until now only constitute a footnote in the surgical litterature. Meanwhile, the current results with adjunct techniques to CABG and ring annuloplasty, such as the papillary muscle approximation

technique introduced by Hvass et al. (307) and the papillary muscle relocation technique introduced by Kron et al. (285) and further developed by Langer et al. (289) are gaining continuing support in the surgical community since these techniques can be used with only little added time consumption but with very good clinical outcome.

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