

THE SECRET LIFE OF MITRAL VALVE

Antonio Calafiore¹, Antonio Totaro², Nicola Testa³, Cosimo Sacra⁴, Gaetano Castellano¹, Stefano Guarracini⁵, Massimo Di Marco², Sotirios Prapas⁶, Mario Gaudino⁷, Roberto Lorusso⁸, Domenico Paparella⁹, and Michele Di Mauro¹⁰

¹Gemelli Molise

²Affiliation not available

³John Paul II Foundation for Research and Treatment

⁴Fondazione di Ricerca e Cura Giovanni Paolo II

⁵Private Hospital Pierangeli Srl

⁶Henry Dunant Hospital Center

⁷NewYork-Presbyterian Hospital/Weill Cornell Medical Center

⁸Maastricht University Medical Centre

⁹University of Bari “Aldo Moro”

¹⁰Maastricht UMC+

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Abstract

In secondary mitral regurgitation, the concept that the mitral valve (MV) is an innocent bystander, has been challenged by many studies in the last decades. The MV is a living structure with an intrinsic plasticity that reacts to changes in stretch or in mechanical stress activating bio-humoral mechanisms that have, as purpose, the adaptation of the valve to the new environment. If the adaptation is balanced, the leaflets increase both surface and length and the chordae tendinae lengthen: the result is a valve with different characteristics, but able to avoid or to limit the regurgitation. However, if the adaptation is unbalanced, the leaflets and the chords do not change their size, but become stiffer and rigid, with moderate or severe regurgitation. These changes are mediated mainly by a cytokine, the transforming growth factor β (TGF- β), which is able to promote the changes that the MV needs to adapt to a new hemodynamic environment. In general, mild TGF- β activation facilitates leaflet growth, excessive TGF- β activation, as after a myocardial infarction, results in profibrotic changes in the leaflets, with increased thickness and stiffness. The MV is then a plastic organism, that reacts to the external stimuli, trying to maintain its physiologic integrity. This review has the goal to unveil the secret life of the MV, to understand which stimuli can trigger its plasticity and to explain why the equation “large heart=moderate/severe mitral regurgitation” and “small heart=no/mild mitral regurgitation” does not work into the clinical practice.

ABSTRACT

In secondary mitral regurgitation, the concept that the mitral valve (MV) is an innocent bystander, has been challenged by many studies in the last decades. The MV is a living structure with an intrinsic plasticity that reacts to changes in stretch or in mechanical stress activating bio-humoral mechanisms that have, as purpose, the adaptation of the valve to the new environment. If the adaptation is balanced, the leaflets increase both surface and length and the chordae tendinae lengthen: the result is a valve with different characteristics, but able to avoid or to limit the regurgitation. However, if the adaptation is unbalanced, the leaflets and the chords do not change their size, but become stiffer and rigid, with moderate or severe regurgitation. These changes are mediated mainly by a cytokine, the transforming growth factor β (TGF- β), which is able

to promote the changes that the MV needs to adapt to a new hemodynamic environment. In general, mild TGF- β activation facilitates leaflet growth, excessive TGF- β activation, as after a myocardial infarction, results in profibrotic changes in the leaflets, with increased thickness and stiffness. The MV is then a plastic organism, that reacts to the external stimuli, trying to maintain its physiologic integrity. This review has the goal to unveil the secret life of the MV, to understand which stimuli can trigger its plasticity and to explain why the equation “large heart=moderate/severe mitral regurgitation” and “small heart=no/mild mitral regurgitation” does not work into the clinical practice.

Keywords. Mitral valve; Mitral regurgitation; ischemic adaptation; ischemia; left ventricle.

For decades the diseases that can affect the mitral valve (MV) were considered to follow a precise scheme: infectious, inflammatory, congenital, degenerative, etc. In case of secondary mitral regurgitation (MR), the valve and its chords were supposed to remain “normal”, while the regurgitation was due to geometric changes of the left ventricle (LV). If this were true, MR grade had to be directly proportional to the displacement grade of the papillary muscles (PMs). However, in the clinical setting some patients with large hearts and severely displaced PMs have sometimes absent/mild MR (fig. 1) and sometimes severe MR (fig. 2). On the other side, other patients, in spite of normal volumes and similar interpapillary distance, have either absent/mild or moderate/severe MR (fig. 3).

However, during the same time frame many studies slowly started to show that the MV was not only a passive bystander of the morphologic changes of LV geometry, but was able to induce structural modifications in response to external stimuli.

In human hearts with ischemic and non-ischemic dilated cardiomyopathy, Hueb et al.¹, in a study aimed to analyze annular modifications, found that, compared with cardiomyopathy, by 24% if ischemic and by 50% if non-ischemic. The degree of ante-mortem MR was not reported. In transplant recipients, Grande-Allen et al.² demonstrated that mitral leaflets and chordae tendinae were fibrotic and showed significant changes in the extracellular matrix (ECM), with more cellularity and collagen than normal. The ALs and the PLs were longer (+28% and +26% respectively) and thicker (+26% both) than normal. The leaflets and the chords were biochemically different from normal and were stiffer, less extensible and less viscous than controls, due to a dysfunctional remodeling in these subset of patients³.

These studies demonstrate that the MVs and the chords of patients with end-stage dilated ischemic or non-ischemic cardiomyopathy changed morphology and composition, in a process that we can term “adaptation to disease”. Then the MV is not a structure that remains inert if the environment around it changes, but is able to modify its shape and its characteristics in the attempt to react to different geometry and stress distribution to avoid or to reduce regurgitation. Under this aspect the MV is a living organism, capable to respond to external stimuli due to its intrinsic plasticity (a term that defines the adaptability of a living structure to changes in its environment) in order to counteract any change that can impair its function (regurgitation). Mitral plasticity can be balanced (adaptation is complete and MR is absent or mild, as in fig. 1 and 3, A and B) or unbalanced (adaptation is uncomplete and is unable to control the MR degree, that progresses to moderate or severe, as in fig. 2 and 3, C and D).

BIOLOGICAL MECHANISMS OF MV PLASTICITY

Mitral leaflets

Mitral leaflets (MLs) consist of an extracellular matrix (ECM) layered with valvular endothelial cells (VECs), that adhere each other through a transmembrane protein (vascular endothelial (VE)-cadherin). VECs are anchored basally to the basement membrane, a 50- to 100-nm layer of specialized ECM protein complex which separates cell monolayers from the underlying connective tissue, through integrin adhesion complexes⁴, that mediates adhesion between the cells and their ECM. VECs can migrate into ECM changing phenotype to replenish the turnover of valvular interstitial cells (VICs), major producers of the valve ECM needed to insure durability and function. This mechanism is known as endothelial to mesenchymal transition (EndMT) (fig. 4).

The ECM is composed of two main classes of macromolecules: proteoglycans (PGs) and fibrous proteins (collagen, elastin, fibronectin and laminin). Collagen is the most abundant fibrous protein within the interstitial ECM and constitutes up to 30% of the total protein mass of a multicellular animal. The bulk of interstitial collagen is transcribed and secreted by VICs that reside or are recruited into the ECM.

The ECM of the MV consists of four histologically distinct layers (fig.4): the atrialis and the ventricularis, both of which are thin elastin-rich layers, the spongiosa, which consists mainly of PGs, and the fibrosa, the main load-bearing layer, composed of circumferentially oriented collagen fibers. In the atrialis hemodynamic shear stresses can result in the deposition of more radially oriented collagen.

VICs, present in the ECM, are responsible for the structural integrity of the valve through protein synthesis and enzymatic degradation.

Quiescent VICs regulate low-grade ECM synthesis and degradation. Quiescent cells, in particular conditions, change phenotype and become *activated VICs*, that take the features of myofibroblasts, facilitate valvular remodeling, but also play a role in fibrotic changes of the MV. These cells contribute to mitral adaptation, but, if the process becomes dysregulated, permanent scarring and fibrosis occurs. *EndMT VICs* are VECs undergoing EndMT that enter ECM and change phenotype becoming myofibroblasts. Other VICs can come from circulating blood, directly or from neovascularization, as *myeloid cells* that take myofibroblasts functionality.

When the integrity of the endothelial layer is reduced due to different stimuli (mechanical stress or stretching or inflammatory response following MI), cells from the circulating blood (mostly leukocytes and/or myeloid cells, which infiltrate valve tissues and differentiate into macrophages⁵) can be recruited into the valve, After having infiltrated the tissue, macrophages release inflammatory cytokines such as TNF- α , IL-1 β , and TGF- β leading to cardiac valve inflammation and inducing EndMT.

Mechanical stimuli that are outside of the normal physiological range induce VICs phenotypic transition into a biosynthetically active myofibroblast-like phenotype (mechanotransduction). This transition leads to increased synthesis of PGs, cytokines, as TGF- β , collagen⁶, as well as increased proteolytic enzyme expression and activity. This suggests that the in vivo mechanical environment plays a fundamental role in VICs response to external mechanical stimuli caused by pathological factors.

Chordae Tendinae

The chordae tendineae of the mitral valve function to transmit the contractions of the papillary muscles to the leaflets of the MV complex. They also serve to secure the leaflets to maintain valve closure and prevent mitral valve prolapse. In order to perform these functions, the chords must contain a high degree of elasticity, as well as considerable strength and endurance. These chords are composed of collagen and elastin fibers arranged in parallel. A study conducted by Millington-Sanders et al.⁷ showed that the chordae tendineae are composed of multiple layers of elastic fibers, an inner collagen core, and an outer layer of endothelial cells (fig. 5). During stretching, when papillary muscle contraction straightens the chords, the collagenous wavy pattern disappears and transfers the peak stress during contraction to the leaflets. The sleeve-shaped elastic network that surrounds the internal collagen suggests that on relaxation of tension, the elastic fibers would tend to restore the collagen to their wavy configuration.

Τρανσφορμινγ μηχανη φαστορ β

The motor of EndMT is the transforming growth factor β (TGF- β) pathway, which includes multipotent cytokines that are important modulators of cell growth, inflammation, matrix synthesis and apoptosis. TGF- β regulates as well the change of VICs from quiescent to active and is able to differentiate mesenchymal cells into myofibroblasts and to regulate multiple aspects of the myofibroblast phenotype.

Beyond the TGF- β superfamily, there are other mediators of EndMT. Several stimuli or pathways, converging with TGF- β signaling, as shear stress⁸, glucose⁹, endothelin-1¹⁰ and angiotensin II¹¹, can stimulate EndMT (fig. 6). Others, as fibroblast growth factors and Wnt/ β -catenin signaling inhibit with different mechanisms

EndMT. Other factors, as non-coding RNAs, can degrade the messengerRNA, inhibiting its translation into protein¹². This mechanism can favor or inhibits EndMT.

TGF- β is secreted as a large latent complex, unable to associate with its receptors. The extracellular concentration of TGF- β activity is primarily regulated by conversion of latent TGF- β to active TGF- β : activation of only a small fraction of this latent TGF- β generates maximal cellular response¹³. Latent TGF- β is considered to be a molecular sensor that responds to specific signals by releasing TGF- β . These signals are often associated with phenomena such as angiogenesis, wound repair, inflammation and, perhaps, cell growth. Other modes of activation have been proposed, including integrin-mediated release, which can result from mechanical force transduction¹⁴.

Activated TGF- β mediates its effects by binding specific transmembrane receptors at the cell-membrane¹⁵ that phosphorylate specific transcription factors which translocate to the nucleus, where they regulate the transcription of specific target genes, which induce myofibroblast activation and matrix deposition. This mechanism facilitates tissue remodeling and wound healing but also plays a pathological role in fibrotic disease. After completion of remodeling activities, myofibroblasts are eliminated by apoptosis¹⁶; however, when the myofibroblast life cycle is not regulated properly, myofibroblasts persist with continued force generation and ECM production, resulting in pathological fibrosis, scarring, and fibrocontractile disease¹⁷. (fig. 7).

The renin-angiotensin system is markedly activated in response to acute myocardial infarction (AMI) and directly induces cellular responses in both cardiomyocytes and interstitial cells¹⁸. Angiotensin II stimulates fibroblast proliferation and expression of proteins¹⁸, through ECM interactions involving the Angiotensin Type 1 (AT1) receptor. Extensive evidence suggests a direct functional association between the renin-angiotensin system and the TGF- β pathway, indicating that TGF- β 1 acts downstream of Angiotensin II (fig. 6)¹⁸. In addition, angiotensin II increases VICs responsiveness to the fibrogenic actions of TGF- β ¹⁹.

How the mitral valve increases its dimensions

Increase of MV (leaflets and chordae tendinae) dimensions include ECM adaptation. A natural model of these changes is represented by pregnancy, where MV adapts to new hemodynamics. During pregnancy, an increased demand in oxygen to support fetal development drives an increase in maternal blood volume by up to 40%. This volume overload results in cardiovascular adaptation. As the heart adapts to increased oxygen demands by ventricular hypertrophy, dilation of the periannular tissue increases the MV orifice area (around 12%). These geometric changes alter the radius of curvature and the tension of the leaflets and are at the basis of tissue growth and remodeling²⁰.

In pregnant bovines the AL enlarges uniformly to 40% of the basal size, in both radial and circumferential directions, with a rapid 33% increase in leaflet area within the first 2 months of pregnancy²⁰, similar to the 35% increase in systolic leaflet area reported in an echocardiographic assessment of patients with LV dysfunction²¹. Collagen fibers are crimped both in leaflet (fig. 8 A) and in chordae tendinae (fig. 5). The increase of the area of the leaflets and of the length of leaflets/chordae is accompanied by a remarkable loss in collagen fiber crimp (fig. 8 B), with the percentage area occupied by crimp nearly halved, and the crimp length nearly doubling. The overall thickness of the leaflets remains unchanged. The simultaneous increase in area and maintenance of thickness implies that this change is not (entirely) due to elastic deformation but also due to the addition of mass, that is, growth²². Loss of collagen crimps lengthen the leaflets, but adds mechanical compression to VICs^{23,24}. VICs deformation (fig. 9) induces VICs phenotypic activation and subsequent transition into a biosynthetically active myofibroblast-like phenotype. Adding new fibrillar material into existing fibers, collagen crimp is gradually restored (fig. 8 C). VICs can be activated by compression caused by stretched collagen fibers (fig. 8 B and G), but it can be due as well to TGF- β activation or to EndMT mediated by mechanical stress or stretching.

Based on these findings, we can speculate that MV leaflet area and leaflets/chords length increase because of loss of collagen crimp, due mainly to stretching or mechanical stress. The thickness of the leaflet/chords is maintained by addition of new collagen due to activated VICs as a consequence of mechanical forces or

through the activation of TGF- β . New collagen is added, mainly to increase leaflets thickness. It is possible that, in a pathologic situation, variability in the intensity of the stimulus or of the cellular and humoral reaction can up or downregulate the response to the stimulus itself, and different levels of adaptation can occur. Leaflet area, leaflet/chords length can or cannot increase in proportion to the stimulus and can only thicken without increasing the size.

Then, it is possible that collagen uncrimping through mechanical stress causes mitral leaflets/chords increase of dimensions and length, and a secondary mechanism, mediated by VICs directly or stimulated by TGF- β , increases the thickness of the leaflet/chords. It is likely that individual response to mechanical stress, collagen distensibility and excess of new collagen are at the basis of the different grade of mitral plasticity.

Triggers that stimulate mitral valve plasticity.

When there is a change in the dynamics of the mitral valve, induced by any cause external to the valve itself, a mechanism of adaptation starts in order to maintain the valve function.

Trigger not related to the mitral valve geometry . This is typical of aortic

regurgitation, where the trigger is the stretching of the AL from the regurgitant jet²⁵. This is able to slowly elongate the leaflet and the chords and to increase the mitral area in order to close the enlarged annular area avoiding or minimizing regurgitation (fig. 10). This mechanism of adaptation happens even if there is no MR.

Trigger related to change in mitral valve geometry . This mechanism was

demonstrated by Dal-Bianco et al²⁶ in sheep where the PMs were retracted apically, short of producing MR, changing only the mechanical stress exercised on the leaflets. Changing curvature is a known cause of increase of mechanical stress²⁷ and, even without MR, it is enough to trigger a MV adaptive response. After 61 days, AL lengthened of 18% and PL of 9%, with increase in thickness. Chords lengthened (anterior 20% and posterior 12%) with increased diameter. Mechanical stresses imposed by PMs tethering increase MV leaflet area and matrix thickness, with cellular changes suggestive of reactivated embryonic valve development pathways. These findings support the concept of an actively adapting MV even in absence of regurgitation but only in presence of mechanical stress. This can happen in the initial process of non-ischemic dilated cardiomyopathy, where, in the early phase of dilation, the mitral valve is solicited to adapt to changes in stress (fig. 1).

Trigger related to mitral regurgitation. In sheep after tachycardia-induced

cardiomyopathy the presence of MR increases the mechanical stress on the valve. The mitral leaflets lengthened significantly^{28,29}, in particular on the free edge²⁹. Myofibroblasts were present in the extracellular matrix of as expression of change of phenotype in activated cells. In another experiment Stephens et al.³⁰ caused MR in sheep by punching the PL and causing a hole of 2.8 to 4.8 mm if diameter. After 12 weeks, the AL remodeled. Elevation of matrix metalloproteinases (enzymes that are able to degrade the basal lamina allowing the cells to go through toward the matrix) mirrors an increased cellular turnover (VECs moving to the ECM). These mechanisms can follow the onset of regurgitation any cause, both anatomic and due to change of MV geometry.

Trigger related to myocardial infarction . AMI is a powerful trigger of MV

plasticity, which often includes excessive TGF- β upregulation. This can be due to post-MI angiotensin II activation, which in turn can activate TGF- β expression enhancing its profibrotic activity⁶.

Since 1997, it was noted in an experimental setting by Quick et al.³¹ that induction of AMI with/out mitral regurgitation caused upregulation of collagen in the MV, mainly in the AL. In a consecutive series of 91 patients with inferior AMI³², 53.7% developed MR moderate or more, 28.4% in patients who showed mitral plasticity (60/91, 66%) and 67.8% in patients who did not (31/91, 34%) (p<0.003). Interestingly, the most striking differences in length in patients with no or mild MR vs. moderate or more MR were seen for the AL

(25.5 ± 3.3 vs 22.4 ± 3.1 mm; $p < 0.001$) and the chordal length (28.4 ± 7.2 vs. 24.1 ± 8.2 mm; $p < 0.01$). The PL length difference was not significant (16.1 ± 2.6 vs. 15 ± 3.1 mm; $p = 0.08$). It is as well evident in many studies that the AL increases its length more than the PL^{32,33}.

In patients who had AMI, and early revascularization in almost all cases, Beaudoin et al³⁴ demonstrated increased thickness of the mitral leaflets 2 years post AMI and a further increase thereafter. There was a progressive reduction of the AL excursion and patients who developed more than mild MR had thicker mitral leaflets than patients who did not.

It is worth noting the importance of the role of **chordae tendinae** in the process of mitral plasticity. The length of the chords is essential to reduce the regurgitation grade. In patients with ischemic and non-ischemic cardiomyopathy chords longer 10 mm than normal contributed, in large hearts, to reduce MR grade to absent or mild³³. In patients with the same annular diameter and MV leaflet area, a difference of 2.5 mm in chordal length made the difference from MR grade moderate or more and mild or absent, having this latter group larger LV volumes³⁵.

CONCLUSIONS

Stretching and mechanical stress are the initial mechanisms that trigger MV adaptation to a new hemodynamic situation. Increase in leaflets area and length and in chordal length is due to collagen uncrimping, which is able to increase leaflets and chordal dimensions by 30 to 50%. To maintain the same thickness, it is necessary to produce more collagen by activated VICs, either because of mechanical stress or TGF- β activation. The purpose is to maintain the same thickness even with a longer or larger MV, but the process can become dysregulated, such as in presence of an AMI.

TGF- β is present in the MV in a latent form. Many stimuli (stretching, mechanical stress, inflammation, turbulent flow, and others), can trigger the release of active TGF- β , which binds to a membrane receptor that in turn activate signal transducers that accumulate into the nuclei and transcripts specific genes, targeted to induce fibrotic changes. Targets can be quiescent VICs, present in the ECM, that change in activated myofibroblasts, but VECs as well. As a consequence, VECs activate and lose the adhesion to neighbor cells. The basement membrane is eroded by enzymatic secretion and the VECs migrate into the ECM, where transition to mesenchymal cells, which in turn can differentiate in other cells, such as myofibroblasts, etc. Myofibroblasts produce collagen and the excess of collagen production causes an excessive accumulation of ECM components. If this process becomes dysregulated, as often it happens after AMI, permanent scarring and increased leaflet fibrosis occurs. After a MI, VECs undergo EndMT, VICs are activated to become myofibroblasts that secrete and compact ECM, and there is evidence for valve neovascularization and leukocyte infiltration^{6,26,36}. Infiltrating macrophages and leukocytes release growth factors and cytokines, such as TGF- β family members, which can further promote angiogenesis, collagen production, attraction of additional inflammatory cells, and transform VICs to myofibroblasts that also secrete growth factors and cytokines.

Activated TGF- β can induce phenotype changes in quiescent VICs, which change morphology and function, contributing to pathologic changes. In the ischemic setting, excessive TGF- β signaling occurs, that stimulates exuberant EndMT, resulting in profibrotic changes of the leaflets, such as markedly increased thickness, cellular proliferation, and excessive ECM turnover with collagen deposition.

It is not clear if the activation of the ECs is directly dependent by the trigger, such as mechanical stress, or induced by TGF- β since the beginning.

Therapeutic implications

The different anatomical pictures that result from MV plasticity can provide many anatomical aspects. The most favorable is a *balanced adaptation*, with long leaflets and long chords, with absent or mild MR. On the other extreme there is an *unbalanced adaptation*, where leaflet area and length are not adequate to respond to increased annular area and changed LV geometry. Leaflets are fibrotic and chords are thick and retracted, with resulting moderate or severe MR. In the middle there are many possibilities, with different

anatomical aspects and MR grade. Among them, it is worthy noting that we can have *partial adaptation*, such as long leaflets and tethered chords or relatively short and thick leaflets and normal or long chords. Then the necessity to look carefully at the anatomy of the MV apparatus, which can change from case to case.

The comprehension, even if partial, of the mechanisms of adaptation of the MV led to the search of pharmacological prevention of a possible maladaptive evolution of the process. Given the role of angiotensin II as TGF- β activator after MI, the use of losartan, a selective inhibitor of angiotensin II receptor-1, was explored successfully both in vitro³⁷ and in an animal model³⁸. In this latter experiment profibrotic changes of tethered MV leaflets post-MI were modulated by losartan without eliminating adaptive growth. Losartan decreases production of TGF- β and its receptor and angiotensin II-induced release of latent TGF- β ³⁹. It blocks the interaction of angiotensin II with its AT1 receptor, decreasing TGF- β signaling¹⁸. Losartan inhibits angiotensin II-induced expression of endoglin, which promotes the fibrogenic effects of TGF- β ¹⁹. Through such effects on the MV, losartan can potentially inhibit fibrosis⁴⁰, while maintaining adaptive leaflet growth with flexible leaflet closure.

In a clinical study on 40 patients with 2 serial echocardiograms (6 days and 12 years) after an inferior MI, leaflet thickness increased over time and was correlated with MR. Most of the patients were treated with angiotensin converting enzyme inhibitors or angiotensin receptor blockers. In the subgroup taking high dose, late echocardiogram showed thinner leaflets than in patients where small dose was used³⁴. In another study on patients with end stage renal disease, losartan more effectively suppressed myocardial fibrosis than did enalapril or amlodipine despite a comparable antihypertensive effect among the three drugs⁴¹.

The length of the leaflets can be used as a predictor of the reversibility of untreated mild or moderate IMR after CABG. Yoshida et al.⁴² found that the estimated coaptation length was a determinant of MR improvement after 2.9 years from surgery, with a cutoff of 6.5 mm. In patients where MR improved, leaflets were longer than in patients where MR did not improve.

Finally, understanding the mechanisms of mitral plasticity can provide a new paradigm in surgical treatment of IMR. Surgical repair with reductive mitral annuloplasty alone imposes abnormal biomechanics on the MV. Serial cardiac computed tomography 1 to 5 years postoperatively demonstrated that MV leaflet thickening occurred in 69% of 45 patients⁴³. Patients with thicker leaflets also presented with elevated transmitral pressure gradients, indicating progressive valve stenosis. In a swine experimental model of moderate IMR pathogenic biological changes in the MV leaflets were demonstrated within a short period of 3 months. Collagen levels were elevated in these stressed leaflets and the profibrotic changes in the valve paralleled increase in TGF- β ⁴⁴. Surgical repair with restrictive mitral annuloplasty alone frequently do not restore physiological leaflet configuration and, if mechanical strains remains elevated, pathogenic changes in valve leaflets can be induced.

The role of reparative surgery should be to “take up where the nature left” and complete the process of adaption by intervening at different levels on the MV and mimicking the natural adaptive mechanism. We have termed this surgical approach “surgical mitral plasticity”⁴⁵. To complete what nature could not, the AL has to be augmented and lengthened (by an autologous glutaraldehyde-treated or heterologous pericardial patch or any biological patch) and the second order chords have to be cut to increase the effective AL length and area (fig. 11). It is worth emphasizing the necessity of second-order chords transection, as the fibrotic process, once started, can be progressive⁴⁶. Moreover, by eliminating apical tethering, the AL can recover its normal curvature by removal, or reduction, of the tenting area. In selected cases, when the AL is sufficiently long, it is not necessary to augment it, but chordal cutting, performed through aortotomy, is sufficient (fig. 12). This maneuver causes an important reduction of leaflets stress²⁷. Restrictive mitral annuloplasty should then complete the repair. None of these technique is new, but the rationale behind is. We prefer to target the surgical augmentation on the AL as the PL, after restrictive mitral annuloplasty, is positioned vertically, representing a doorjamb for the AL which, as recovers its length and mobility, is able to close the annular area with a long coaptation length.

Mechanisms of failure after isolated annuloplasty can be due to shortness and thickness of the AL, with persistent chordal tethering and critical tenting area (fig. 13). Many techniques to be added to isolated restrictive mitralo annuloplasty have been described and are currently used to improve results of MV repair. A longer follow up and a critical review of the results will give us a guide to correct secondary MR, a disease more complex than perceived.

FIGURES

Fig. 1 – Patients with idiopathic dilated cardiomyopathy, severely dilated hearts, displaced papillary muscles and mild MR. Balanced mitral adaptation, with longer leaflets and chords.

Legend. EDV, end diastolic volume; EDD, end diastolic dimension; EF, ejection fraction; IPd, interpapillary distance; AML, anterior mitral leaflet; PML, posterior mitral leaflet; MR, mitral regurgitation.

Fig. 2 – Patient with idiopathic dilated cardiomyopathy, severely dilated heart, displace papillary muscles and severe MR. Unbalanced mitral adaptation, with nor elongated leaflets and tethered chords.

Legend. EDV, end diastolic volume; EDD, end diastolic dimension; EF, ejection fraction; IPd, interpapillary distance; AML, anterior mitral leaflet; PML, posterior mitral leaflet; MR, mitral regurgitation.

Fig. 3 – Patients with ischemic cardiomyopathy after an anterior AMI, not dilated heart and distance between the papillary muscles within the range. A and B, mild MR: C and D, severe MR.

Legend. AMI, acute myocardial infarction; EDV, end diastolic volume; EDD, end diastolic dimension; EF, ejection fraction; AML, anterior mitral leaflet; PML, posterior mitral leaflet; MR, mitral regurgitation.

Fig. 4 – The leaflet consists of four layers, the atrialis and the ventricularis, both of which are thin elastin-rich layers, the spongiosa, which consists mainly of GAGs and collagen, and the fibrosa, the main load-bearing layer, composed of circumferentially oriented collagen fibers. In a stressed valve, or in a valve stimulated by TGF- β , the endothelial cells undergo EndMT, increasing the number of matrix-producing cells.

Legend. GAGs, glycosaminoglycans; TGF- β : transforming growth factor β ; EndMT, endothelial-to-mesenchymal transition; VIC, valve interstitial cell.

From Levine et al⁴⁷, with permission.

Fig. 5 – Scanning electron micrograph of external aspect of the endothelial cells of the chorda, obtained from a 23-y-old subject (x3170). (B) The elastic fibers, situated underneath the endocardium which was removed (x1720). (C) Interior of a split chorda. Waves of collagen fibrils with similar dimensions (10.7 μ m) to the reflections shown in A and undulations in B (x3260).

From Millington-Sanders and Stolinski⁷, with permission.

Fig. 6 – Diagrammatic representation of other pathways involved in EndMT regulation. Molecular signaling pathways beside the TGF- β pathways that induce or inhibit the EndMT process. These include endothelin (ET)-1, NOTCH, caveolin (CAV)-1, Wnt, high glucose, and hypoxia inducible factor (HIF)-1 α pathways. Shear stress forces (represented by undulating arrows) induce EndMT through several different molecular mechanisms. One mechanism is initiated by the mechanical force-induced release and liberation of TGF- β from the latency associated peptide (LAP) followed by activation of the TGF- β canonical pathway. Legend. EndMT, endothelial-to-mesenchymal transcription; TGF- β , transforming growth factor- β .

From Piera-Velazquez and Jimenez⁴⁸, with permission.

Fig. 7 – Myofibroblasts play a central role in in the progression of fibrotic disease in the heart. One important mechanism yielding MyoFBs is EndMT (A), by which endothelial cells lose their endothelial markers. Valvular interstitial cells and cardiac fibroblasts can differentiate into MyoFBs in response to high mechanical strain (B) with the degradation of initial ECM and a corresponding decrease in tissue stiffness. Quiescent VICs and CFs can also differentiate into MyoFBs in response to high mechanical stress (C), caused by both increased tissue stiffness and increased tissue forces. MyoFBs increase the overall stress in the

environment by producing excess ECM and contracting existing ECM through increased cellular contractility. MyoFBs also release profibrotic signaling factors, including TGF- β 1 and Wnt, that promote further MyoFB differentiation and tissue stiffening. This forms a positive feedback loop leading to progressively worsening fibrosis.

Legend. MyoFBs, myofibroblasts; ECM, extracellular matrix; VICs, valve interstitial cells; CFs, cardiac fibroblasts; TGF- β 1, transforming growth factor- β 1; Wnt, wntless Int-1; EC, endothelial cell; EndMT, endothelial-to-mesenchymal transition; FGF, fibroblast growth factor; α -SMA, smooth muscle α -actin.

From Schroer and Merryman⁴⁹, with permission.

Fig. 8 – A, anterior leaflet of a never-pregnant heifer. B, anterior leaflet of a cow in early phase of pregnancy (110 days). C, anterior leaflet of a cow in the late phase of pregnancy (240 days). Collagen fibers are crimped in heifers, but lose crimp in early pregnancy. Cells are notably deformed, possibly becoming activated VICs. In late pregnancy crimping is restored, but the period is almost the double than in heifer. D, schematic of the possible mechanism of valvular growth via the serial addition of collagenous fibrillar material as well as the deposition of new collagen fibres. As existing fibres elongate, their crimp amplitude and slack are gradually restored, relieving VICs compression and restoring normal homeostatic function.

Legend. VICs. Valvular interstitial cells.

From Rego et al²³, with permission

Fig. 9 – Cellular deformation demonstrate nonlinear tissue micromechanics at higher strain levels. Mitral valve interstitial cells from the fibrosa layer from samples stretched at different strain levels (increasing from left to right). Scale bar: 5 μ m.

Legend. T, transmural/thickness; C, circumferential; NOI, normalized orientation index. A NOI value of 100% represents a highly oriented fibre network, whereas a NOI value of 0% represents a more randomly oriented network.

From Ayoub et al²⁴, with permission.

Fig. 10 – Patients with dilated cardiomyopathy due to severe aortic regurgitation. The heart is severely dilated heart, but MR is mild. Balanced mitral adaptation, with longer leaflets and chords.

Legend. EDV, end diastolic volume; EDD, end diastolic dimension; EF, ejection fraction; IPd, interpapillary distance; AML, anterior mitral leaflet; PML, posterior mitral leaflet; MR, mitral regurgitation.

Fig. 11 – 3D reconstruction of the mitral annulus and leaflets in systole. Severe chronic IMR. A, preoperatively the tenting volume is high and the AL is directed toward the apex because of tethering of the second-order chords. B, postoperatively the tenting volume is minimal and the AL reaches easily the PL because of the increased length and the lack of tethering. The PL is positioned vertically.

Legend. 3D, three-dimensional; AL, anterior leaflet; IMR, ischemic mitral regurgitation; PL, posterior leaflet

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Fig. 12 – Patient with severe dilated cardiomyopathy. A, severe MR, with a long AL and tethering of the second order chords (B, red arrow). 3D reconstruction of mitral annulus and leaflets in systole. C, the AL is moved toward the apex and the second order chords are tethered (red arrow). D, after mitral annuloplasty and second order cutting through aortotomy, the AL coapts with the PL with a coaptation length of 9 mm. Chordal tethering disappeared.

Legend. MR, mitral regurgitation; AL, anterior leaflet; PL, posterior leaflet.

Fig. 13 – Failure after isolated restrictive mitral annuloplasty for ischaemic mitral regurgitation. (A) Transthoracic echocardiography. The anterior leaflet is short (21 mm) and tethered (red arrow) and is not able to coapt with the posterior leaflet. There is moderate mitral regurgitation. (B and C) Transoesophageal

echocardiography. There is a significant tenting volume, which pushes the mitral valve inside the left ventricle. The anterior leaflet has reduced mobility and cannot coapt with the posterior leaflet due to chordal tethering.

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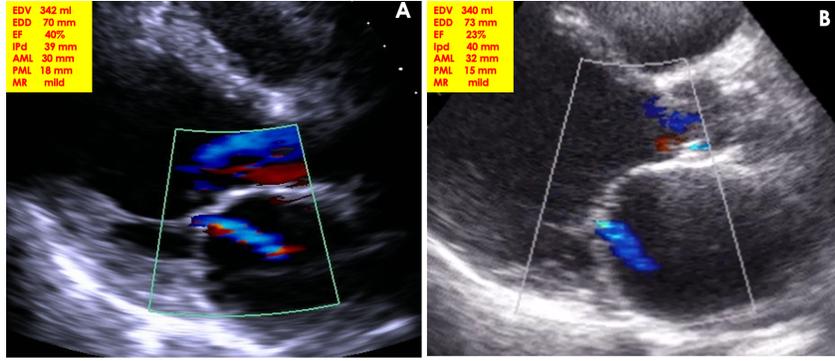


Fig. 1

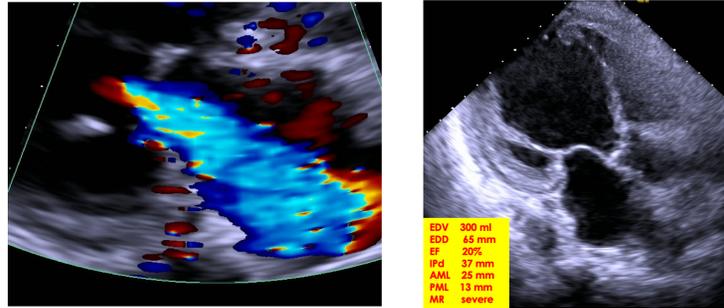


Fig. 2

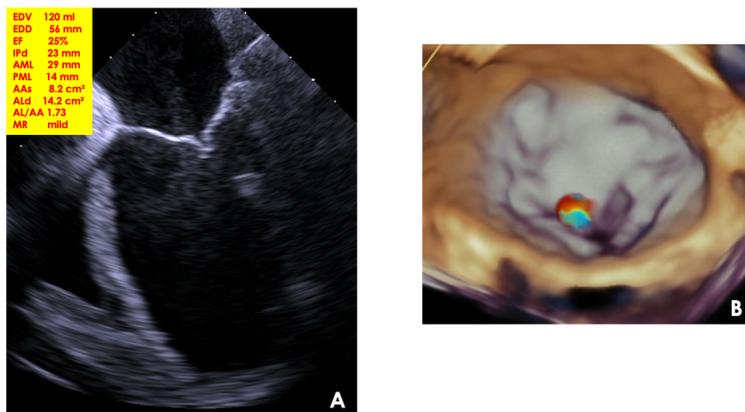


Fig. 3, A and B

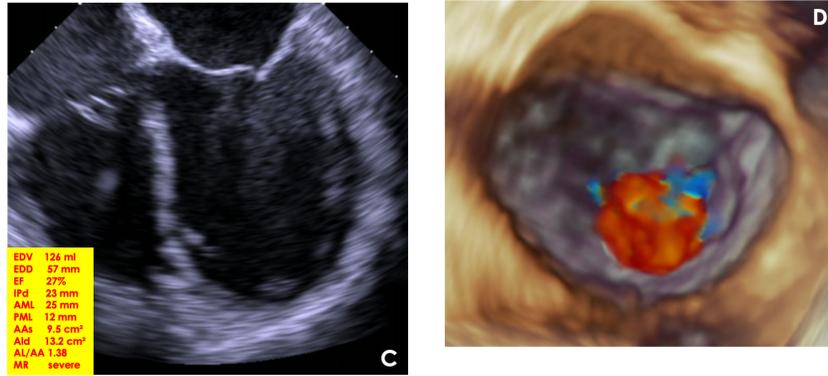


Fig. 3, C and D

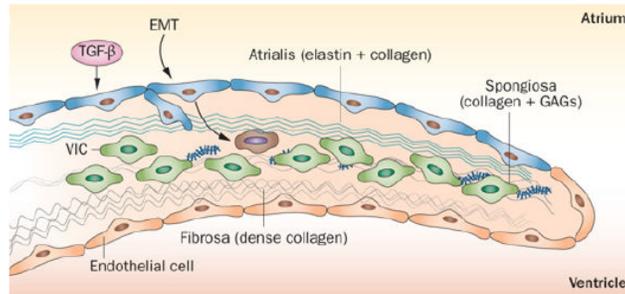


fig. 4

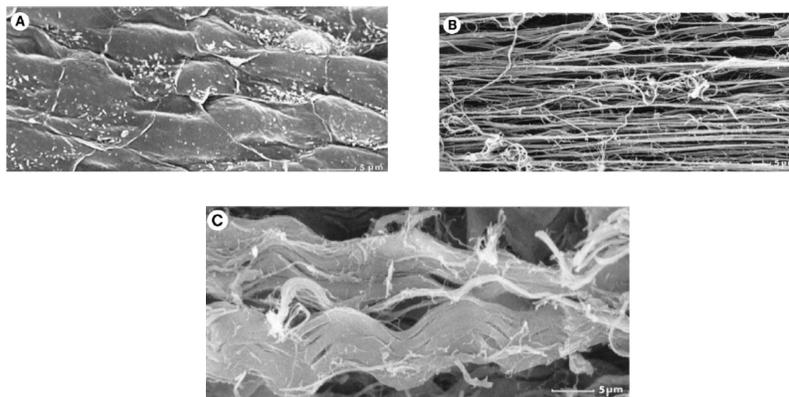


fig. 5

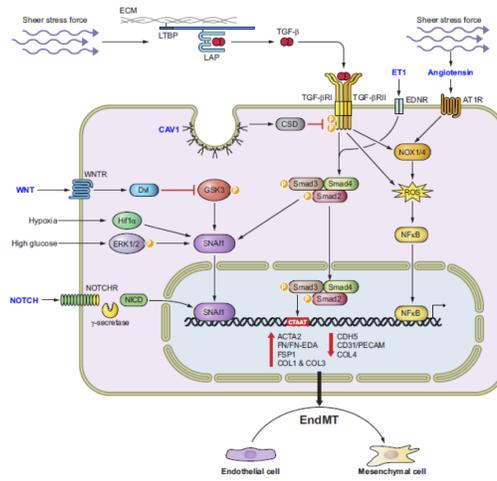


fig. 6

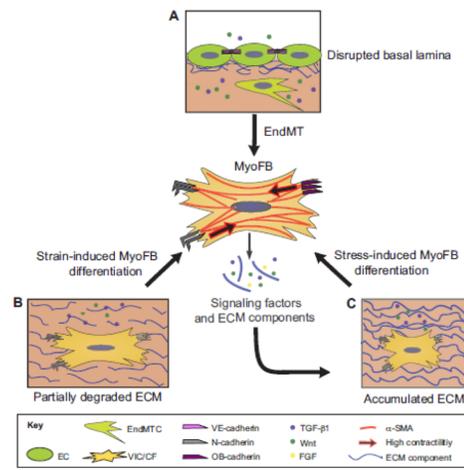


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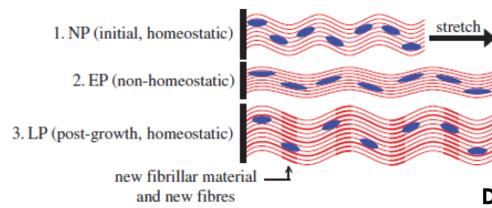
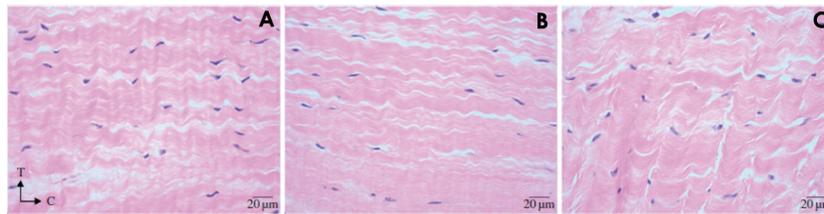


fig. 8

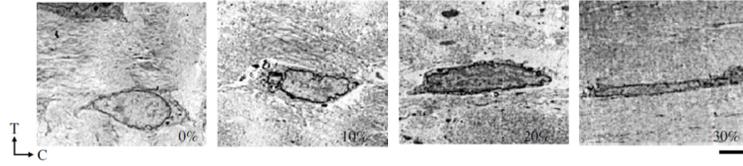


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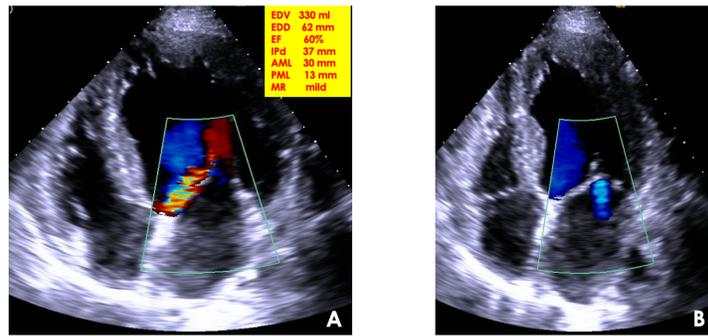


Fig. 10

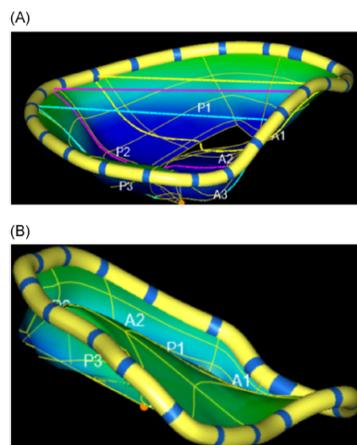


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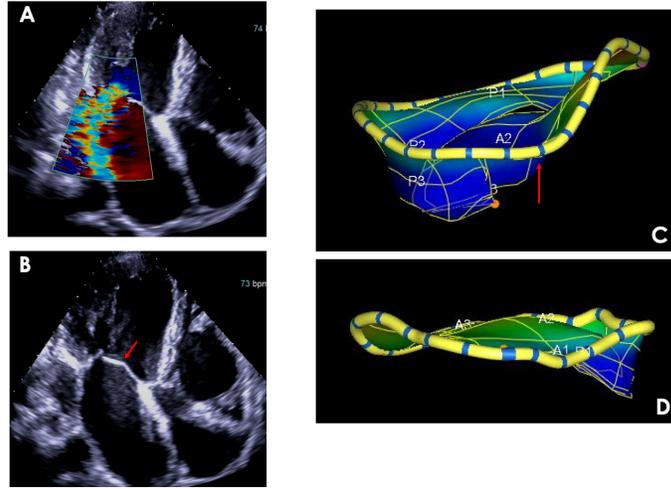


Fig. 12

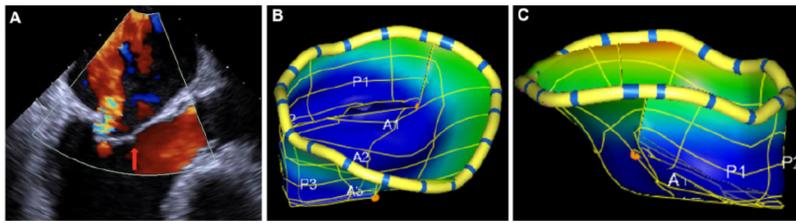


Fig. 13