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Review

Plasticity and pathological remodeling of the mitral valve in ischemic mitral regurgitation. After an infarction, insufficiency with «normal valves»? Or structural damage to the mitral valve accompanying the remodeling of the ventricle?

Plasticidad y remodelación patológica de la válvula mitral en la regurgitación mitral isquémica. ¿Después de un infarto, insuficiencia con «válvulas normales»? ¿O daños estructurales en la válvula mitral que acompañan a la remodelación del ventrículo?

Luis Alberto Fernández Calix,* Wilman A de León López,* Alberto Aranda Fraustro,‡ Ricardo Álvarez Santana,§ Héctor Herrera-Bello,¶ Nydia Ávila-Vanzzini||

* Outpatient Care Department, Former Resident, National Institute of Cardiology Ignacio Chavez. Mexico City, Mexico.
‡ Pathology Department, National Institute of Cardiology Ignacio Chavez. Mexico City, Mexico.
§ Autonomous University of Ciudad Juarez. Mexico.
¶ Medica Sur Clinical Foundation. Mexico City, Mexico.
|| Department of Outpatient Care; National Institute of Cardiology Ignacio Chavez. Mexico City, Mexico.

ABSTRACT. Ischemic mitral regurgitation (IMR) is a spectrum of mitral regurgitation with a complex mechanism; its presence increases the incidence of heart failure and mortality of patients. It is resulting from a displacement of the papillary muscles and tethering of the valve after a myocardial infarction. For many years it has been accepted that the mitral valve is essentially normal and in the context of an infarction, the left ventricle undergoes remodeling and displacement of the papillary muscles, which leads to the tethering of the valve and this conditions mitral regurgitation. There are many mechanisms associated with the poor mechanical coaptation of the valve that contribute to mitral regurgitation; but it is also true (considering multiple studies) that the valve undergoes a transformation of its structure and that therefore it is not structurally normal. In the late stages of IMR, the thickness and stiffness of the leaflets and the sub valvular apparatus contribute to the degree of mitral regurgitation, showing that the damage to the valve is clearly structural. The objective of this manuscript is to give an overview of the physio pathogenesis of IMR.
Keywords: Ischemic mitral regurgitation, plasticity, thickening, fibrosis.

RESUMEN. *La regurgitación mitral isquémica (RMI) es un espectro de regurgitación mitral con un mecanismo complejo; su presencia aumenta la incidencia de insuficiencia cardiaca y la mortalidad de los pacientes. Es el resultado de un desplazamiento de los músculos papilares y del anclaje de la válvula tras un infarto de miocardio. Durante muchos años se ha aceptado que la válvula mitral es esencialmente normal y que, en el contexto de un infarto, el ventrículo izquierdo sufre una remodelación y un desplazamiento de los músculos papilares, lo que provoca el anclaje de la válvula y condiciona la regurgitación mitral. Hay muchos mecanismos asociados a la mala coaptación mecánica de la válvula que contribuyen a la regurgitación mitral; pero también es cierto (teniendo en cuenta múltiples estudios) que la válvula sufre una transformación de su estructura y que, por tanto, no es estructuralmente normal. En las últimas fases de la RMI, el grosor y la rigidez de las valvas y del aparato subvalvular contribuyen al grado de regurgitación mitral, lo que demuestra que el daño de la válvula es claramente estructural. El objetivo de este manuscrito es ofrecer una visión general de la fisiopatogenia de la RMI.*
Palabras clave: *Regurgitación mitral isquémica, plasticidad, engrosamiento, fibrosis.*

Correspondence:
Nydia Ávila-Vanzzini
E-mail: vazzny74@yahoo.com

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INTRODUCTION

Ischemic mitral regurgitation (IMR) is a spectrum of mitral regurgitation (MR), where segmental alterations and remodeling of the left ventricle (LV) due to a myocardial infarction result in displacement of the papillary muscles and tethering of the valve. In the case of inferior infarction, remodeling is asymmetric and is produced by the apical, posterior, and lateral displacement of the posteromedial papillary muscle, pulling the valve (this is named tethering) and generating an increase in the tension area (tenting); the same scenario occurs in anterior infarction, where both papillary muscles pull on the mitral valve (MV) through a symmetrical mechanism. All this pathophysiological mechanism alters the geometry of the valve, reducing the coaptation area and causing MR *(Figure 1)*.[1]

CELLULAR PLASTICITY OF THE VALVES

Currently it is known that MV is not an inert structure and has the ability to adapt to hemodynamic and traction stimuli, this versatility has been called «cellular plasticity» and in healthy valve tissue implies the ability to change its morphology, generally increasing the length and thickness of the leaflets to adapt to a new hemodynamic condition; the latter can occur during growth or pregnancy.[2] After embryonic development and during adult life, human valves maintain cell plasticity and their dynamic structure. Healthy heart valves can adapt to stress, and repair injury through connective tissue remodeling mediated by the synthesis, repair, and remodeling of extracellular matrix (ECM) components; in addition, interstitial valvular cells (IVCs) continually repair damage to collagen and other components of the extracellular matrix.[3]

IVCs comprise a diverse and dynamic population of resident cells that can modulate a spectrum of phenotypes regulated by environmental conditions. Although most IVCs in the normal valve are quiescent (inactive), IVCs are highly plastic and can shift from one phenotypic state to another during valve homeostasis, in response to adaptation to injury. The five distinct IVCs phenotypes include embryonic progenitor endothelial/mesenchymal

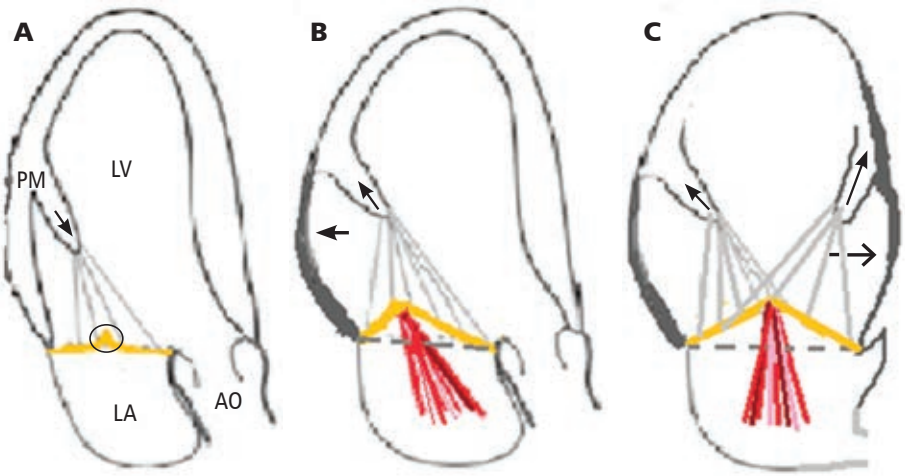

Figure 1: Schematic representation of the symmetric and asymmetric tenting area, and their evaluation by echocardiography. **A)** Schematic showing of apical long axis with normal coaptation of the mitral valve, close to its annulus, the red circle shows the coaptation surface of both leaflets. **B)** Schematic representation of an apical long axis, showing a lower infarct zone (dark gray area), observe the apical displacement of the papillary muscle and asymmetric tethering of the mitral valve. **C)** Representative diagram of a two-chamber axis with special angulation, showing both papillary muscles with apically displaced. The leaflet is pulled on both sides causing a symmetrical tethering of both leaflets, the dark gray areas represent areas of anterior and inferior infarction.
PM = papillary muscle; LV = left ventricle; LA = left atrium; AO = aortic valve.

cells (eIVCs), quiescent IVCs (qIVCs), activated IVCs (aIVCs), post developmental/ adult progenitor IVCs (pIVCs), and osteoblastic IVCs (ob-IVCs). The importance of knowing all these cellular components lies in the fact that they are the main protagonists of changes in the structure of the valve both in physiological and pathological scenarios.[4] Research suggest that IVCs in adult valves can be continually replenished through circulating endothelial or mesenchymal cell precursors derived from bone marrow. These precursors contribute to vascular healing and remodeling under physiological and pathological conditions.[5]

PATHOBIOLOGY OF VALVULAR HEART DISEASE

There are four types of pathological changes of valves: (1) disruption of the formation of the functional valve architecture, for example: congenital abnormalities; (2) damage or inadequate collagen leading to leaflets weakness, exemplified by degeneration of the myxomatous valve; (3) nodular calcification beginning in the IVCs, as in calcific aortic sclerosis/stenosis; and (4) fibrotic thickening with neovascularization.[3] Depending on the type of pathological change, the expression and mechanism of valve injury is different.

Regarding ischemic myocardiopathy, the ischemic myocardium can stimulate the growth of the MV leaflet and production of collagen through the secreting of TGF-β, which is elevated both in infarcted and remote non-infarcted myocardium.[5,6] Other research lines have showed that the turbulent MR jet may further signal the MV leaflets to change.[7,8] In the study by Dal-Bianco et al[9] using adult sheep in which a tethering of the MV was surgically generated, in order to simulate the effect of tethering in an infarction, the authors observed that mechanical stresses imposed at the valve increase the leaflet area and thickness, with cellular changes and they concluded that this suggest reactivated embryonic development pathways. On the other hand, in patients with chronically tethered leaflets evaluated by three-dimensional echocardiography, have been evident that MV leaflet surface area is greater by an average of 35% in compared with normal controls.[10] It would be reasonable to assume that in this pathologic IMR scenario an increase in surface mitral leaflet area might compensate for ventricular remodeling and tethering after myocardial infarction, and at least, decrease the degree of valvular regurgitation. However, not all patients have this valve plasticity, that is, they do not increase in size or thickness their mitral valve, some factors have already been associated with plasticity such as smoking associated with a loss of valve adaptability and diabetes mellitus of long evolution was associated with greater plasticity of the valve, possibly as a consequence of the trophic effects of insulin.[11] Ischemic and volume overload lesions, may have other local and paracrine effects on valve growth that may help explain the frequent failure of leaflet adaptation to prevent IMR.[7]

THE ECHOCARDIOGRAPHY AND EVALUATION OF MITRAL VALVE PLASTICITY

In a previous study of our research group, we defined plasticity in patients with inferior infarction as an increase in the length of the anterior and/or posterior mitral leaflets and first order posterior tendinous chords measuring these structures linearly on a parasternal long axis, with two-dimensional echocardiography.[11] The value accepted as normal for valve lengths was derived from anatomopathological studies of normal human hearts, where the length of the leaflets (measured from the annulus to the free edge of each leaflet) is 22-23 and 12-13 mm, for the anterior and posterior leaflets, respectively; normal length of tendinous cords is 18-22 mm.[12,13] In *Figure 2* there is an example of plasticity measure and some of the most important measurements in the IMR by bidimensional echocardiography.

ISCHEMIC MITRAL REGURGITATION WITH PLASTICITY AND / OR STRUCTURAL DAMAGE TO THE LEAFLETS

Ischemic mitral regurgitation had been considered as a «functional» valvular disease

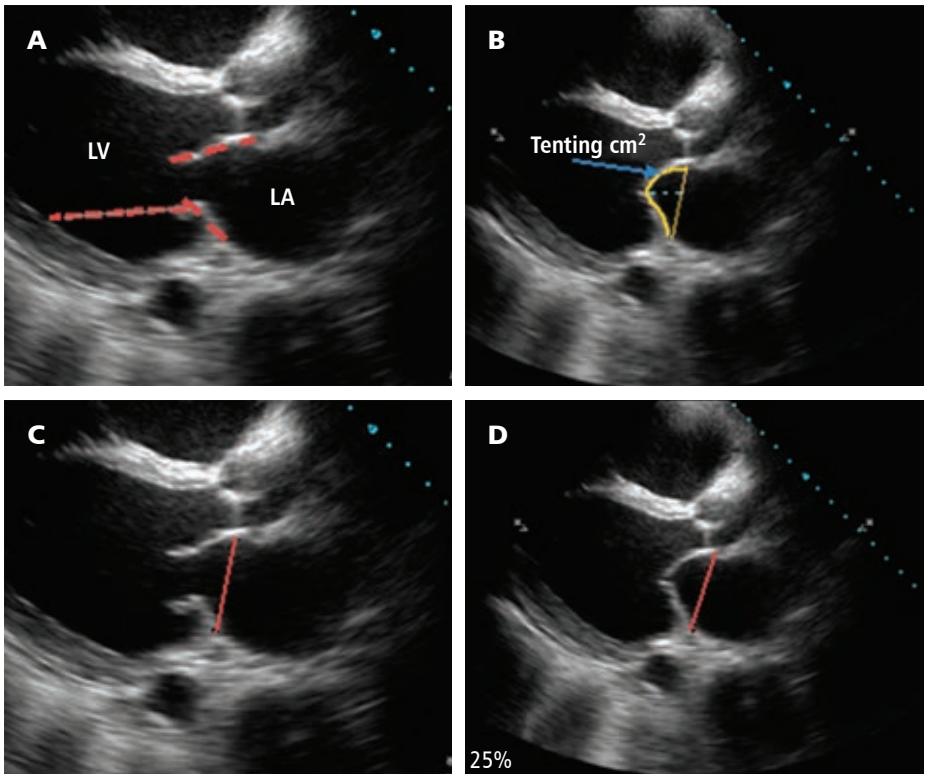

Figure 2: Evaluation by echocardiography 2D of ischemic mitral regurgitation. Long parasternal axis in a patient with inferior infarction and ischemic mitral regurgitation. **A)** Showing in diastole the longitudinal measurement of the anterior and posterior leaflets and chordae tendineae (from its union with the valve to the papillary muscle), dotted red line, the increase in the length of these structures denotes plasticity. **B)** Tenting is the area that borders the valve in the meso-systole (yellow line). The increase of it, denotes tethering of the valve; the dotted blue line shows the depth of coaptation going from the valve annulus to the coaptation site of both leaflets, both the tenting and the depth of coaptation denote the restrictive closure of the valve. **C** and **D)** Show how the annulus is measured in end-diastole **(C)** and early-systole **(D)**, red line, it should normally shorten antero-posteriorly at least 25%.
LV = left ventricle; LA = left atrium.

for many years, this meant that, there is no structural damage in the MV, and the leaflets are essentially reported as «normal», only with tethering due to ventricular remodeling; in others words, an abnormal left ventricular (LV) shape and function with a valvular manifestation.[14] This concept has been changing and in recent years the research has shown us that the advancement of IMR actually involves structural damage to the valves, that has been identified histologically, and also by echocardiography.[10,15]

In the study by Beaudoin[15] the investigators observed that the leaflets shown an increase in thickness in the cusps that is proportionally associated with the time of evolution of IMR. This thickening causes stiffness of the cusp of the leaflet, preventing normal coaptation and allowing regurgitation of Flow. In the experimental study in sheep, the post-myocardial infarction histopathology analysis showed expansion of the spongiosa central layer and focal subendothelial collagen deposition, mainly on the atrial leaflet surface, and expression of α-smooth muscle actin (α-SMA) point out endothelial mesenchymal transformation.[15] This study conclude MV thickness increases after myocardial infarction and correlates with MR, suggesting an organic component to IMR, and the fibrotic

remodeling of MV could be a focus of future treatments.

In *Figure 3* are showed the analysis the echocardiographic analysis of a patient before surgery of mitral valve replacement by severe ischemic mitral regurgitation. In *Figure 4* is showed the explanted mitral valve and its histological analysis of the same patient.

OPINION AND PERSPECTIVE

Analyzing the researchers' findings, it has led us to think that mitral valve remodeling has possibly several phases: the initial one is plasticity, that is, the increase in the length of the leaflets and with the passage of time it is possible that remodeling it becomes pathological and appears thickening of the valve and the insufficiency is greater.

Trying to find a logical order of the events that occur in the MV after a cardiac infarction, we can think that the remodeling in the LV causes the tethering of the valve; This pull of the valve activates the endothelial cells (VECs), which in turn, activate the interstitial cells (IVCs), this activation leads to the transformation of the extracellular matrix with endothelial-mesenchymal transformation, which also produces infiltration and transformation of the interstitial cells, mainly myofibroblasts.

Thus, changes begin in the cellular structure of the valves, mainly affecting the spongiosa layer, which begins to increase in

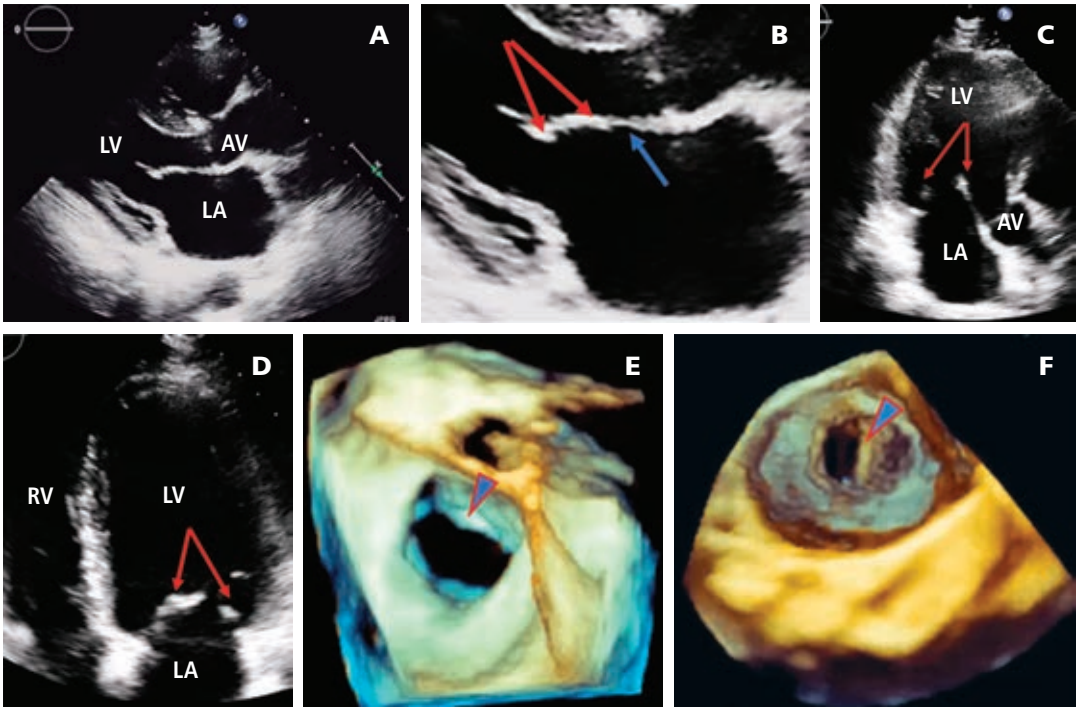

Figure 3: Echocardiographic analysis of explanted human valve in a patient with ischemic mitral regurgitation. **A)** 2D parasternal long axis shows increased length of the leaflets and dilation of the annulus (anterior leaflet 32 mm, posterior leaflet 22 mm, anulus in end diastole 39 mm). **B)** Approach to the mitral valve, the red arrows mark the thickening of the cusp and middle portion of the anterior leaflet (0.5 and 0.4 cm respectively) contrasting with the normal thickness of the base of the valve (0.2 cm) blue arrow. **C** and **D)** Apical long axis and four chambers showing the thickening of the cusps of the anterior and posterior leaflets in the same patient, red arrows. **E)** 3D echocardiography image of the mitral valve in face, arrow points to the site of distal thickening of the anterior leaflet. **F)** 3D echocardiography with approach from the ventricle. Note the anterior leaflet elongated, the posterior leaflet retracted, the arrow points to the site of distal valve thickening in anterior valve.
LV = left ventricle; AV = aortic valve; LA = left atrium; RV = right ventricle.

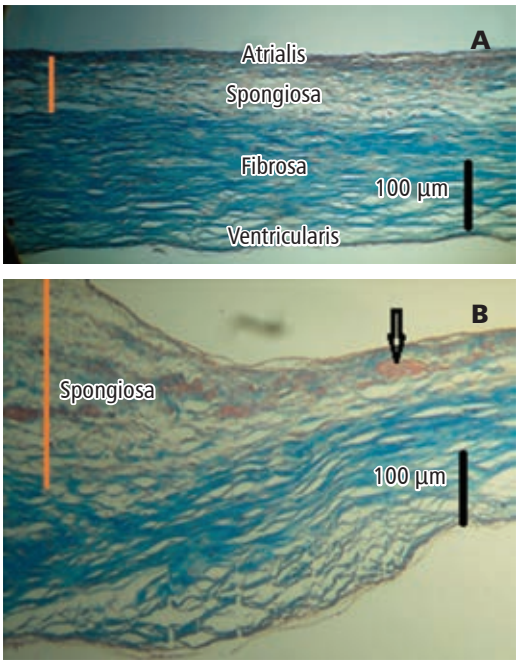

Figure 4: Histopathological analysis of the explanted valve in a patient with ischemic mitral regurgitation and its comparison with normal mitral valve. **A)** Histology of the anterior leaflet cusp with Masson's trichrome stain of normal human mitral valve. Notice the different layers and their normal proportion. Masson 2.5x. **B)** Histology of the anterior leaflet cusp with Masson's trichrome stain from a patient with ischemic mitral regurgitation who underwent valve replacement. Note the severe proliferation thickening of myxoid tissue in the Spongiosa layer (white and marked with the orange line). The arrow marks vascular neoformation in atrialis layer. Masson 2.5x.

size, but there is also a deposit of collagen fibers which give strength and support to the valve. At this point, and thanks to the transformation of the extracellular matrix, the valve increases its size and thickness, but it remains strong thanks to the joint deposition of collagen fibers, this has been recognized as cellular plasticity and is considered until now as a favorable compensatory or remodeling phenomenon.

At some point in the evolution of IMR and due to mechanisms not well understood, a disproportionate increase in the spongiosa layer begins as a consequence of a large number of fibroblasts and the generation of glycosaminoglycans and myxoid tissue, a deposition of fibrous tissue is produced, and the collagen fibers begin to decrease in quantity as do elastin fibers with the consequent loss of support and flexibility of the leaflets. This part appears to be the form of pathological remodeling and has been seen to occur late in IMR. Little is known about the triggers of this pathological evolution, possibly local or systemic factors are associated, but knowing more about pathophysiology opens up therapeutic possibilities to be able to stop the pathological course of IMR, if it exists; many more studies are needed to determine the events that occur in the physiology of this valve disease.

But at present, and analyzing the different investigations, we can affirm with certainty that in IMR the leaflets in late stages «are not normal» and have frank structural damage with thickening and fibrosis that contributes to the loss of adequate cooptation and forms a mechanism more associated with the degree of mitral regurgitation.

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