STATE-OF-THE-ART REVIEW ARTICLE

Novel Pathogenetic Mechanisms and Structural Adaptations in Ischemic Mitral Regurgitation

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Ischemic mitral regurgitation (MR) is a common complication of myocardial infarction thought to result from leaflet tethering caused by displacement of the papillary muscles that occurs as the left ventricle remodels. The author explores the possibility that left atrial remodeling may also play a role in the pathogenesis of ischemic MR, through a novel mechanism: atriogenic leaflet tethering. When ischemic MR is hemodynamically significant, the left ventricle compensates by dilating to preserve forward output using the Starling mechanism. Left ventricular dilatation, however, worsens MR by increasing the mitral valve regurgitant orifice, leading to a vicious cycle in which MR begets more MR. The author proposes that several structural adaptations play a role in reducing ischemic MR. In contrast to the compensatory effects of left ventricular enlargement, these may reduce, rather than increase, its severity. The suggested adaptations involve the mitral valve leaflets, the papillary muscles, the mitral annulus, and the left ventricular false tendons. This review describes the potential role each may play in reducing ischemic MR. Therapies that exploit these adaptations are also discussed. (J Am Soc Echocardiogr 2013;26:1107-17.)

Keywords: Ischemic mitral regurgitation, Epithelial-mesenchymal transition, Papillary muscles, Mitral annulus, Left ventricular false tendons, Ventricular-valvular continuity, Atriogenic leaflet tethering, Echocardiography

PATHOGENESIS OF ISCHEMIC MITRAL REGURGITATION

Ischemic mitral regurgitation (MR) is a common complication of myocardial infarction that substantially worsens prognosis.[1] It is believed to result from left ventricular (LV) remodeling that takes place during the chronic phase of infarction.[2] As the left ventricle remodels, the papillary muscles (PMs) are displaced away from the annular plane. This exerts traction (a tethering force) on the chordae tendineae, causing leaflet effacement, loss of coaptation zone height and an increase in regurgitant orifice area (Figure 1). Consequently, the otherwise negligible LV closing force required to shut the mitral valve becomes insufficient to maintain valve competence.[2] Postinfarction LV remodeling also causes perturbations of mitral annular geometry and motion that interfere with leaflet coaptation and further promote MR.[3]

Left atrial remodeling (enlargement) in patients with ischemic MR may reflect the effects of volume overload of the atrium, reduced LV compliance, or atrial fibrillation. It is here proposed that enlargement of the left atrium has the potential to increase mitral leaflet tethering and worsen MR through a mechanism unrelated to LV remodeling, that might aptly be termed *atriogenic leaflet tethering*.

Anatomically, the posterior mitral annulus separates the left atrium internally from the inlet of the left ventricle externally (Figure 2).[4] I would like to suggest that as the left atrium enlarges, the attached posterior mitral annulus must, of anatomic necessity, be displaced basally onto the crest of the LV inlet, as depicted by the curved arrow in Figure 2. Such a geometric change could potentially increase annulopapillary distance, thereby augmenting posterior leaflet tethering (Figure 3). Displacement of the posterior annulus might also reduce the effective height of the posterior mitral leaflet, such that its available coaptation surface becomes reduced. Finally, as the posterior annulus mounts the crest of the LV inlet, it might also exert torque on the anterior annulus at the aortomitral curtain, causing it to pivot basally across its intertrigonal axis. In so doing, the anterior annulus may be drawn away from the PMs, causing tethering of the anterior mitral leaflet. The extent of anterior annulus displacement would likely, however, be limited by virtue of its attachment to the fixed aorta. It is important to emphasize that the foregoing considerations are meant to be hypothesis generating and that validation of atriogenic leaflet tethering as a legitimate mechanism that contributes to and/or causes MR remains to be proven.

ADAPTATIONS TO ISCHEMIC MITRAL REGURGITATION

The left ventricle compensates for MR by dilating to preserve forward output using the Starling mechanism.[5] LV dilatation, however, worsens MR by increasing leaflet tethering, leading to a vicious cycle in which MR begets more MR. Recent studies suggest that certain structural adaptations play a role in reducing ischemic MR, and in contrast to the compensatory effects of LV enlargement, these reduce, rather than increase its severity. These adaptations involve the mitral valve leaflets, the PMs, the mitral annulus, and the LV false tendons.[6-14] In this review, I discuss the role each may play in reducing ischemic MR. Therapies which exploit these adaptations are also discussed.

Mitral Valve Leaflets

Maintaining mitral valve competence requires an adequate amount of apposing leaflet tissue overlap at the coaptation zone. The height of the coaptation zone, which can be measured echocardiographically (Figure 4), is normally about 1 cm.[2] Recent three-dimensional

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Abbreviations

EMT = Epithelial (endothelial)–mesenchymal transition

LV = Left ventricular

MR = Mitral regurgitation

PM = Papillary muscle

VVL = Ventricular valvular loop

echocardiographic[7,8] and marker fluoroscopic[9] studies suggest that the size of the mitral valve does not remain static but that adaptive remodeling (increases in area), particularly in the region of the coaptation zone,[9] takes place in response to increased leaflet tethering force.

This is thought to be mediated by epithelial (endothelial)–mesenchymal transition (EMT), an ancient biologic process that facilitates organogenesis, carcinogenesis, and the physiologic response to injury.[15] Tethering-induced mitral valve remodeling is thought to represent an example of the latter. The observation that EMT also facilitates valvulogenesis in the endocardial cushions[15-19] suggests that tethering-induced mitral valve remodeling represents a recapitulation of this embryologic process.[8]

EMT promotes tethering-induced remodeling by means of several signaling pathways (e.g., transforming growth factor–β, Notch, and Erb-B).[15] The process is initiated by signaling factors that trigger a specific subset of endothelial cells to shed their cell-to-cell connections, resulting in delamination from the valve's surface. These cells also develop invasive and migratory properties that enable them to pass through the basement membrane into the valve's interstitium. The stem cell–like properties of these cells facilitate differentiation into a number of mesenchymal cell phenotypes, including fibroblasts, myofibroblasts and smooth muscle cells (Figure 5). As the interstitium becomes populated with these cells, extracellular matrix is elaborated and remodeling ensues, resulting in increased mitral valve area and thickness.[15-19] A more detailed discussion of EMT is beyond the scope of this review, and the interested reader is referred to the articles cited herein.

PMs

The mitral valve complex—PMs, chordae, annulus, and leaflets—functions as an integrated unit. As the annulus descends toward the LV apex in systole, tension is maintained on the chordae by the simultaneous contraction of the PMs, thereby preventing the leaflets from prolapsing into the left atrium.[20,21] As a result, annular descent is able to effectively contribute to the forward LV stroke without regurgitation into the atrium. Two-dimensional echocardiographic studies reveal that normal PMs shorten approximately 1.0 cm, resulting in a fractional shortening of about 33%, which offsets annular descent by a comparable amount (annulopapillary balance; Figure 6).[20] After infarction, PM fractional shortening is reduced by about one half.[11] This loss of contractility is a compensatory adaptation that attenuates the severity of ischemic MR by reducing leaflet tethering.[10,12] Even more robust adaptive reductions in leaflet tethering and MR occur when the PMs undergo paradoxical systolic elongation[13] (Figure 7), thought to result from the tension exerted on them by mitral valve closure (transmitral pressure).[10]

PM lengthening due to scar formation after myocardial infarction, as depicted in Figure 8,[21] likely represents aborted PM rupture. Nevertheless, the increase in PM length may reduce leaflet tethering and MR severity by decreasing annulopapillary distance.[13] Extreme increases in PM length, however, can worsen MR by causing the mitral leaflets to prolapse into the left atrium.[22,23]

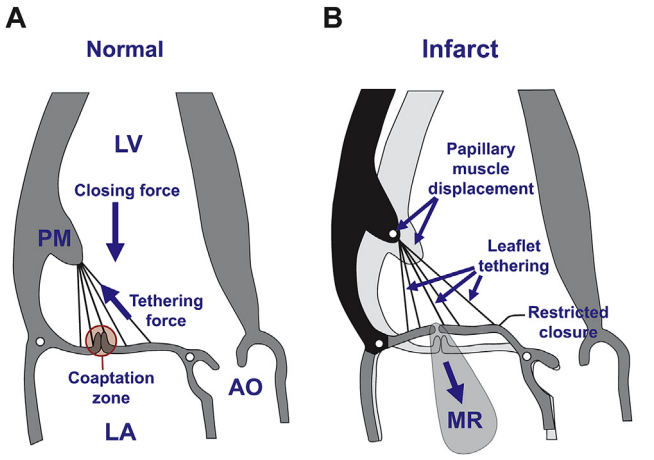

Figure 1 Closing and tethering forces move the mitral leaflets in opposite directions. **(A)** In a normal left ventricle, the mitral leaflets are well seated in the annular plane during systole, with an adequate coaptation zone height (*red circle*), because tethering forces are not increased. **(B)** The remodeled posterior wall, depicted in *black*, displaces the medial PM. This increases tethering forces that pull the mitral leaflets away from the annular plane and reduce the height of the coaptation zone (see text). *Ao*, Aorta; *LA*, left atrium. Reproduced with permission from Liel-Cohen N, Guerrero JL, Otsuji Y, Handschumacher MD, Rudski LG, Hunziker PR, et al. Design of a new surgical approach for ventricular remodeling to relieve ischemic mitral regurgitation: insights from 3-dimensional echocardiography. Circulation 2000; 101:2756-63.

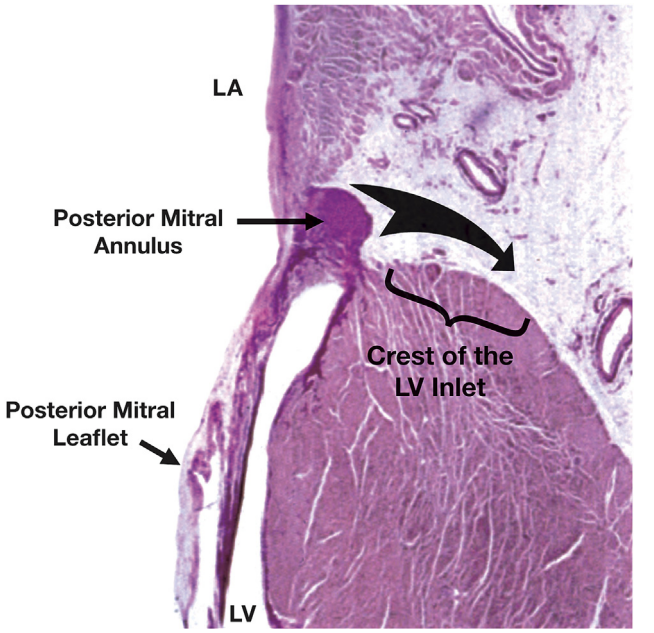

Figure 2 Histologic section through the posterior mitral annulus. Note that the posterior mitral annulus is related to the left atrium internally and to the crest of the LV inlet externally. The curved arrow depicts basal displacement of the posterior annulus onto the crest of the LV inlet. This decreases the available coaptation surface of the posterior leaflet. Reproduced with permission from Wilcox BR, Cook AC, Anderson RH. Surgical anatomy of the heart. Cambridge, UK: Cambridge University Press; 2004:55.