

## Mitral Valve Leaflet Remodeling After Myocardial Infarction Good or Evil?

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*When you are feeling fit and the sun is shining and you do not want to believe that the whole universe is a mere mechanical dance of atoms, it is nice to be able to think of this great mysterious Force rolling on through the centuries and carrying you on its crest.*

—C.S. Lewis

It is a matter of force. It is a balance of valve closing force and tethering force that affects mitral valve coaptation. Ischemic mitral regurgitation develops secondary to left ventricular dysfunction generally with structurally normal leaflets. However, it seems it is not simply a matter of force when we see the fact that valve leaflets histologically change after myocardial infarction. The leaflets can stretch, can grow in area, and can increase in thickness. Recent studies have shown evidence of leaflet remodeling and have proposed new insights from the biological reaction of the leaflet.<sup>1-3</sup> Some specific biological markers are activated in the ischemic environment and cause histopathologic changes in the leaflet. Thus, it is not just about the force, and we cannot ignore the leaflet pathology and function when we consider the mechanism of ischemic mitral regurgitation. Mitral valve complex is becoming more complex.

### See Article by Beaudoin et al

Ischemic mitral regurgitation had been traditionally explained as papillary muscle ischemic dysfunction that causes the loss of support of both anterior and posterior leaflets, before the concept of leaflet tethering caused by ischemic left ventricular remodeling was proposed as a main mechanism of loss of coaptation in the 1990s.<sup>4</sup> Since then, the role of papillary muscle displacement (outward and apical shift caused by regional or global left ventricular remodeling) on the geometric changes in the valvular/subvalvular components has been studied mainly by 2-dimensional/3-dimensional echocardiography both in the experimental and

clinical settings.<sup>4-6</sup> Clinical observational studies proved that the greater the papillary muscle tethering distance, the larger the leaflet tenting and degree of mitral regurgitation.<sup>7,8</sup> Mitral leaflet tenting toward the left ventricular apex in addition to annular dilation has been shown by 3-dimensional techniques with its heterogeneous configurations in relation to the various patterns of left ventricular remodeling.<sup>9-11</sup> Through experimental and clinical studies on the new concepts of secondary mitral regurgitation, the valve tethering phenomenon has been widely accepted as a major mechanism of ischemic mitral regurgitation. An altered balance of tethering force versus coapting force causes the loss of coaptation, which results in the regurgitant orifice in the postischemic heart. Hence, ischemic mitral regurgitation has been generally considered to be functional, occurring with structurally normal leaflets and chordae. Because of the functional nature, the degree of ischemic mitral regurgitation can dramatically change during the course of myocardial infarction along with the left ventricular remodeling and reverse remodeling over time.<sup>12</sup>

In this issue of *Circulation: Cardiovascular Imaging*, Beaudoin et al<sup>13</sup> attempt to prove their hypothesis that mitral valve leaflet remodeling after myocardial infarction (MI) contributes to mitral regurgitation in the postinfarct state in both clinical and in vivo experimental settings. The authors' group has previously reported on the histological changes in the mitral valve leaflets after acute MI, and they have suggested that increased valve thickness and stiffness contribute to progressive postinfarct regurgitation.<sup>2,3</sup> Several in vivo and in vitro experimental studies have shown postinfarct valve remodeling and have proved that the activation of endothelial cells and thickening of the interstitial matrix with an altered cell biology indicate endothelial mesenchymal transdifferentiation. Endothelial cell marker (CD31+) was increased and expressed  $\alpha$ -smooth muscle actin in stretched mitral valve tissue and chordae, which was not observed in the unstretched valve model. Interestingly, stretch plus infarct animal model showed valve thickening with a profibrotic increase in valvular cell activation and CD 45+ endothelium. CD45+ endothelial cells were activated in response to transforming growth factor- $\beta$ 1 and found to contribute to mitral valve adaptation and fibrosis. Those results suggested that (1) the biological markers were activated in mechanically tethered mitral valve leaflets and then contributed to increase the postinfarct mitral valve area, and (2) the postinfarct environment can also contribute to the valve thickening by activating fibrocytes through molecular mechanisms, separate from the simple effect of valve tethering force. The article by Beaudoin et al<sup>13</sup> in this issue has 2 components: (1) retrospective clinical study to evaluate the changes in

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the leaflet thickness after MI in its early phase and late phase, and (2) in vivo experimental study to prove the infarct-related biological effect on the mitral valve leaflet by using a less leaflet-tethering animal model with apical infarction. In the clinical observational study, the authors measured the thickness of the anterior leaflet with serial transthoracic echocardiography after MI. What they found was that the leaflet thickness was increased over time after acute MI while the baseline thickness in the acute phase was similar to the control group. The late-MI group (>5 years) had more thickened leaflets, which showed no significant progress during the observation period. The increased valve thickness was associated with ischemic mitral regurgitation. These results support the concept of the previous reports on the mitral valve leaflet remodeling in the postinfarct condition, and the present results suggest that the valve thickening mainly progresses in the early phase after acute MI, and the organic changes in the leaflet can contribute as a mechanism of ischemic mitral regurgitation. In the experimental study, strong transforming growth factor- $\beta$  staining was observed in the apical myocardial infarct model but was absent in the stretch-only model, which confirmed their hypothesis that the ischemic environment itself can activate CD45 even in the absence of valve tethering and contribute to increasing valve thickness and stiffness. Thus, biological reactions induced by mechanical stress and ischemic environment would play an important role in the postinfarct mitral valve remodeling. Subanalysis of the clinical study suggested the possible effect of angiotensin-converting enzyme inhibitor or angiotensin receptor blockers on the prevention of mitral valve remodeling after MI. The recent publication by the same authors has reported that losartan-mediated transforming growth factor- $\beta$  inhibition reduces endothelial-to-mesenchymal transformation of mitral valve endothelial cells.<sup>14</sup> The positive effect of angiotensin-converting enzyme inhibitors on secondary mitral regurgitation has been previously attributed to their hemodynamic effect as vasodilators,<sup>15,16</sup> and the effect of the renin-angiotensin system blockade on valve remodeling should be the next issue to be tested.

The present article raises a new question on leaflet remodeling; should it be prevented? Is it evil? Mitral valve remodeling has been recently recognized as valve adaptation by increasing in area as a biological response to the dilated left ventricle. It has been considered as beneficial in keeping effective coaptation despite the tethering effect of left ventricular remodeling.<sup>17-19</sup> Increasing in area and increasing in thickness; benefit or harm? Good or evil? It is probable that both points of view are correct, that mitral valve remodeling can work as protection and cause of mitral regurgitation at the same time. The more we know, the more questions arise. It is certain that postinfarct mitral valve regurgitation has an adverse effect on patients' prognosis<sup>8</sup>...but what actually plays the major role as a mechanism of ischemic mitral regurgitation? The miraculous balance which is made by valve leaflets and subvalvular components result in effective coaptation. Leaflets can even stretch, probably contributing to effective valve closure.<sup>20,21</sup> Tethering force, closing force, leaflet pathology, and function...., there are several confounding factors based on the heterogeneous underlining ischemic condition in each individual. Although the study of Beaudoin et al<sup>13</sup> has made an important

contribution, there is still much to be learned before we have a complete understanding of the pathophysiology of ischemic mitral regurgitation.

## Disclosures

None.

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