Mitral Leaflet in Functional Regurgitation
Passive Bystander or Active Player?

Gerald Maurer, MD

In a population-based study, mitral regurgitation (MR) has been found to be the most common form of valvular heart disease in the United States.1 The incidence of MR rises sharply at \( \approx 65 \) years of age: moderate or severe MR is estimated to occur in 1% of the 55 to 64 age group, increasing to 6.4% for individuals aged 65 to 74 and to 9.3% for those older than 75.1 In view of the increasing life expectancy of the general population, we can anticipate encountering a substantial rise in the number of patients with hemodynamically significant MR. Because heart failure, ischemic heart disease, and other disorders affecting the left ventricle become more prevalent with older age, one can speculate that it is particularly functional MR that will contribute to the overall increase in MR cases, with the numbers caused by degenerative disease rising less dramatically with age.

As the rate of rheumatic disease has decreased dramatically in the Western world, degenerative disease, largely resulting from myxomatous degeneration, constitutes the most common reason for mitral valve surgery. The true incidence of functional MR, in which the primary cause of regurgitation does not originate from the leaflets themselves, is not well known. Many patients with functional MR never undergo surgery, and the disease can remain silent for some time or can be masked by the underlying pathology of the left ventricle and the coronary arteries.

Functional MR is an entity that was poorly understood until some years ago. Whereas it was believed that in the setting of ischemic heart disease, MR is often caused by “papillary muscle dysfunction,”2 we now know that in the absence of rupture, isolated ischemia or even infarction of a papillary muscle; global left ventricular size, sphericity, and systolic function had little additional independent association with the degree of functional MR.5

The study6 published in this issue of Circulation evaluates the concept that the mitral valve actively adapts to the mechanical stretch caused by tethering and studies the underlying mechanisms of cell activation and matrix production. Although there is mounting evidence that the mitral leaflets are not merely passive structures in the disease process, our understanding of their adaptive changes is at an early stage. Mitral leaflet changes under tension have been described in vitro, and their stress-strain characteristics have been studied.7 Because other tissues, including skin, blood vessels, and bone, have been observed to increase in size after being exposed to chronic tension,8 the changes taking place in the mitral valve in vivo are not surprising.

Mitral valves from transplant recipient hearts of patients with congestive heart failure have been found to be biochemically different from normal hearts, with increased levels of DNA, glycosaminoglycan, and collagen but less water.9 The observed changes in the extracellular matrix were believed to be responsible for the finding that mitral leaflets and chords in this setting were stiffer and less extensible, and the authors hypothesized that the permanently distended and fibrotic tissue might be unable to sufficiently stretch to cover the valve orifice.10

Leaflet elongation has been reported in a sheep model of tachycardia-induced cardiomyopathy and functional MR in which radiopaque markers had been sewn on the central meridian of the anterior and posterior mitral leaflets.11 Echocardiographic and fluoroscopic measurements performed before and after the induction of cardiomyopathy by prolonged tachypacing revealed lengthening of the leaflets, particularly near the free edge, although no leaflet tethering or shape changes were observed.

Three-dimensional echocardiography now offers previously unavailable in vivo insights into the alterations of mitral leaflet geometry and function. This technology was applied both in a sheep model and in patients with functional MR caused by either isolated inferior wall motion abnormality or dilated cardiomyopathy.12 Leaflet area was found to be substantially increased (by 35% on average) in patients with leaflet tethering resulting from either cause of left ventricular dysfunction. Moreover, the ratio of total leaflet area to the leaflet area required to close the orifice during systole was found to be decreased in patients with MR. This finding was...
thought to suggest that leaflet area failed to increase adequately to compensate for the tethering caused by papillary muscle displacement in patients with ischemic MR, in contrast to those with left ventricular remodeling and no MR.

The present study expands on these observations and was designed to observe leaflet adaptation over time in a controlled in vivo setting. An ingenious newly developed sheep model was used in which the papillary muscle tips were retracted apically short of producing more than minimal MR. This model is designed to study the effects of tethering itself, without interference from regurgitation-induced turbulence. Over the course of approximately 2 months, tethered leaflets were found to increase their total diastolic leaflet area by an average of 17% and were 2.8 times thicker than normal, whereas no changes were seen in control sheep, which had undergone only bypass surgery. Chordae of tethered valves were significantly longer and thicker than in controls, suggesting adaptive mechanisms similar to those in the leaflets themselves.

The authors were able to demonstrate that the mechanical stress-induced increase in leaflet area and matrix thickness was caused by endothelial-mesenchymal transdifferentiation. Convincing evidence for this transdifferentiation is provided by the identification of endothelial cells in the leaflets expressing not only the endothelial marker CD31 but also the myofibroblast marker α-smooth muscle actin. In addition, the authors show that these cells appeared to penetrate the valve interstitium. An ancillary in vitro study demonstrated the ability for endothelial-mesenchymal transdifferentiation in leaflets obtained from actual patients with ischemic MR, corroborating the relevance of the animal model. It seems particularly remarkable that this ability for transdifferentiation was preserved even in the tissue of these elderly patients with chronic disease.

Open Questions and Future Research

The insights offered by this experimental model serve as a reminder that our understanding of the adaptive mechanisms taking place in functional MR is still at an early stage. At present, most of our knowledge pertains to the changes taking place in the leaflets themselves. Many questions about the morphological and cellular adaptive alterations taking place in the chordae and mitral annulus and about the interaction of the various components still need to be answered. The additional effects of the regurgitant jet and of myocardial ischemia on adaptive mechanisms deserve further study.

We also need to enhance our understanding of the significance of the compensatory effects in a clinical setting. Does the adaptive alteration of the leaflets actually alter the clinical course, and if so, how often, how effectively, and how durably? Does it make a difference how quickly tethering effects develop? Can we affect these adaptive phenomena with our clinical interventions? A possible contribution of resident or circulating progenitor cells in this process deserves attention.

Clinical Implications

Leaflet size is obviously only one of the variables in the equation of functional MR. Other variables include left ventricular size, geometry, and function; chordal length, arrangement (including insertion sites) and distensibility; and size, shape, and function of the mitral annulus. Importantly, the interaction of all these parameters needs to be considered.

Treatment of functional MR has been attempted by correcting ≥1 of these variables in a given patient. The outcome of surgical valve repair in functional MR has been far less successful than for structural MR, and there is increasing understanding of the mechanisms leading to recurrence of regurgitation in both an ischemic and a nonischemic setting.

It is conceptually appealing to address the cause of functional MR and to treat the changes in the left ventricle that led to its development. Medical regimens have largely been unsuccessful, as has revascularization in chronic ischemic MR. In the Surgical Treatment for Ischemic Heart Failure (STICH) trial, adding surgical ventricular reconstruction to revascularization did not improve outcome compared with coronary artery bypass grafting alone, but the effects on the subset of patients with functional MR are not yet known. Cardiac resynchronization therapy may lead to a reduction of MR but works only in selected cases. New, surgically implanted devices have been developed to mechanically prevent the progressive left ventricular dilation and shape changes that occur during the evolution of heart failure. Their use, in conjunction with mitral valve repair, appears to offer a benefit; however, this procedure is not widely used, and more experience is needed.

Thus, currently available options to treat functional MR suffer from substantial limitations, and the need to pursue new therapeutic strategies continues. Perhaps understanding and influencing the adaptive processes that lead to changes in leaflet size and structure will contribute to the development of new alternatives for the treatment of this common and often devastating disorder.

Disclosures

None.

References


Mitral Leaflet in Functional Regurgitation: Passive Bystander or Active Player?

Gerald Maurer

Circulation. 2009;120:275-277; originally published online July 13, 2009; doi: 10.1161/CIRCULATIONAHA.109.879957

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2009 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/120/4/275

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/