Is It Time to Update the Definition of Functional Mitral Regurgitation?

Structural Changes in the Mitral Leaflets With Left Ventricular Dysfunction

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Functional mitral regurgitation has traditionally been defined as a disorder of regional or global left ventricular remodeling in which anatomically normal leaflets fail to coapt adequately. The abnormal closure pattern, most easily appreciated with echocardiography, is one of apical tethering of one or both leaflets. Based on a series of in vitro, animal, and human studies, we have embraced the concept that pathological tethering and concomitant regurgitation occur when an imbalance is present between closing and tethering forces. Tethering forces are increased when increased traction on the leaflets exists through a combination of annular dilation and geometric remodeling of the left ventricle. Closure forces are reduced as a consequence of left ventricular systolic dysfunction. The leaflets have largely been viewed as passive participants in this disease process. Consequently, therapies to reduce or eliminate mitral regurgitation have focused on annular and ventricular remodeling.

In the present issue of Circulation, Chaput et al\(^5\) present in vivo evidence of structural changes in the mitral leaflets of patients with functional mitral regurgitation. They employ a new 3-dimensional echocardiographic method of measuring diastolic mitral leaflet area to compare leaflet size in normal subjects with that in patients with left ventricular dysfunction on the basis of either dilated cardiomyopathy or inferior wall infarction. In the left ventricular dysfunction group, patients with mitral regurgitation are contrasted to those without. The authors report larger-than-normal leaflets in patients with both global and regional left ventricular dysfunction. Moreover, in the group of patients with dilated cardiomyopathy, the leaflets are larger in those without versus those with mitral regurgitation.

By also measuring the leaflet area required to close the valve, the authors are able to demonstrate that regurgitation is associated with a reduced valve area/closing area ratio. They conclude that in functional mitral regurgitation, the mitral leaflets are not passive bystanders but adapt to annular dilation and geometric changes in the left ventricle by increasing their surface area. They argue that mitral regurgitation occurs when this compensatory mechanism is inadequate.

This is the first study to address mitral leaflet area in humans in vivo and highlights the capability of noninvasive 3-dimensional echocardiographic techniques. It complements prior in vitro human studies\(^6,7\) and in vivo animal studies\(^8\) that have identified structural changes in the leaflets with functional mitral regurgitation.

Grande-Allen et al\(^9\) reported that the leaflets and chords in hearts explanted at the time of cardiac transplantation were stiffer than controls and suggested that this might contribute to functional mitral regurgitation. Presumably such leaflets would be less able to stretch in systole, adversely affecting leaflet coaptation. The same group\(^7\) reported biochemical changes including increased collagen and glycosaminoglycan concentrations in the mitral leaflets that might account for these different mechanical properties. The current study does not evaluate in vivo systolic distensibility and thus cannot confirm the in vitro findings of Grande et al. However, if one accepts the validity of both groups’ observations, mitral leaflet adaptation to the stresses associated with functional mitral regurgitation includes responses that mitigate the regurgitation (leaflet enlargement) as well as those that exacerbate it (increased stiffness).

Using an ovine model of tachycardia-induced cardiomyopathy and radio-opaque mitral leaflet markers, Miller’s group\(^8\) reported lengthening of the mitral leaflets particularly near the free edge. However, their assessment was based on the size of the leaflets exclusively at end-systole and may reflect changes in leaflet distensibility rather than an increase in unstretched size. Moreover, although it is assumed that their animals were euthanized permitting a comparison of in vivo marker measurements of the leaflets with those obtained at autopsy, these data were not reported.

In the current study, although leaflet area is larger in patients with left ventricular dysfunction, diastolic leaflet length is not significantly different, although a trend toward leaflet lengthening can be observed in the left ventricular dysfunction group. Possible explanations for the seemingly different findings of the Chaput and Miller studies include interspecies differences and variability in the chronicity and pathogenesis of the left ventricular dysfunction, as well as the possibility that leaflet lengthening exclusively reflects passive stretch. It is also possible that, with a larger sample size,
leaflet lengthening would reach statistical significance in the Chaput study.

Prior 3-dimensional echocardiography studies have shown different tethering patterns in patients with ischemic versus nonischemic left ventricular dysfunction. In addition, in the logistic regression analysis presented in the Chaput study, patients with dilated cardiomyopathy are nearly 4 times more likely to develop mitral regurgitation than those with inferior wall infarction and comparable left ventricular ejection fractions. Nonetheless, the current study combines these groups in most of the analyses even though they report differences between the two with regard to the association of leaflet size and mitral regurgitation. Leaflet areas are just as large in patients with inferior wall infarction with versus without mitral regurgitation whereas larger leaflets are found in the dilated cardiomyopathy subgroup without as opposed to with significant mitral regurgitation. In both groups, leaflet area is larger than in the normal controls. Additional ischemic/nonischemic subgroup analyses would be helpful for there may be fundamental differences in the magnitude of and adequacy of the adaptive responses of the mitral leaflets based on the pathogenesis and spatial distribution of the systolic dysfunction. These are testable hypotheses for future studies.

Another limitation of the study is that the control group consists of only 20 patients, all of whom were referred for echocardiographic evaluation. The conclusions would be more robust with a larger control group drawn from a pool of nonpatient normal volunteers. Because the methods used have not been previously reported and it is known that normal values for many cardiac parameters vary with size, age, and sex, it would be important to know whether mitral leaflets are a one-size-fits-all structure. The authors infer that this may not be the case by providing a secondary analysis with body surface area correction and by noting that no overall difference was found in the composition of the groups as to age, sex, or bovine serum albumin. However sex-, age- and bovine serum albumin–matched normal controls would have been preferable. Moreover, it is notable that mitral leaflet area in the sheep used to validate the 3-dimensional method had areas that varied from approximately 9 to 19 cm², a >2-fold difference. Although no basis for the variability is provided, it is apparent that the size of normal sheep mitral leaflets varies widely.

To the same point, while the authors suggest that leaflets grow in response to the stresses of functional mitral regurgitation, the study demonstrates only association and not cause and effect. Arguably, patients who do not develop mitral regurgitation are simply those whose leaflets are larger at baseline, and in this context it would be useful to have some information as to the chronicity of illness in their study group. It would be unlikely that leaflets could grow with acute-onset left ventricular dysfunction. Human natural history studies are needed to resolve definitively this uncertainty. In this context, it is intriguing that the Llaneras ovine model of ischemic mitral regurgitation induced by circumflex infarction is successful in only approximately 1 in 3 animals (unpublished data). Perhaps leaflet size at baseline, the degree of its adaptive increase, or both are at play here, as well.

The article by Chaput et al highlights the importance of 3-dimensional echocardiographic methods as a tool for evaluating the mitral valve. Whereas Miller’s group has contributed enormously to our understanding of mitral pathophysiology using radio-opaque markers attached to the mitral annulus and leaflets of sheep, their techniques cannot be applied to humans. Because it is recognized that differences exist between sheep and human mitral valves, in that sheep have smaller coaptation areas relative to the mitral orifice, noninvasive methods for studying humans valves in vivo such as those used in the current study are essential.

The ability to use echocardiography for studies such as these has depended both on advances in echocardiographic equipment as well as the development of sophisticated analytic tools. Levine, Handschumacher, and colleagues are to be commended for the leadership role they have played in developing software that harnesses 3-dimensional echocardiography as a tool for evaluating the mitral valve.

**Future Studies**

Now that a noninvasive in vivo technique is available for assessing mitral leaflet area, it will be important to better define the range of normal values and address the potential confounding influences of age, sex, and body size. Natural history studies will be essential to establish a cause-effect relationship between ventricular dysfunction and leaflet enlargement and to confirm the importance of leaflet size as a predictor of functional mitral regurgitation. The differences between ischemic and nonischemic left ventricular dysfunction must be probed and consideration must be given to the differences between anterior and inferior wall infarction.

**Clinical Implications**

Confirmation of the existence and importance of leaflet enlargement in functional mitral regurgitation in future studies should prompt a redefinition of functional mitral regurgitation to include alteration in the ventricle, annulus, and leaflets. This paradigm shift might spark the development of new therapeutic strategies aimed at preventing or mitigating mitral regurgitation on the basis of promoting adaptive leaflet enlargement. Understanding leaflet remodeling at the cellular and subcellular level will be important in developing such interventions, and the basic scientist will be an increasingly important member of the valve team. Finally, current surgical options for functional mitral regurgitation based on annular reduction are imperfect because of recurrence of mitral regurgitation and because of their failure to result in improved patient outcomes. The possibility of novel treatment options for this common and clinically important disorder would be welcome indeed.

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**Disclosures**

None.
References


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