New Concepts in Functional Mitral Regurgitation

It Is Not Just a Disease of the Left Ventricle*

Paul A. Grayburn, MD
Dallas, Texas

Functional mitral regurgitation (FMR) has long been considered to be secondary to underlying left ventricular (LV) dysfunction. FMR is a complex and heterogeneous disorder that results from an imbalance between the closing force of LV contraction and the tethering forces that prevent the leaflets from prolapsing into the left atrium (1). Various mechanisms, such as symmetrical or asymmetrical annular dilation (2), tethering of the leaflets by outward and/or apical displacement of the papillary muscles and their supporting LV walls (3,4), reduced LV systolic function (5), and abnormal LV shape (6), alone or in combination, have been shown to cause FMR. Accordingly, a common clinical “pearl” is that FMR is a disease of the left ventricle. There is consistent, strong evidence that FMR of any severity portends an adverse prognosis in patients with ischemic heart disease or dilated cardiomyopathy (7–13). Hence, it is important to identify FMR and quantitate its severity (14), as well as develop effective therapies for it, a problem that has remained elusive (15).

In this issue of the Journal, Beaudoin et al. (16) challenge the accepted hypothesis that FMR is purely a disease of the left ventricle. If that were the case, it would be anticipated that patients with chronic severe aortic regurgitation (AR), in whom LV dilation is common and often severe (cor bovinum), would have FMR. In a retrospective review of 816 patients with at least moderate AR, only 46 (5.6%) had more than mild FMR. Predictors of FMR were age, higher LV end-diastolic and end-systolic dimensions, and lower LV ejection fraction. The authors then performed prospective 3-dimensional echocardiography on 30 patients with chronic AR, 30 patients with moderate or severe FMR, and 30 normal control subjects matched to the AR group for age and sex. AR and FMR patients had similarly enlarged LV end-diastolic volume index (82 ± 22 ml/m² and 86 ± 23 ml/m², respectively), which was larger than controls (51 ± 12 ml/m²), along with similar increases in LV sphericity index, leaflet tethering, and mitral annulus area. Despite this, only 1 patient in the AR group had more than mild FMR, indicating that significant FMR is uncommon in chronic AR, a somewhat surprising finding if FMR is purely a consequence of LV dilation and associated leaflet tethering. To explain this paradox, the authors demonstrated by 3-dimensional echocardiography that the total mitral leaflet area was 31% larger in chronic AR patients than in control patients. This enlargement of the mitral leaflet area allowed sufficient coapation to prevent FMR, as manifested by similar ratios of leaflet area to closure area and leaflet area to annulus area in chronic AR and control patients, but not in FMR patients. In a multivariate analysis, FMR was predicted by the ratio of leaflet area to closure area independently of LV ejection fraction, LV end-systolic volume index, and LV end-systolic wall stress.

The findings of Beaudoin et al. (16) indicate that mitral leaflet expansion in chronic severe AR protects against FMR despite LV dilation and increased tethering distance. This is consistent with a previous autopsy study reporting enlarged mitral leaflet area in chronic AR (17). That mitral leaflets can undergo expansion is not surprising. Maron et al. (18) have shown that mitral leaflets are elongated in hypertrophic cardiomyopathy. The most classic form of mitral leaflet enlargement is Barlow’s disease, a form of mitral valve prolapse characterized by markedly thickened, elongated, and redundant leaflets (19,20). This inherited connective tissue disorder is associated with a markedly thickened leaflet spongiosa layer, activated myofibroblasts that express high levels of proteolytic enzymes, and an abnormal collagen matrix (21). In a sheep model of FMR, mitral leaflet collagen content is increased and the leaflets are thickened and stiffer than normal (22). An autopsy study of patients with heart failure and FMR confirms mitral leaflet thickening (23). Gradual stretching of mitral leaflets in sheep results in increased endothelial cells coexpressing CD31 and smooth muscle alpha-actin, indicating that leaflet enlargement is a biological adaptation and not merely passive stretching of elastic tissue (24). Finally, in FMR due to inferoposterior myocardial infarction or dilated cardiomyopathy, leaflet expansion to a similar degree (>30%) as that seen in the Beaudoin et al. study was observed (25). However, patients with FMR had a lower leaflet area to closure area ratio than those without FMR (25). Thus, it could be hypothesized that inadequate leaflet expansion to compensate for LV dilation is part of the mechanism of FMR. Why the mitral leaflet area enlarges in some patients with LV remodeling and does not enlarge in others remains...
an unanswered question. However, it could explain why some patients with ischemic or dilated cardiomyopathy do not have FMR, whereas other patients with similar degrees of LV enlargement do (25). Understanding the physiological and molecular determinants of leaflet expansion could lead to novel medical therapies to prevent FMR by increasing mitral leaflet surface area. Surgical approaches to increasing the leaflet surface area could augment traditional methods such as annuloplasty, realigning the papillary muscles, cutting basal chords, or reshaping the left ventricle (26, 27).

There are many remaining areas of research in this arena. Of note, the patients with FMR in the Beaudoin et al. study (16) were more than 20 years older than the chronic AR and control patients. Because aging is well known to affect tissue regeneration and wound healing, this may partly explain the inadequate mitral leaflet enlargement in their FMR patients. Chronic AR typically leads to gradual LV dilation, which may allow time for compensatory mitral leaflet enlargement. This may not be the case in FMR, particularly in ischemic cardiomyopathy or after acute myocardial infarction. Such patients may also have other comorbidities, such as hypertension, diabetes, hypercholesterolemia, and chronic kidney disease, which could adversely affect the ability of the mitral leaflets to enlarge as much as in younger patients with chronic AR. MR imposes a pure volume overload on the LV and therefore the mitral leaflets. Chronic AR imposes a combined pressure and volume overload. Whether these hemodynamic differences influence the ability of the mitral leaflets to enlarge requires further investigation. It is also possible that direct contact of the AR jet with the anterior mitral leaflet could somehow stimulate leaflet enlargement. It is also possible that the neurohormonal activation associated with LV remodeling or the medications used to counteract neurohormonal activation could differ between chronic AR patients and FMR patients. Finally, longitudinal studies are needed to document enlargement of the leaflets within individual patients as opposed to group differences in leaflet surface area. In the absence of longitudinal studies, it is apparent that some patients have a larger leaflet surface area than others, but not that their leaflets enlarged over time.

Beaudoin et al. (16) have made a valuable contribution to the existing knowledge about FMR that challenges traditional thinking and opens the door to new avenues of investigation and possibly therapy. FMR is even more complex and heterogeneous than previously thought. It seems that it may be more than simply a disease of the left ventricle.

Reprint requests and correspondence: Dr. Paul A. Grayburn, Baylor Heart and Vascular Institute, 621 North Hall Street, Suite H030, Dallas, Texas 75226. E-mail: paulgr@baylorhealth.edu.

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