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EDITORIAL COMMENT

A New Chapter in the Biology of Mitral Regurgitation as Told by the Left Atrium*

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Mitral regurgitation (MR) is usually viewed as a disease that affects the left ventricle wherein the volume overload of severe MR, if uncorrected, leads to left ventricular (LV) damage, heart failure, and death. This mechanical problem, at present, has only the mechanical solution of repairing or replacing the incompetent mitral valve. Studies of the timing of this intervention have been ongoing for half a century, but their application is complicated by ever improving and safer methods of therapy that make progressively earlier intervention more attractive.

From our LV-centrist viewpoint, we sought to time MR intervention on the basis of the detection of LV dysfunction. The left ventricle is a muscle, and like all muscles its function is to generate force in order to move objects, in this case to propel blood from the LV cavity. This basic property of contractility, the innate ability of force development independent of pre-load, is key in measuring LV function. Thus, force generation should be incorporated into any assessment of LV function. Literally dozens of indexes of LV function were aimed at accomplishing this feat but were proved too complex for use in daily clinical practice. Unable to use a tool that measured force, we made the assumption that because force is translated into LV motion, we could measure this motion to judge contractility. Three tools were used to do this: ejection fraction (EF), end-systolic dimension (or volume), and LV strain.

EF became cardiology's workhorse: easy to understand, easy to measure but plagued by its dependence upon loading conditions, highly distorted in MR. It seemed clear that in most cases of MR, when EF falls to 55%, LV damage already exists. Because outcomes improve if mechanical correction of MR occurs before EF falls to 60%, this number has been used as a marker indicating LV dysfunction. As such, MR correction should occur before LV EF falls below that level (1).

End-systolic dimension or volume is the result of the total extent of sarcomere shortening at end-systole. It is dependent upon overall LV volume, contractility, and afterload but independent of pre-load, thus avoiding one of the confounders in assessing LV function in the volume-overloading lesion of MR. End-systolic dimension and volume have demonstrated utility in timing mitral intervention, and end-systolic dimension has assumed a prominent position in the guidelines for managing valvular heart disease (1).

Global longitudinal strain examines LV shortening in its long axis, where pathology seems to take its toll first. Thus, global longitudinal strain, although still load dependent, may be abnormal even when EF in MR is >60% and may be more sensitive to early LV dysfunction. Strain likely will become a prognostic tool for timing MR intervention in the near future (2).

In 1991, in a study of 176 patients with MR, Reed et al. (3) concluded that left atrial (LA) size was as important as LV parameters in predicting the outcome of mitral surgery, and this concept has been confirmed in several more recent studies. The mechanisms of the left atrium's gravity in predicting the outcome of an LV disease could be manifold. LA size and function likely reflect the severity and duration of MR, obviously important prognostically. However,

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the study by Butts et al. (4) in this issue of *JACC: Basic to Translational Science* goes much deeper into delineating LA pathology in MR. LV and LA function in patients with MR were assessed using magnetic resonance imaging. LA biopsies at the time of mitral surgery were compared with samples taken from the normal hearts of transplant donors. The investigators found serious LA pathology in patients with MR in whom LV function was "normal" (i.e., EF exceeded 60%). In these patients, LA EF was reduced and LA volumes were increased. LA ultrastructural examination found myofibrillar fragmentation with abnormal mitochondria, blurring of the Z discs, and replacement fibrosis. These changes were associated with a large increase in chymase activity. Chymase is a proteolytic enzyme produced primarily by mast cells that induces angiotensin II, transforming growth factor-β, and endothelin that could easily affect myocardial structure, and detection of its activation could be a sign of early irreversible LA damage.

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The ultimate goal in treating patients with severe primary MR is to restore mitral competence before the destructive nature of volume overload causes irreparable damage to the heart. This damage has been viewed through the prism of the left ventricle, whereby we have tried to assess its health by examining its contraction, inferring that damage was beginning to occur if contraction was reduced (1). However, even when we follow current guidelines quantifying contraction, some patients still have less than ideal post-operative outcomes. It is now clear that the left atrium experiences prognostic damage even when the left ventricle appears relatively normal, and more attention must be paid to the left atrium in helping time MR correction. More important, all of these changes in the structure and function of both the left atrium and the left ventricle logically must be presaged by measurable biologic events, and the list of these is growing. As the left ventricle becomes damaged, it relies upon preload reserve and adrenergic activation to maintain output, compensations that mask underlying LV dysfunction. Catecholamine levels may be several times normal, maintaining a normal EF until beta-blockade unmasks LV dysfunction (5). We already measure natriuretic peptides as an indicator of reliance on pre-load reserve. Catecholamine levels would likely also add significant prognostic value if they could be more easily measured. The investigators of the present study have added chymase activation as a likely precursor to LA damage, in turn a prognosticator of outcome in MR, and its measurement could have prognostic importance.

Given that the current management of primary MR is less than perfect, improvement in management will certainly occur. It might be that as both surgical and transcatheter techniques improve, they will become so easy and safe to apply that this issue will become moot. We currently recommend mitral repair for asymptomatic patients with apparently "normal" LV function if the likelihood of repair is almost certain. Repair techniques might become so safe and durable that we might even recommend correction for less than severe MR, well before any LV or LA pathology has ensued. Alternatively, we might develop a highly sophisticated approach to assessing cardiac health prior to MR correction. Such an approach might involve cardiac magnetic resonance imaging to examine for early fibrosis, LV strain to assess very early LV dysfunction, an in-depth evaluation of LA function, and/or an extensive list of biomarkers assessing systems abnormalities that precede our ability to detect structural and functional pathology.

Today we examine the extent of LV contraction as our key determinant of function in MR and use it to time mechanical correction. Moving forward, we must continue to examine LV contraction in MR but add an extensive analysis of LA function coupled with markers of the biologic abnormalities responsible for cardiac dysfunction in primary MR.

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