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EDITORIAL COMMENT

The Pathology of Primary Mitral Regurgitation

The Matrix Is at the Heart of the Matter*

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The mitral valve is composed of the mitral leaflets, the chordae tendineae, the papillary muscles, the left atrium (LA), and the mitral annulus. Primary mitral regurgitation (PMR) has several etiologies leading to disease of 1 or more of those components, causing the valve to leak. If the amount of resultant regurgitation is severe and prolonged, it leads to left ventricular (LV) and LA damage, heart failure, and death. However, timely mitral repair (when repair is possible) can prevent heart failure and return life span to normal.[1] At issue is knowing exactly what "timely" means. Currently, the American College of Cardiology/American Heart Association guidelines for treating PMR list the onset of symptoms, an ejection fraction (EF) of ≤60%, or an end-systolic dimension (ESD) approaching 40 mm as Class I indications for surgical correction of PMR.[1] Mitral repair is favored over valve replacement because of superior outcomes with repair. However, even when these guidelines are adhered to, poor outcomes occasionally occur.

The onset of symptoms worsens the prognosis of nearly all valvular heart diseases, and PMR is no exception. The presence of symptoms reflects a summary of the pathobiology of a given lesion. Systolic and diastolic dysfunction of the LV, right ventricle, LA, or all 3 leads to elevated filling pressure and reduced cardiac output, in turn causing the patient to be symptomatic. It may not be apparent which of these abnormalities causes the patient's symptoms, but their presence reflects a failure of the circulatory system and thus a worsened prognosis. Unfortunately, symptoms may occur late in the disease process after much myocardial damage has already occurred, especially true in PMR where LV compliance is often increased, lowering filling pressures, masking symptoms.[2] Accordingly, the presence of symptoms should cause alarm, but their absence may not be reassuring.

Although EF has been used for over 50 years to help assess prognosis for most heart diseases, this parameter is dependent upon preload, afterload, and contractility. Despite load dependence, reduced EF is often taken to indicate impaired contractility. Although this is usually the case in ischemic and cardiomyopathic disease, the use of EF in valve disease where both preload and afterload are altered is difficult. In PMR, load dependence makes the use of EF especially problematic because preload is increased and, simultaneously, the MR pathway unloads the LV tending to normalize or even decrease afterload in the most extreme cases. These loading abnormalities cause EF to increase; thus, PMR is the rare disease where an EF of 60% (instead of 50% or 55%) is used as a cutoff for "normal" LV function, and even then, LV function may be abnormal. ESD is not confounded by preload, making it useful in assessing PMR. Unfortunately, it varies directly with eccentric hypertrophy, increased afterload, and decreased contractility, and varies indirectly with reduced afterload and increased contractility, all making ESD a less than perfect guide to LV function in PMR.

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Because of these limitations, the use of global longitudinal strain and measurement of natriuretic peptides is gaining favor in improving the assessment of function in PMR.[1] Still, we have much more to learn regarding the pathology of PMR, which is an impediment to better timing of PMR surgery.

The study by Ahmed et al[3] in this issue of *JACC: Basic to Translational Science* advances our understanding of PMR by integrating LV function/mechanics using cardiac magnetic resonance (CMR) and measurements of myocardial structure in 55 patients with PMR before mitral valve surgery. These findings were compared with those of 55 referent normal subjects with no history of cardiovascular disease or medical illness.[3] Using CMR and tissue tagging, this study assessed LV strain and twist, as well as LA size and function. Through myocardial biopsies, myocyte ultrastructure and oxidative stress was examined, along with assessment of extracellular matrix (ECM) content using histochemistry.

The main findings from this study were that in these PMR patients presenting for surgical correction, LV twist both during systole and diastole was impaired, circumferential myocardial strain was reduced, and LA function was abnormal. These functional changes were associated with abnormal myocyte ultrastructure with abnormal mitochondrial architecture and myofilament organization. After staining for fibrillar collagen, these investigators reported areas within the ECM devoid of staining, and in blood samples collected, increased peptide fragments were identified consistent with collagen degradation. In a companion set of studies, the authors reported increased isolated myocyte length and oxidative stress in a canine model of PMR. Taken together, the authors provided results at the functional, structural, and ultrastructural level to suggest that the abnormalities in LV mechanics with PMR (ie, twist) are caused by a loss in ECM integrity and normal myocyte ultrastructure.

Their data fit well with previous studies from our laboratory using a large animal model of PMR,[4] which found that fibrillar collagens undergo an initial degradative process that results in a loss of collagen support and interaction with adjacent myocytes.[4] The creation of PMR in this animal model caused an early and persistent induction of a family of ECM degradative enzymes, the matrix metalloproteinases (MMPs).[4] As a consequence, LV dilation occurs with diminished translation of myocyte shortening to overall force production. Accordingly, Ahmed et al[3] found impaired systolic LV twist consistent with the loss of homogenous transmission of myocyte shortening into myofiber twist mechanics. However, a weakness in the present study was that ECM proteolytic activity in patients with PMR was measured only indirectly. Although fibrillar collagen loss/remodeling is a likely contributory mechanism for the abnormal LV geometry and function in PMR, this observation is insufficient in and of itself. The ECM is a highly complex entity containing several signaling and inflammatory molecules along with the most numerous cell type in the myocardium—the fibroblast. What remains unclear in PMR is how localized bioactive signaling molecules contribute to a fibroblast degradative phenotype and, more importantly, if this process can be interrupted.

The current study as well as past work by this laboratory[5] found that in PMR, isolated myocyte length increases and cross-sectional diameter decreases. These findings help explain the LV dilation and remodeling that occur. Moreover, ultrastructural abnormalities found in this animal model of PMR[5] are very similar to the findings in myocardial biopsies taken from patients with PMR in the study by Ahmed et al.[3] Specifically, mitochondrial vacuolization and disruption was observed in PMR patients. Although these ultrastructural changes will likely be associated with mitochondrial metabolic stress, this was not directly measured in the myocardial biopsies taken from PMR patients. To address this limitation, Ahmed et al[3] performed parallel studies in a canine model of PMR in which indexes of oxidative stress were measured and which identified increased reactive oxygen species. However, the investigators did not address what the downstream consequences of these observations might mean in the context of PMR. One important consequence of mitochondrial dysfunction and oxidative stress is the induction of a localized inflammatory pathway, the inflammasome. Specifically, mitochondrial metabolic stress and the release of reactive oxidative species, such as those identified by Ahmed et al,[3] can cause the intracellular formation of the inflammasome, notably the NOD-LRR pyrin containing protein 3 (NLRP3), which in turn causes release of cytokine signaling molecules.[6] Localized cytokine signaling is a potent stimulus for MMP induction and activation. Thus, the mitochondrial stress in PMR likely sets in motion a continuous cycle of NLRP3 induction, MMP-mediated ECM degradation, and, in turn, a loss of myocyte support. This postulate warrants further study, as small molecule therapeutics for NLRP3 are in preclinical/clinical development.

The study by Ahmed et al[3] provides additional support for the postulate that LV twist and circumferential strain are abnormal in patients with PMR, and contributory mechanisms are abnormal myocyte

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and ECM structure and function. However, it must be recognized that these measurements were performed in patients with long-standing PMR and a recognized need for surgical correction. Thus, these measurements reflect LV dysfunction with PMR that has *already* occurred. What is needed is insight into the intrinsic pathology of the LA and LV that leads to dysfunction *before* it occurs. Nevertheless, the study by Ahmed et al[3] provides a potential roadmap for future directions into the early pathogenesis of PMR.

Recognizing that early surgery is preferable, the guidelines also recommend repair for severe PMR even before established benchmarks are reached (ie, symptoms, reduced EF, increased ESD; Class IIa recommendation) and suggest also incorporating biomarkers and global longitudinal strain into the decision-making process. The current study used plasma profiling of collagen degradation products. Although satisfactory, advancements in multiplex technologies allow for the measurement of a greater number of ECM related molecules.[7] Thus, developing a point of care, blood-based biomarker assay that is reflective of the underlying pathobiology of PMR may aid in early detection of progressive LV dysfunction. For example, the induction and activation of MMPs appear to play a pivotal role in the initiation of LV remodeling with PMR. Thus, direct assessment of MMP activation and its relation to LV regional mechanics could be pivotal in assessing early myocardial dysfunction. Indeed, using hybrid single-photon emission computed tomography/computed tomography approaches, MMP imaging and regional mechanics are becoming feasible and may be a novel approach in identifying when inflection points in the PMR process occur,[7] thereby providing a potential means for quantitative staging of this disease process.

The importance of advancing LV functional and molecular assessment for PMR beyond symptoms and ejection fraction cannot be overstated. The study by Ahmed et al,[3] as well as past basic studies indicate that LV and LA remodeling may not be readily reversible. This underscores the need and perhaps provides a means to identify critical inflection points early in this disease process before irreversible damage has occurred.

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