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EDITORIAL COMMENT

Ischemic Mitral Regurgitation

In Search of the Culprit*

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Ischemic mitral regurgitation (IMR) is either acute or chronic mitral insufficiency, caused by myocardial ischemia and/or infarction. Chronic IMR is an important cardiac disease that carries a grave prognosis after myocardial infarction (MI). In some studies, it has been shown to more than double the risk of short-term mortality and increase the risk of developing congestive heart failure (1,2). Even mild IMR diagnosed at the time of MI has been shown to confer a significant mortality risk in long-term studies (3).

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Many aspects of IMR remain controversial. The basic mechanism of IMR is commonly ascribed to leaflet tethering as a result of the displacement of papillary muscles (PMs) due to ventricular remodeling (4). Papillary muscle dysfunction seems central to this mechanism, which was described by Burch et al. (5) in 1963. While it is clear that the PMs are not the sole players in IMR, they have been the main suspect despite a number of controversies concerning their contribution to IMR. Several studies have suggested a strong role for PM in IMR. Large-animal models have shown that both left ventricular dilation and posterior PM infarction (PMI) were necessary for the development of MR (6). A retrospective study by Okayama et al. (7) in patients with single-vessel coronary disease using cardiac magnetic resonance (CMR) to quantify PMI and MR found an association between the presence of DE in PM and MR, specifically in patients with large infarctions and bilateral PM enhancement.

Other lines of evidence, however, point to a weaker or even reversed role for PM in IMR. Using Doppler strain imaging, PMI has been shown to mitigate rather than exacerbate the degree of IMR in basal inferior infarction (8). Dog models of IMR showed that when PM was selectively infarcted, it did not produce MR, whereas larger infarctions encompassing the PM and adjacent myocardium did produce MR (9). Another dog model showed that global myocardial hypoperfusion but not PM hypoperfusion would produce MR (10). In the same study by Okayama et al. (7), patients with single vessel right coronary artery disease as well as PMI had less MR than patients who had no PMI. Another relatively large cohort of patients with ST-segment elevation MI who were imaged with echocardiography and CMR post-infarction concluded that PMI was common and was not necessarily associated with IMR (11).

In this issue of *iJACC*, Chinitz et al. (12) shed light on these debates through a detailed, quantitative study of the role of PMI and lateral wall infarction in IMR. In a large prospective cohort of 153 patients with first ST-segment elevation MI without intrinsic mitral valve disease, the investigators evaluated the incidence and severity of IMR as well as coronary and ventricular anatomy. Echocardiography was used to quantify MR, angiography to identify culprit coronary lesions, and a high resolution DE-CMR sequence to define the extent of PMI (partial vs. complete) and ventricular infarction. The imaging studies were performed 3 to 4 weeks after MI. The results of these studies showed that neither complete nor partial PMI necessarily led to the development of MR. However, the amount of infarcted myocardium was significantly associated with the development of MR. Not surprisingly, the degree of PMI tracked with the overall infarct burden, where larger infarction was more likely

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to be associated with complete PMI and any degree of PMI was associated with larger left ventricular (LV) infarction. The primary determinants of MR were related to the function of the adjacent LV myocardium and the overall geometry of the ventricle, PM, and the mitral valve. The presence of large lateral wall infarction and associated dysfunction were associated with the development of MR even after multivariate analysis. Chinitz et al. (12) clearly delineated that the infarcted LV myocardium was the main determinant of IMR, not the PMs.

Let us then review the components of the mitral apparatus and their respective dysfunction in IMR. There is mitral leaflet tethering (13), and mitral leaflet area increases over time but fails to compensate adequately for tethering caused by ventricular remodeling (14). There is mitral annulus dilation and abnormal behavior (15). There is PMI and dysfunction, and there is dysfunctional lateral ventricular wall and ventricular remodeling. Despite the popular focus on leaflet tethering and PM dysfunction in IMR, the work of Chinitz et al. (12) have shown more definitively than ever before that the valves and the PM are merely accomplices in the crime; the primary culprit for the development and progression of chronic ischemic MR is the underlying ventricular infarction and adverse remodeling.

With this knowledge, how can we treat IMR better? Surgical techniques have evolved to address IMR at all of the components of the mitral apparatus. Such methods have included restrictive annuloplasty, chordal cutting to relieve tethering, PM modification, and LV plication. Traditional mitral annuloplasty rings have not been uniformly successful, and in some studies they were associated with excess mortality compared to revascularization procedures alone (16). There is a large surgical clinical trial (17) ongoing to test the strategy between mitral valve replacement and mitral valve annuloplasty in treating patients with severe IMR. As demonstrated by a sheep model of IMR, ring annuloplasty does not address the underlying abnormal leaflet tethering and PM dysfunction caused by lateral wall infarction (18). Some innovative procedures directed at addressing the mechanism of IMR are emerging as viable options. One such example is the Coapsys device, which reshapes the ventricle to improve mitral leaflet coaptation and reduce IMR. Despite the unfortunate demise of the manufacturer of the device, the results of the randomized prospective multicentered study using this device as compared to conventional indicated surgery showed a mortality benefit at 2 years (19).

As the focus of the pathophysiology of chronic IMR shifts to the lateral wall infarction and associated reverse remodeling, we should consider treating these patients earlier in the course of the disease. Using innovative therapies early after infarction such as ventricular restraint (20) and papillary muscle reposition by polymer injection in the adjacent myocardial wall (21), one might halt or slow the adverse remodeling that would ultimately result in severe IMR. Future work using computational models that incorporate anatomic and tissue information obtained from CMR might be able to predict future development of significant IMR. The work of Chintz et al. (12) has shown us the underlying cause of IMR in a contemporary cohort of patients with ST-segment elevation MI. Armed with this knowledge, we need to continue to work on targeting effective therapies early in the course of the disease that would ultimately address the underlying mechanism.

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Key Words: delayed enhancement ■ ischemic mitral regurgitation ■ papillary muscle ■ ventricular remodeling.