Ischemic Mitral Regurgitation
Is Mitral Valve Physiology Moving From Global to Local?*

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Mitral regurgitation (MR) affects nearly 2 million Americans with coronary artery disease, conferring an increased risk of heart failure, arrhythmia, and death. Commonly referred to as ischemic mitral regurgitation (iMR), this condition has generally been attributed to papillary muscle displacement, leaflet tethering, and annular dilation in the setting of myocardial infarction. Treatment is challenging. As recently shown in a National Institutes of Health–sponsored trial, iMR recurred in approximately one-third of patients undergoing mitral annuloplasty (1). Traditional cardiac remodeling indexes provide limited value for predicting iMR progression and therapeutic response. For example, left ventricular (LV) chamber dimensions can be similar among patients in whom iMR recurs or improves after surgical intervention. Other markers such as annular diameter are nonspecific for different causes of mitral valve incompetence and thereby provide limited utility for developing mechanistically guided therapies to treat underlying causes of iMR.

In this issue of the Journal, Kalra et al. (2) examine the impact on iMR of interpapillary muscle distance (IPMD) shortening, driven by the hypothesis that, rather than global LV size, an increase in IPMD secondary to localized myocardial dysfunction is a primary determinant of iMR. To do so, parallel studies of iMR physiology were performed in clinical patients, laboratory animals, and computational models. Among patients (N = 67), cardiac magnetic resonance (CMR) was used to assess cardiac remodeling, infarct extent, and iMR severity. IPMD shortening from end-diastole to end-systole, measured as the diameter between the anterolateral and posteromedial papillary muscles in the midventricular short axis, was decreased among patients with moderate or severe iMR (regurgitant fraction ≥30%) compared with those without (9.6 ± 2.8 mm vs. 11.5 ± 3.4 mm; p = 0.02), despite similar end-diastolic IPMD and global LV size and function. Reduced IPMD shortening directly correlated with infarct transmurality and hypocontractility in LV myocardium underlying the papillary muscles.

In the second set of experiments, iMR was assessed by echocardiography 1 week after targeted obtuse marginal branch occlusions in swine to create either subpapillary infarctions (involving myocardium subtending the papillary muscles) or nonpapillary infarctions (involving nearby myocardium but not the papillary insertion). Advanced iMR consistently developed in swine with subpapillary infarctions (regurgitant fraction: 30.4 ± 9.3%), whereas iMR did not develop in those with nonpapillary infarctions (10.7 ± 3.5%; p < 0.001). Although the swine model implies reduced IPMD shortening only in subpapillary infarcts, the actual IPMD was not reported. Moreover, although pathology specimens were studied, detailed descriptions of infarct location, size, and transmurality were not provided.

To further test the significance of IPMD shortening, the investigators employed a computational model in which LV and papillary remodeling indices were modified and related to resultant change in mitral regurgitant orifice. Consistent with their previous results, reduced IPMD shortening greatly affected...
mitral valve integrity: mitral orifice size increased with impaired IPMD reduction and mitral annular dilation, but did not differ further with the addition of global LV dilation. Conversely, LV dilation alone only slightly increased the mitral orifice area. Of note, the magnitude of IPMD shortening (or LV dilation) entered into this model was not specified by the authors, raising the question of whether the computational simulations paralleled physiological range of values observed in patients.

Taken together, the results of this comprehensive multiparametric study provide further insight into mechanisms responsible for iMR, particularly with respect to papillary muscle-related geometry and function. These findings add to a growing body of literature demonstrating that a key determinant of iMR is localized LV injury to the myocardium subtending papillary muscle insertion and that the extent of papillary dysfunction parallels that of the adjacent LV wall. Clinical studies showed increased iMR prevalence after inferior and lateral wall infarcts (3,4). Previous animal models also demonstrated iMR to result from infarction in LV myocardium underlying the papillary muscles (5,6). More recently, CMR studies confirmed a similar independent association of infarct location with iMR, even after controlling for global LV remodeling indexes (7,8). Hypokinesis in these myocardial territories is expected to reduce IPMD shortening—the current results provide convincing data that IPMD remodeling indexes (7,8). Hypokinesis in these myocardial territories is expected to reduce IPMD shortening (or LV dilation) entered into this model was not specified by the authors, raising the question of whether the computational simulations paralleled physiological range of values observed in patients.

Applied clinically, the findings of this study further support that imaging approaches for iMR should be tailored for assessment of mitral apparatus physiology rather than global indexes of cardiac chamber remodeling. Yet LV and annular size remain important, as demonstrated by the authors’ computational model, where increases in both structures with preserved IPMD shortening still resulted in significant MR. These data also emphasize the need for treatment strategies that target underlying mechanisms of iMR rather than the final common endpoint of valvular regurgitation itself. To this end, papillary muscle repositioning and LV infarct plication techniques have been tested in pilot studies (13,14). Mitral annular support techniques are also being refined to better address regional impairments in mitral valve integrity. Can IPMD shortening be used as a marker to discern MR etiology and guide application of such emerging therapeutic strategies? Further studies to test the reproducibility and discriminatory capability of this index to differentiate iMR from other etiologies of mitral valve incompetence are certainly warranted. Research is also necessary to test whether IPMD
yields superior predictive value to more complex indexes (i.e., LV infarct distribution) with respect to iMR progression and therapeutic response. Moreover, as iMR can result from several different structural determinants, it remains uncertain whether the causal substrate for impaired IPMD shortening (i.e., ischemia vs. infarction) affects its predictive utility, as well as how global and/or regional LV remodeling influence the complex interaction between altered papillary muscle function and iMR. The current study provides a valuable proof-of-concept as to IPMD’s potential utility as a straightforward index, while more broadly emphasizing localized myocardial dysfunction as a key determinant of iMR.

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