Left Ventricular Systolic Function in Ischemic Mitral Regurgitation: Time to Look beyond Ejection Fraction

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Chronic ischemic mitral regurgitation (IMR) is a frequent complication after myocardial infarction (MI)[1-3] and is associated with poor outcomes,[4-7] even after coronary revascularization and/or mitral valve surgery.[8-11] This negative impact on outcomes is proportional to the severity of mitral regurgitation (MR).[4,12]

The exact prevalence of IMR in the community remains unclear, ranging from 13% to 59%, with about one third of patients having moderate or greater MR.[1] Furthermore, the rising incidence of MR due to the "epidemic" of obesity, diabetes, and metabolic disorders, combined with improvements in treatment during the acute phase of MI, will likely result in significant changes in the prevalence of IMR in the coming decades.

THE COMPLEX MECHANISM OF IMR

Chronic IMR is the result of the imbalance between *closing forces* (i.e., impaired left ventricular [LV] contractility, LV dyssynchrony, papillary muscle insertion site dyssynchrony, and reduced mitral annular systolic contraction) and *tethering forces* (i.e., mitral annular dilatation, LV local and global remodeling and dilatation, and papillary muscle displacement). Some studies have also suggested that the concomitant increase in pushing forces (i.e., increased left atrial pressure) contributes to mitral valve tenting and thus to a lack of mitral leaflet coaptation.[13] Chronic IMR is categorized as type IIIb according Carpentier's classification,[14] given that leaflet restriction leading to MR occurs only during systole. Agricola *et al.*[15] described two main patterns of mitral valve geometry alteration resulting from leaflet restriction and tethering: (1) the symmetric pattern, generally caused by global LV remodeling with spherical LV enlargement, which involves tethering of both anterior and posterior leaflets and mainly creates a central MR jet, and (2) the asymmetric pattern, more often caused by local inferior wall remodeling with predominantly posterior leaflet restriction, asymmetric leaflet apposition, and a posteriorly directed MR jet. Symmetric remodeling arises mainly from anterior MI, whereas asymmetric remodeling is more frequently related to inferior MI. This classification has interesting clinical implications because patients with symmetric remodeling are at higher risk for recurrent MR[16] and a lower incidence of reverse LV remodeling[17] after surgery for IMR.

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ASSESSMENT OF LV SYSTOLIC FUNCTION IN IMR: BEYOND LV EJECTION FRACTION (EF)

As opposed to what is often believed, the mitral valve itself is not completely normal in IMR. Indeed, some compensatory mechanisms are involved, including the enlargement of the surface of the mitral valve leaflets to reduce leaflet tethering.[18,19] Nevertheless, IMR is more a ventricular disease rather than a valvular disease. Although LV systolic dysfunction is a determinant of chronic MR, there is only a weak correlation between LV EF and quantitative parameters of MR severity (i.e., effective regurgitant orifice area [EROA] and regurgitant volume both at rest[20] and during exercise[21]). This may be explained, at least in part, by the vast heterogeneity in the extent of myocardial injury and LV remodeling in patients with chronic IMR. Furthermore, even if LV EF is a powerful determinant of poor prognosis and an accurate marker of LV systolic dysfunction, it often underestimates the degree of dysfunction in volume-overload diseases such as MR. Indeed, in patients with significant MR (both primary and secondary), LV EF is often normal or only mildly reduced despite marked alteration of LV myocardial function. LV EF is not a pure marker of myocardial contractility. It is also highly influenced by LV geometry, loading conditions, and the severity of MR.[22] Indeed, for a given level of contractility, a significant increase in LV preload, which is common in chronic MR, and/or a decrease in LV afterload will result in a higher LV EF. This mechanism may explain why LV EF is often preserved in patients with severe primary MR, despite obvious myocardial impairment. In patients with chronic IMR resulting from adverse LV remodeling after MI and requiring surgery, LV EF is often about 45% to 50%.

Hence, LV EF grossly underestimates the extent of myocardial impairment in patients with MR. In patients with primary MR, the LV EF is often maintained within the normal range because of increased preload and reduced afterload. However, after mitral valve repair, preload and afterload are normalized and LV EF decreases, thereby unmasking myocardial dysfunction, which was not evident before surgery. This phenomenon may also explain, at least in part, the limited improvement in LV EF frequently observed after successful mitral surgery and revascularization in patients with IMR.

The LV EF may also be artificially maintained within, or close to, the normal range by the presence of the MR itself.[22] The LV EF is the LV stroke volume divided by the LV end-diastolic volume. However, LV stroke volume is the sum of LV "forward" stroke volume ejected through the LV outflow tract and regurgitant volume. Hence, when the regurgitant volume increases, LV EF may increase, although myocardial contractility and LV forward stroke volume are reduced.

These findings emphasize the fact that there is a profound need for better assessment of LV systolic function in patients with chronic MR. The use of the LV "forward" EF (i.e., LV forward stroke volume divided by LV end-diastolic volume) may be useful to assess the real consequences of MR on LV function and may partially overcome the issues described above. However, there is little information about the prognostic value of the parameter.

LV MYOCARDIAL STRAIN: READY FOR PRIME TIME IN CLINICAL PRACTICE

In clinical practice, the use of LV myocardial global or regional strain and strain rate may help better assess LV dysfunction and may, at least in part, obviate the limitations of the measurement of LV EF in patients with chronic MR. However, when derived from Doppler tissue imaging, LV strain measurements are highly angle dependent. Two-dimensional (2D) speckle-tracking echocardiography (STE) is based on grayscale frame-by-frame tracking of tiny echo-dense speckles within the myocardium and subsequent measurement of LV deformation.[23] Considering myocardial mechanics, LV systolic function is the result of the longitudinal and circumferential shortening and radial thickening. In addition, the specific helical arrangement of the LV myocardial fibers leads to a LV systolic wringing motion as a result of the concomitant opposite rotation of the LV apex and base. The gradient between apex and base in the rotation angle along the LV longitudinal axis is called twist and contributes significantly to LV systolic function. There is increasing evidence that LV twist is superior to LV EF in characterizing hemodynamic abnormality in patients with heart failure. Two-dimensional speckle-tracking echocardiographic analysis may be useful for the noninvasive quantification of LV longitudinal, circumferential, radial, and rotational functions. Recently, three-dimensional STE was also introduced, with encouraging results.[24] In patients with primary chronic MR, LV longitudinal function, as assessed by 2D STE, was identified as a good predictor of impaired postoperative LV function in patients with preserved preoperative LV EF,[25] and a recent study also demonstrated that this parameter is useful to assess prognosis.[26]

Because IMR is essentially a ventricular disease, the meticulous and precise assessment of myocardial function is of high potential clinical interest, and in this context, 2D speckle-tracking echocardiographic analysis may be helpful to better understand the mechanisms involved in LV myocardial dysfunction and in the imbalance between tethering and closing forces.

NEW DATA, NEW QUESTIONS

The study by Zito *et al.*[27] in this issue of *the Journal* is an interesting new contribution with regard to the relationship between LV dysfunction and IMR severity. Several studies have reported high rates (15%–75%) of persistent or recurrent MR after restrictive mitral annuloplasty in patients with IMR.[1,8] These disappointing results have been attributed, in large part, to the perpetuation of the progressive negative LV remodeling,[28] even after successful coronary revascularization (Figure 1).

Zito *et al.*[27] report echocardiographic data from 57 patients with LV EF $< 45\%$ and chronic IMR. They aimed to explore whether LV myocardial deformation and LV rotational parameters assessed using 2D STE are related to IMR. Because it has been shown that the localized negative LV remodeling in the basal segment region is in part responsible for the greater incidence and severity of IMR generally observed in patients with inferior MIs compared with those with anterior MIs,[29] they logically hypothesized that impairment of basal LV rotational function may play a role in the occurrence and severity of IMR. To test this hypothesis, they compared patients in whom only anterior LV segments were affected by ischemic injury (group A, $n = 26$) with those with MIs in the inferoposterior or both inferoposterior and anterior territories (group B, $n = 31$). As expected, the symmetric pattern of IMR was more frequent in group A, whereas the asymmetric pattern was predominant in group B. The two groups were statistically similar in terms of baseline demographic and clinical characteristics, medications, LV volumes, and LV diastolic function. However, despite no difference in LV EF, patients in group B had significantly worse wall motion score indexes, suggesting more extensive ischemic injury. In addition, patients in group B had higher degree of MR severity, mainly because of markedly reduced mitral annular contraction.

The strength of the study resides in the fact that the investigators provide comparisons between the two groups for LV longitudinal, circumferential, and radial strain as well as for LV rotational parameters in the three LV regions (i.e., basal, midventricular, and apical), as well as in the LV segments involved in the MI (i.e., anterior and inferoposterior). Of interest, the LV myocardial deformation parameters (i.e., longitudinal, circumferential, and radial strain) were systematically lower in group B than in group A, except for apical parameters, which tended to be better in group B. In addition, basal rotation was also markedly lower in group B but was compensated for by greater rotation in the apical segment in group A, resulting in similar LV twist in both groups. The investigators also report a strong correlation between basal rotation and EROA or mitral annular contractility in group B. These important findings suggest that injury within the inferoposterior basal LV segment may lead to marked reduction in mitral annular dynamics, which may in turn worsen MR severity. Accordingly, the independent determinants of MR severity were the asymmetric pattern and the basal rotation in group B, whereas in group A, the determinants of MR severity were the parameters related to the global LV remodeling (i.e., end-diastolic volume) and its consequences (i.e., mitral valve tethering).

In light of these findings, the investigators propose an elegant hypothesis that could explain the relationship between basal rotation and IMR severity. In patients with normally functioning left ventricles and mitral valve, the LV basal rotation shortens the distance between the mitral valve and the papillary muscle tips, reducing the tethering forces and thus improving leaflet coaptation. Conversely, the reduction in basal rotation typically observed in patients with inferoposterior MIs may hinder this mechanism and thus increase the leaflet tethering forces and ensuing IMR. Nevertheless, and as well acknowledged by the authors, the reduction in LV basal radial function and rotation that occurs in patients with inferoposterior MI may also lead to IMR by reducing mitral annular contraction and thereby limiting leaflet coaptation during systole.

This study by Zito *et al.*[27] also has limitations. In particular, the relatively small sample size limits the robustness and completeness of the multivariate analyses, particularly in group A. Furthermore, group B is rather heterogeneous, as it includes patients with both anterior and inferoposterior MIs. It is possible that in a group including only patients with inferoposterior MIs, the results of the multivariate analysis would have been different, and the basal strain parameters or the annular contractility would have come out as independent predictors of IMR. This would then suggest that the lack of leaflet coaptation observed in these patients is more related to reduced LV basal function and annular contraction rather than reduced LV basal rotation.

The data reported by Zito *et al.*[27] do not allow definitive conclusions, but the speculative mechanism they propose requires particular attention and encourages new studies aiming to explore and corroborate these hypotheses.