Left ventricular dyssynchrony and dynamic functional mitral regurgitation: relationship or association?

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This editorial refers to 'Myocardial asynchronism is a determinant of changes in functional mitral regurgitation severity during dynamic exercise in patients with chronic heart failure due to severe left ventricular systolic dysfunction' by P.V. Ennezat et al., on page 679.

Numerous parameters are associated with a dismal prognosis in heart failure patients. Some of these factors may be mechanistically related, such as increased left ventricular (LV) volume, functional mitral regurgitation (MR), QRS widening, and LV dyssynchrony. Indeed, LV dilation produces distortion of ventricular geometry. The apical and outward displacement of the mitral leaflets restricts their ability to close through tethering forces. QRS widening is frequently mechanistically related, such as increased left ventricular (LV) volume, functional mitral regurgitation (MR), QRS widening, and LV dyssynchrony. Indeed, LV dilation produces distortion of ventricular geometry. The apical and outward displacement of the mitral leaflets restricts their ability to close through tethering forces. QRS widening is frequently associated with LV dyssynchrony. Both dysfunction and dyssynchrony, notably the dyssynchronization of the segments containing papillary muscles1 reduce LV-generated mitral valve closing force.

Functional MR varies dynamically depending on aneural size, loading conditions, and a balance of closing force and mitral valvular deformation. Dynamic MR can be reliably quantitated during exercise testing. Large exercise-induced increases in ischaemic MR are associated with acute pulmonary oedema2 and a high risk of morbidity and mortality.3 In patients with normal QRS duration but reduced LV contraction, exercise-induced changes in MR are not associated neither to the degree of MR at rest nor to the changes in global LV function, but are related to the changes in local LV distortion and in mitral deformation.4 But are the determinants of exercise-induced changes in functional MR similar in patients with LV dyssynchrony? In other words, does the reduction in closing force play a more important role in this setting?

Ennezat et al.5 tested the hypothesis that myocardial dysynchrony at baseline contributes to worsening of functional MR during exercise. They studied 70 heart failure patients; half of the population had ischaemic cardiomyopathy. Pulsed-wave Doppler tissue imaging was performed to assess and quantify LV dyssynchrony at rest. The proximal flow convergence technique was used to quantify MR both at rest and during exercise. Exercise-induced changes in MR were individually variable and were associated with the presence and the degree of LV dyssynchrony. The authors conclude that LV dyssynchrony at rest is related to worsening of functional MR during exercise in patients with systolic heart failure.

Although functional MR and dyssynchrony are obviously continuous variables, cut-off values have been proposed for delineating their significance: effective regurgitant orifice (ERO) of functional MR \( \geq 20 \text{ mm}^2 \), exercise-induced increase1 in MR \( \geq 13 \text{ mm}^2 \) or LV dyssynchrony \( \geq 65 \text{ ms} \), defined as the maximum delay between peak systolic velocities among basal LV segments.5 Using, for instance, this latter cut-off value for analysing Figure 2 in the article published by Ennezat et al.,5 we see that approximately half of their patients have no 'significant' LV dyssynchrony. In this subgroup, the absence of correlation between LV synchronicity and changes in mitral ERO is obvious; two-thirds of the patients exhibited a decrease in ERO during exercise and only one had a large (>13 mm²) exercise-induced increase in MR. The correlation between the two parameters is apparent in the other half of the population who presented with significant LV dyssynchrony; no patient had a decrease in mitral ERO during exercise and seven (roughly 20% of this subgroup) developed a large exercise-induced increase in ERO. In the overall population, LV dyssynchrony at rest and exercise-induced changes in systolic mitral annular diameter were the two parameters independently associated with exercise-induced changes in functional MR. LV dyssynchrony was associated with changes in MR severity in patients with ischaemic and non-ischaemic cardiomyopathies. Exercise-induced changes in annular diameter were related to changes in MR only in patients with non-ischaemic cardiomyopathy.

The dynamic component of chronic functional MR, revealed by exercise testing has clinical implications. Some patients exhibit small changes in the amount of MR; others have a sizeable decrease in ERO mainly because of recruitable contraction of the basal LV segments.4 These patients have a good long-term prognosis. In contrast, a large rise in MR during exercise is associated with more frequent hospital admission for decompensated heart failure or flash pulmonary oedema. Repetitive acute exacerbation of functional MR accentuates left atrial and LV overload and...
contribute to increased mortality. The dynamic changes in MR are correlated mainly with changes in systolic mitral valve tenting area, a marker of leaflet deformation due to tethering forces, changes in end-systolic sphericity index, more apical coaptation of leaflet tips, and systolic expansion of the mitral annulus. All these parameters relate to increased distortion of the mitral apparatus and of LV geometry.

Dynamic MR characterized by exercise-induced increases in regurgitant volume represents the cornerstone of rapid QRS widening and in turn development and rapid progression of LV dyssynchrony. At this stage, the role of reduced mitral valve closing force as a determinant of exercise-induced increases in MR may proportionally be higher. In this respect, changes in mitral ERO found by Ennezat et al. did correlate with those in transmural pressure gradient. A reduction in this gradient during exercise may be due to increased left atrial pressure through increased MR and decreased LV pressure resulting from low contractile reserve, worsened dyssynchrony, and/or inducible ischaemia. Although difficult to formally exclude, inducible ischaemia was not observed in this and other studies. Changes in LV dP/dtmax, as estimated from the steepest increasing segment of the continuous-wave Doppler regurgitant jet, could have been helpful to clarify the role of the closing force, but this parameter has only been validated at rest.

Does LV synchronicity or dyssynchrony remain stable during exercise in heart failure patients? Ennezat et al. measured time intervals between the beginning of the QRS complex and the onset of regional mechanical activation by pulsed-wave Doppler tissue imaging. In contrast to colour-coded Doppler tissue imaging, the pulsed-wave mode does not allow assessment of regional timing differences during a single beat and is technically challenging to catch during exercise. Colour-coded measurements, although not necessarily more accurate, are obtainable during exercise to reconstitute pulsed-wave Doppler velocity profiles and to analyse them off-line. Important changes in LV synchronicity during exercise have been shown; these dynamic changes vary substantially from patient to patient, similarly as the individual changes in the severity of functional MR. Exercise improves the synchronicity of the LV in some patients. In contrast, the activation of basal LV segments can be more asynchronous during exercise in the absence of detectable myocardial ischaemia. Overall, exercise-induced changes in LV dyssynchrony strongly correlate with those in MR and in forward stroke volume.

Thus, close correlations or relationships do exist between closing or tethering forces and functional or ischaemic MR, not only at rest but also during exercise and probably during daily life activities. A practical implication is that dynamic testing and careful recording and interpretation of Doppler echocardiographic parameters should be encouraged to unmask what might be otherwise considered a mild MR or a relatively synchronized LV.

The study of Ennezat et al. in light of previous studies, has clinical importance, notably because biventricular pacing is a widely validated non-pharmacologic treatment option for reducing the severity of functional MR. Cardiac resynchronization therapy acutely decreases MR. Such a reduction is determined at least in part by improved mitral valve closing force, as it is quantitatively related to an increase in transmural pressure gradient and in LV dP/dtmax. The immediate reduction in MR also results from improved co-ordinated timing of the papillary muscle insertion sites. Furthermore, biventricular pacing decreases MR severity not only at rest but also during exercise; its dynamic component is also reduced. When the LV is resynchronized, exercise-induced changes in MR are associated with changes in mitral valvular deformation. This association acutely disappears when pacing is halted. As soon as the biventricular pacing mode is deactivated, exercise-induced changes in MR are no longer correlated with changes in systolic tenting area, a marker of tethering force, but are related to exercise-induced changes in mitral closing force. Persistence in this improvement over time might contribute to reverse LV remodelling and further reduction in MR. A temporary interruption of long-term cardiac resynchronization therapy might lead to both a decline in LV contractility, as indicated by a significant decline in LV dP/dtmax, and an increase in functional MR.

In summary, LV dilation, distortion, and dyssynchrony are linked to functional MR in patients with heart failure and LV systolic dysfunction. There is an association between exercise-induced changes in mitral valve deformation, severity of MR, LV distortion, and dyssynchrony. These different components are interrelated and determine a deleterious vicious circle. Dynamic MR is probably both a cause for progressive LV dyssynchrony and a result of it. When potential responders are appropriately identified, cardiac resynchronization therapy attenuates or interrupts this vicious circle and contributes to improvement in symptoms, exercise capacity, quality, and duration of life.

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References


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**Clinical vignette**

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Multimodality imaging of percutaneous closure of the left atrial appendage

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An 81-year-old woman with a past history of systemic hypertension, chronic paroxysmal atrial fibrillation, three-time recurrent ischaemic cerebrovascular accidents, and major intestinal haemorrhagic accident despite optimal warfarin therapy was considered ineligible for warfarin therapy and referred for percutaneous occlusion of the left atrial appendage (LAA). The left atrium and the LAA were visualized by transoesophageal echocardiography, multislice computed tomography, and conventional X-ray angiography after successful percutaneous trans-septal implantation of a self-expanding PLAATO® device. After an uneventful hospital stay, the patient was discharged on aspirin (75 mg OD) and clopidogrel (75 mg OD).

Multimodality visualization of the occluded LAA. LA, left atrium; LV and RV, left and right ventricles. Arrow indicates PLAATO® device.

Panel A. Transoesophageal echocardiography.

Panel B. Conventional X-ray angiography.

Panel C. Multislice computed tomography long-axis volume rendered reformat.

Panel D. Multislice computed tomography virtual endoscopic view.

See online supplementary material available at *European Heart Journal* online for a colour version of this figure.