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Left Ventricular Dyssynchrony and the Mitral Valve Apparatus: An Orchestra That Needs to Play in Sync

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Functional mitral regurgitation (FMR) is a major driving factor increasing heart failure and mortality in left ventricular (LV) dysfunction.(1–4) Normal valve closure requires the coordinated interaction of the mitral leaflet-chordal apparatus and a favorable balance of competing forces: transmitral closure force that depends on LV contractility, and tethering forces exerted by the papillary muscles (PMs) and mitral annulus.(5,6) In FMR, displacement of the LV walls underlying the PMs restricts mitral valve (MV) closure; the balance of closure and tethering forces creates a dynamic regurgitant orifice that varies within the cardiac cycle and with exercise.(7–9) LV dyssynchrony compounds this dynamic dysfunction both by reducing LV-generated closure force and by increasing tethering from discoordinated motion of PM-bearing walls (Figure 1).(10–14) Understanding the interplay of force and structure in FMR is important to tailor therapy for individual patients and in particular determine the optimal application of cardiac resynchronization therapy (CRT) to reduce FMR.(11)

In the current issue of the *Journal*, Bartko and colleagues provide new data and insights into the relationship of FMR and dyssynchronous PM function and the opportunity for CRT to reduce FMR severity and its associated morbidity and mortality.(15) They studied 269 symptomatic patients with reduced LVEF ($\leq 35\%$) and wide QRS duration ($>130\text{ms}$), and followed the effects of CRT on FMR severity and prognosis. FMR was quantified by echocardiography and dyssynchrony was assessed by tissue Doppler and speckle-tracking ultrasound.

FMR severity correlated with dyssynchrony of radial and longitudinal contraction between LV wall segments underlying the opposing PMs. CRT reduced FMR on average from moderate-to-severe to mild in 24% of patients. Notably, every PM dyssynchrony measure dramatically improved in FMR responders, with no significant changes in FMR non-responders, who also had less baseline MR. The degree of FMR reduction significantly

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correlated with improvement of longitudinal and radial dyssynchrony, suggesting that dyssynchrony in both axes plays an important role in FMR development. Importantly, the authors showed a significant impact on long-term prognosis in CRT FMR responders beyond the contributions of reverse LV remodeling, left bundle branch block, and QRS duration.

Clinical implications relate to the current lack of well-established criteria for guiding CRT optimization specifically targeting FMR.(16) The findings of this study support the possibility that dyssynchrony of PM-bearing walls can be considered a potential new criterion for guiding CRT use and optimization.

In this comprehensive study the authors provide important messages about the mechanism of dyssynchrony-induced FMR and the therapeutic impact of CRT: Radial as well as longitudinal dyssynchrony (linked by conservation of mass) adversely affects MV coaptation, a new observation.(10,11) This is consistent with a previous experimental study demonstrating that heterogenous LV wall deformation not only impairs coaptation of the anterior and posterior mitral leaflets but can also cause malcoaptation between the posterior leaflet scallops, which may respond to PM-guided CRT.(17) The reduction of leaflet tenting with PM resynchronization suggests an improved MV force balance; future studies with 3D echocardiography could evaluate dyssynchrony of mitral apparatus components in greater detail, including regurgitant orifice area variation within systole.(7,13) CRT acutely improves cardiac performance and also reduces LV remodeling and MR over longer times periods; this biphasic effect as well as improvement with exercise would be of value to study in this population to improve long-term outcomes.(18–21)

The study also raises another question: Does heterogenous or multidirectional MV stretch induced by dyssynchronous PM contraction influence MV leaflet anatomy, histology and cellular composition? Compensatory MV leaflet remodeling and enlargement can be induced by mechanical stretch by activating endothelial-to-mesenchymal transformation.(22,23) Such adaptive MV remodeling can be counteracted in ischemic settings by exuberant cell transformation that leaves the MV thick and fibrotic, compounding malcoaptation and MR.(24) For example, a previous canine study, albeit in the myocardium, demonstrated that interstitial and perivascular collagen volumes increased in the late-contracting lateral LV wall more than in the normally contracting anterior LV wall in dyssynchronous hearts induced by right ventricular pacing - changes that were reduced when bi-ventricular pacing improved synchrony.(25) Valve endothelial cell responses depend on both the direction and magnitude of imposed mechanical stresses relative to cellular alignment.(26) Spatially varying excessive stress increases transition of quiescent valve interstitial cells to fibrosis-producing myofibroblasts.(27) Thus, the larger radial and longitudinal dyssynchrony observed in patients with severe FMR could thus favor maladaptive profibrotic cellular responses that compound FMR and may reduce valve responsiveness to therapy over time.

In summary, the study by Bartko and colleagues contributes in an important way to our understanding of FMR, emphasizing the role of dyssynchrony as a mechanism that can be specifically targeted by CRT with potential to improve long-term outcomes. Future directions of study can differentiate FMR induced by PM dyssynchrony to prompt earlier

CRT intervention to reduce FMR by targeting and rebalancing the dynamic interactions of the MV apparatus.

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Figure 1. FMR improvement with CRT.

CRT can reduce FMR by increasing LV-generated closure force (green arrows) and decreasing tethering forces (blue arrows) generated by dyssynchronously contracting PMs and their underlying walls (black arrowheads indicating bulging of a late-activated wall). LA = left atrium.