Mitral Regurgitation in Cardiac Resynchronization
Solving Another Piece of the Puzzle

Kristian Eskesen, MD; Sivajothi Kanagalingam, MD; Theodore P. Abraham, MD

Cardiac resynchronization (CRT) has emerged as a highly beneficial alternative to patients with heart failure (HF), providing symptomatic improvement, reversing remodeling, and reducing mortality rates.1,2 Mitral regurgitation (MR) is an important pathological feature in cardiomyopathy, occurring in a fair proportion of patients with advanced HF and probably inducing additional adverse ventricular remodeling through volume overload.3 Thus, MR may be an important factor influencing the final benefits a patient receives after CRT. Early reports of the effects of CRT on MR were mixed, with a majority of reports suggesting a reduction in MR after CRT.4 In this emerging tale, the missing narrative was a factor influencing the final benefits a patient receives after CRT. Early reports of the effects of CRT on MR were mixed, with a majority of reports suggesting a reduction in MR after CRT.4 In this emerging tale, the missing narrative was a thought about the novel mechanism of CRT in MR. Such insights would help us to better understand the evolution of MR after CRT and potentially suggest means of optimizing MR reduction after CRT. Hence, the work by Solis et al5 examining the potential mechanisms underlying the improvement of MR after CRT is highly instructive. This group of investigators is best positioned to tease out the intricacies of the anatomic and functional factors influencing post-CRT MR, having done pioneering work in animal and clinical models of MR over the last decade, using 2D and 3D echocardiography. Their work has resulted in paradigm-shifting insights into mechanisms of MR in various etiologic settings.6

In the current report, they apply the same systematic approach and address 2 key factors underlying functional MR, namely, the anatomic tethering forces and closing pressure. Ventricular remodeling causes leaflet tethering and incomplete coaptation. Ventricular dysfunction results in inadequate pressure generation and therefore lowers closing forces, again causing inadequate leaflet coaptation. Despite some conflicting theories, it is generally agreed that CRT mediates its benefits through mechanical resynchronization of the heart with modest increments in left ventricular (LV) systolic function. Either or both of these CRT effects could have salutary or adverse effects on MR after CRT. Solis et al examined changes in valve tethering and closing forces in 34 patients with HF who underwent CRT for classic indications. They used noninvasive indices validated in their laboratory. Patients were symptomatically better and had better exercise tolerance after CRT as evidenced by improvements in New York Heart Association class and increase in the 6-minute walk. This was accompanied by a significant reduction in MR regurgitant volume and LV volumes and an increase in ejection fraction. There were changes in mitral valve geometry after CRT, with a decrease in mitral annular area, leaflet closing area, and tenting volume. Similarly, there was an increase in the closing pressure ratio after CRT. Overall, MR decreased significantly in more than half the subjects.

There are several findings in this study that lend themselves to deeper discussion. The LV volumes decreased after CRT in those with and those without decrease in MR. However, increase in ejection fraction was only noted in those with reduced MR. The contrarian view here could be that because published data suggest that a decrease in LV volume best predicts long-term survival, changes in MR really do not matter. It appears that CRT appears to be the major driver of reduced LV volumes and therefore improved outcomes after CRT. The ejection fraction improves in those who had larger decrements in MR. However, ejection fraction changes are rather modest in most CRT clinical trials, so one wonders what this difference really means. Also, the authors demonstrate a significant (10-point increase) in ejection in the group with reduced MR and reverse remodeling. However, they do not compare the final 6-month ejection fraction between these 2 groups. It just could be that there is no statistical difference between the groups at 6 months. The mean values are not too far apart in the high 20% versus mid 20% range, respectively, in the MR reduction/responder group versus the non–MR reduction/nonresponder group.

Similarly, increases in dP/dt were similar in both groups. Although they are not interrogating the same physiology, to some extent one would expect ejection fraction and dP/dt to go in the same direction, given that both are indices of global function. Despite these discrepancies, the MR reduction/responder group showed improvements in MR geometry and increase in closing pressure ratio. Closing pressure ratio was validated in paced sheep. The animal model validation data presented in the report are limited. For example, there is no information on whether pacing did induce dyssynchrony and LV dysfunction, as expected by the authors. Thus, the robustness and implications of the closing pressure ratio remain unclear, given the discrepant findings.

The elephant in the room is dyssynchrony. There was no change in dyssynchrony after CRT in either group. These data are clearly in contrast, on 2 fronts, to those presented earlier.
First, resynchronization has been shown to be related to LV reverse remodeling. In this study, it appears they are not related. Second, resynchronization has been previously shown to underlie the improvement in MR, a connection that was conspicuously absent in this study. The authors chose not to speculate on the possible reasons for this lack of concordance. Their data clearly show that mitral valve geometry and closing pressure ratio improve after CRT and are associated with reduction in MR. So where does dyssynchrony fit in? One could argue that these findings are independent of dyssynchrony. However, this argument would need to explain the lack of agreement with previous studies showing that improvement in dyssynchrony was a major factor in MR reduction. We suggest the former approach, given all the issues relating to measurement of dyssynchrony. Regardless of dyssynchrony, MR reduction appeared to be driven by changes in valve geometry and closing forces. Future studies may be able to better delineate the relationship of these changes with dyssynchrony.

Dyssynchrony in this study was measured using machines that were not the same as those in the previous studies. It is plausible that differences in tissue velocity analysis may influence the timing of peak velocity. Also, it is not clear as to how much spatial resolution was lost when an attempt was made to maximize temporal resolution. It could be that the already reduced spatial resolution in a 3D system was further reduced by increasing frame rates. This change may not significantly affect Doppler-derived velocity; however, it may affect it enough that subtle differences in dyssynchrony are not detected. The issue of tissue velocity or strain being a better parameter for assessment of dyssynchrony also lingers. There was a fair proportion of patients with ischemic cardiomyopathy. It is likely that tethering of ischemic segments by neighboring nonischemic normal segments introduced substantial artifacts into the tissue velocity signal, precluding reliable analysis of regional mechanics.

Another issue that would have been informative is the chronology of change of the various factors examined in this study. For instance, one would expect closing forces to improve rather immediately after onset of CRT, whereas additional benefit would be realized later, when there is reverse remodeling.

Last, one must consider all these findings in the context of sample size. There were approximately 16 to 18 subjects per group. This may be adequate for an initial observation; however, a larger sample with more robust multivariable analysis would provide conclusive data concerning the relative value of mitral valve geometry and closing forces on MR after CRT. One hopes that at that time there will be improved mechanical indices available to help better assess the influence of dyssynchrony.

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References

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