When and how does cardiac resynchronization therapy reduce dynamic mitral regurgitation?

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Online publish-ahead-of-print 19 July 2007

This editorial refers to 'Early and late effects of cardiac resynchronization therapy on exercise-induced mitral regurgitation: relationship with left ventricular dyssynchrony, remodelling and cardiopulmonary performance' by J. Madaric et al., on page 2134.

Cardiac resynchronization therapy (CRT) improves clinical status, quality of life, and exercise capacity, promotes reverse left ventricular (LV) remodelling, and prolongs survival of selected heart failure patients with intraventricular conduction delay. However, 30% of patients do not respond to CRT. Response to CRT largely depends on the extent of LV dyssynchrony, but also on the severity of functional mitral regurgitation (MR). Responders are characterized by a decrease in LV dyssynchrony—restoration of a more normal ventricular activation pattern—and in MR degree.

Functional MR results from an imbalance between tethering forces—annular dilatation, LV dilatation, papillary muscle displacement, and LV sphericity—and closing forces—reduction of LV contractility, global LV dyssynchrony, papillary muscle asynchrony, and altered mitral systolic annular contraction. CRT acutely reduces functional MR by increasing closing forces with an improvement in LV dP/dt and by improving co-ordinated timing of mechanical activation of papillary muscle insertion sites. This benefit appeared to be dependent on continued pacing because withholding pacing resulted in an immediate loss of effect and recurrence of MR.

Functional MR is characteristically dynamic during exercise. The magnitude of exercise-induced changes in MR severity is unrelated to the degree of MR at rest. The increase in MR during exercise identifies a subgroup of patients at high risk of cardiac events. CRT has been shown to reduce MR mildly at rest and attenuate its spontaneous increase during exercise.

The time course of CRT on dynamic MR has been elegantly examined by Madaric et al. In the early stage (1 week after implantation), CRT was accompanied by a decrease in LV dyssynchrony and in MR severity, but not by a reduction of the dynamic component of MR. Surprisingly, although LV synchronicity was improved at rest, exercise was associated with a moderate increase in LV dyssynchrony. In the chronic phase (3 months after implantation), a progressive reduction in resting MR and in LV volumes occurred without additional improvement in LV synchronicity at rest. Synchronicity was maintained during exercise, whereas the magnitude of exercise-induced MR was significantly attenuated. The exercise capacity, i.e. maximal workload, exercise duration, and peak VO2, improved more in patients with smaller changes in MR severity during exercise.

This study confirms that both MR and LV synchronicity are dynamic and can substantially vary during exercise, independently of detectable myocardial ischaemia. The increase in MR results from or is associated with a significant rise in LV dyssynchrony. This dynamic association has been reported in more than one-third of patients with chronic systolic LV dysfunction and is strongly correlated with changes in stroke volume during exercise. Thus, global changes in LV synchronicity and in MR in patients with systolic dysfunction contribute to the limitation of stroke volume adaptation during exercise, and therefore participate in exercise symptoms out of proportion to LV dysfunction and resting MR. Moreover, intermittent increases in MR and in dynamic LV asynchrony may progressively increase myocardial stiffness and accelerate global and local LV remodelling. The mechanisms underlying these dynamic conditions are not completely elucidated. The potential participation of active myocardial ischaemia cannot be entirely excluded. In these patients, the detection of subtle changes in myocardial contractility during a stress test is relatively challenging. The imbalance between oxygen demand and oxygen supply in the LV longitudinal subendocardial fibres, where the conduction system is, could alter the electromechanical coupling generating dynamic LV dyssynchrony. Blunted regional flow-metabolic reserve may result from reduced coronary flow reserve with or without coronary stenosis and increased local systolic wall stress. The acute changes in regional pressure or volume—dynamic MR—loads might favour conduction disorders per se.

CRT produces changes in regional myocardial blood flow, with a more uniform distribution between the myocardial...
walls without increasing global LV oxidative metabolism, resulting in improved myocardial efficiency. During stress, myocardial efficiency and metabolic reserve may be increased. These changes are progressive and seem to be more pronounced in the chronic stage of CRT implantation. 14,15

In the study of Madaric et al., although LV dyssynchrony was reduced at rest, delayed improvement in regional flow-metabolic reserve could maintain the dynamic behaviour of MR and LV dyssynchrony immediately after CRT implantation. In the chronic phase, its progressive improvement could attenuate dynamic MR and participate in recruitable LV function at rest and progressive LV reverse remodelling. Reverse LV remodelling per se might decrease the oxygen demand and have an additive role in correcting mitral valve closure by reduced tethering, i.e. reduction of tenting and LV sphericity, and increased closing forces, and thus in reducing resting MR. Reduction of LV dyssynchrony at rest also triggers LV reverse remodelling. 10

Reduction in exercise-induced MR and LV dyssynchrony in parallel to reverse LV remodelling translates into improved LV function and cardiopulmonary performance. However, for a similar extent of LV remodelling, exercise capacity varies from one patient to another. Exercise performance was greater in patients with smaller changes in MR severity during testing.

In summary, the effects of CRT on both dynamic MR and LV dyssynchrony differ in the early and late stage of implantation. Acutely, exercise-induced LV dyssynchrony persists, whereas no significant reduction in dynamic MR is observed. Chronically, exercise-induced increase in MR is attenuated in parallel to reverse LV remodelling. Cardiopulmonary performance is more increased in patients with smaller changes in MR severity during exercise, indicating the large influence of dynamic MR on exercise capacity. These time course-dependent changes could in part be related to the temporal evolution of regional flow-metabolic reserve. This hypothesis requires further investigations.

Conflict of interest: none declared.

References