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EDITORIAL COMMENT

New Insights Into Ventricular Interactions During Cardiac Resynchronization*

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Cardiac resynchronization therapy (CRT) improves hemodynamics in patients with drug-resistant heart failure, and its efficacy has been clearly demonstrated in large-scale studies in which our group was directly involved (1–3). The initial rationale leading to the development of CRT was the correction of dyssynchrony often present in patients with systolic heart failure. The criterion currently recommended to assess dyssynchrony and select patients eligible for CRT is the electrical dyssynchrony by QRS width, reflecting the ventricular conduction time and QRS morphology (4). But the selection of CRT candidates on this sole criterion is not optimal, given the high rate of nonresponders, consistently approximating 30% in most of the studies. Therefore, criteria assessing mechanical dyssynchrony by echocardiography were initially thought to improve patients' selection, but failed to demonstrate their usefulness in large prospective clinical trials (5).

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Electrical and mechanical activations are closely related. However, patients with wide QRS may exhibit synchronous left ventricular (LV) activation, and those with narrow QRS may have dyssynchrony. The causes underlying such discrepancies are still unknown, and more specific echocardiographic parameters or imaging modalities evaluating dyssynchrony are desperately needed. Many efforts have been made in this field, and the determination of reproducible echocardiographic parameters to approach the results obtained with the electrocardiogram is currently not achieved. In a recently published study, Ploux et al. (6) demonstrated that the 12-lead electrocardiogram was only a general overview of ventricular electrical activation abnormalities, and they used noninvasive electrical mapping to evaluate right ventricular (RV) and LV total activation times and ventricular electrical uncoupling. They demonstrated that, whether patients had left bundle branch block or intraventricular conduction delay, ventricular electrical uncoupling predicted clinical CRT response better than the usual QRS duration criterion with excellent sensitivity and specificity (6).

The "missing link" explaining electrical and mechanical discrepancies is unknown. In this issue of the *Journal*, Lumens et al. (7) bring a potential explanation based on ventricular interactions and particularly on the contribution of the RV on LV function. The authors compared animal, clinical, and computational data to analyze the hemodynamic and electromechanical consequences of left ventricular pacing (LVP) and biventricular pacing (BiVP). Hemodynamic response (LV maximal rate of pressure rise [dP/dt_{max}] changes) and electrical activation (using contact mapping in dogs and a novel noninvasive multielectrode electrocardiographic mapping technique in patients) in response to LVP and BiVP were studied. A similar acute hemodynamic response for LVP and BiVP was found, although only BiVP significantly decreased electrical dyssynchrony. The simulations evidenced that the RV, through ventricular interaction, substantially contributed to the improvement in LV function induced by CRT, especially during LVP. These novel and interesting findings highlight the importance of RV–LV interactions on the electromechanical correlations induced by CRT.

The RV and LV myocardial functions are closely linked. Anatomically, the RV shares oblique fibers in the interventricular septum with the LV. This RV–LV relation through the interventricular septum was demonstrated in ST-segment elevation myocardial infarction patients with septal infarction, in which a decreased RV reserve was demonstrated compared with ST-segment elevation myocardial infarction patients without septal involvement (8). Therefore, a systolic ventricular interaction exists between both chambers such that LV contraction increases RV contraction. An increase in RV afterload will result in increased RV performance through the recruitment of these specific oblique fibers. Conversely, if LV afterload increases and LV dysfunction occurs, RV function will be impaired in parallel to reduced systolic ventricular interaction. Anatomically, such RV dysfunction results in a reduction in the oblique nature of RV septal fibers, impairing further RV function; this is a vicious cycle leading to clinical impairment. Similarly, a diastolic ventricular interaction exists such that RV diastolic impairment increases RV diastolic pressure and decreases LV diastolic filling through pericardial constrain (9).

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Both RV systolic and diastolic dysfunctions frequently coexist with LV dysfunction, highlighting the importance of RV function in patients with heart failure. The involvement of RV function in CRT response is not new and has been studied previously. In a swine model of biventricular pacing, Quinn et al. (10) demonstrated that CRT optimization improved cardiac output by increasing RV contractility. This effect was hypothesized to be a consequence of the transmission of LV pressure across the interventricular septum, as a consequence of systolic ventricular interaction. One would think that RV function would, therefore, be a good reflection of CRT efficacy. However, this assumption was contested in a small hemodynamic study analyzing the RV dP/dt_{max} in response to different VV intervals (11). The RV dP/dt_{max} failed to identify the optimal VV interval when compared with LV dP/dt_{max}, and the authors concluded that this criterion was not useful for VV optimization in CRT patients. Lumens et al. (7) used a mixed electrical and mechanical approach to evaluate systolic ventricular interactions. The simulations performed demonstrated that the improvement of myocardial work was similar in both conditions, although their local distribution was different: in LV pacing, LV work was not increased, but RV work increased significantly; conversely, BiVP resulted in increased work in both ventricles through interventricular dependencies. The correction of mechanical asynchrony and the recruitment of RV myocardial fibers induced by LV stimulation can explain the positive hemodynamic results despite the absence of correction of electrical dyssynchrony in LV pacing (12).

This study raises further questions about systolic ventricular interactions. The mechanistic insight provided by Lumens et al. (7) potentially explains the electromechanical gap currently observed between electrical and mechanical dyssynchrony and highlights the role of the RV myocardium during CRT. Should RV function in response to CRT be assessed routinely, specifically in nonresponders? Can these simulations be reproduced in humans? And more importantly, could this increased amount of RV myocardial work as a result of LV pacing be responsible in the long-term for a progressive RV dysfunction? These questions will require further study to better characterize RV–LV interactions in response to CRT.

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Key Words: cardiac resynchronization therapy ■ dyssynchrony ■ electrophysiology mapping ■ myocardial work ■ ventricular interaction.