Pacing in Heart Failure Patients With Narrow QRS
Is There More to Gain Than Resynchronization?

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Ventricular dyssynchrony is defined as uncoordinated regional myocardial contraction and relaxation and may be either intraventricular or intraventricular. Most of the clinical focus has been on left ventricular (LV) intraventricular dyssynchrony, which in principle may have 3 different origins. First, dyssynchrony may have an electric origin as in left bundle-branch block, which causes nonuniform timing of electric activation. Second, there may be disturbances in excitation-contraction coupling, and this would be apparent as delay in electromechanical activation time. Presently, there are limited data on the clinical relevance of such disturbances. Third, dyssynchrony may have a primary mechanical origin and may occur in ventricles with regional impairment of function, as in myocardial ischemia when systolic shortening in different segments is out of phase. Furthermore, a primary mechanical origin may be found in ventricles with nonuniform distribution of load, and this may occur when there are regional differences in LV wall thickness or differences in local radius of curvature, including septal curvature. In these cases, segmental differences in systolic wall stress may lead to differences in timing of peak contraction.

Effect of External Constraint on LV Filling: How It Works

The pericardium is a relatively stiff structure that has no major restraining effect on the ventricles at normal cardiac volumes but may exert a marked restraining effect when the heart is dilated. In particular, when pericardial volume is increased acutely, even a modest volume increase may cause marked increments in pericardial pressure. Therefore, a small acute pericardial effusion can cause severe compression of the heart and lead to cardiac tamponade. Similarly, when the pericardium is already stretched, a modest reduction in cardiac volume can lead to marked reductions in pericardial pressure and in turn reduction in LV and right ventricular (RV) diastolic pressures. When cardiac enlargement occurs more gradually, as in chronic HF, there is pericardial creep.4 Therefore, in HF patients with atrial pressures in the lower range, the restraining effect of the pericardium is probably modest. In patients with chronic HF and elevated RV and LV diastolic pressures, however, the restraining effect of the pericardium may be substantial.5

In a dilated heart with elevated pericardial pressure, the different cardiac chambers are competing for limited space within the pericardium. Therefore, if RV or atrial volumes are reduced, there will be more space available for the LV, which may increase its end-diastolic volume, and there may be a reduction in LV diastolic pressure. When pressure-volume curves are recorded, this will be evident as a downward shift of the diastolic pressure-volume relationship. The clinical example in Figure 1 illustrates a dramatic downward shift of the LV diastolic pressure-volume relationship after nitroglycerin administration.6 Similarly, an acute increase in LV afterload can shift the LV diastolic pressure-volume relationship upward.7 Tyberg et al8 proposed that these shifts were actually due to corresponding changes in pericardial pressure that were due to changes in heart size and pericardial volume. The mechanism whereby vasoconstricting and vasodilating agents may shift the LV diastolic pressure-dimension relationship is by modulating vascular capacitance, thereby shifting blood to and from the venous circulation and thereby modifying heart size and in turn pericardial pressure.9

A downward shift of the diastolic pressure-volume relation is beneficial in HF because LV end-diastolic pressure can be markedly reduced, whereas there is minimal change in end-diastolic volume and in stroke volume. Direct measurement of pericardial pressure in experimental studies and other sources of pericardial pressure.

Cardiac resynchronization therapy (CRT) is established as an effective treatment option in patients with severe heart failure (HF) and LV electric dyssynchrony as indicated by a wide QRS complex.4 Because CRT corrects electric dyssynchrony, it would be expected that patients with narrow QRS should be responders because they presumably have relatively normal electric conduction. Consistent with this notion, Beshai et al2 found no benefit of CRT in patients with severe HF with QRS <130 ms and echocardiographic evidence of mechanical dyssynchrony. In apparent contradiction to this, Williams et al,3 in this issue of Circulation, demonstrate that CRT causes marked immediate improvement in LV function in HF patients with narrow QRS and no or only minor signs of mechanical dyssynchrony. The authors conclude that CRT caused improvement in LV function in part by reducing the external constraint exerted by the RV and the pericardium. This would reduce pressure external to the LV and therefore increase the effective LV distending pressure and increase LV end-diastolic volume, causing increased cardiac output via the Frank-Starling mechanism.

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estimation of pericardial pressure in patients support the hypothesis that load-induced acute shifts in the LV diastolic pressure-volume relationship are due to changes in pericardial constraint.9,10 William et al measured pericardial constraint using a rather complex methodology.3 A simpler approach is to use right atrial or RV diastolic pressures as estimates of pericardial pressure.11,12

Possible Mechanisms of Improved LV Function by Pacing in HF Patients With Narrow QRS

The study by Williams et al3 represents an extension of previous studies from the same group on ventricular interaction in HF. In this study, they included only patients with narrow QRS complexes, ≤120 ms, which suggests that LV electric dyssynchrony was absent or minor. Hence, improved LV function by CRT in this population was most likely not due to correction of electric dyssynchrony. The authors report a reduction in external constraint in 15 of the 30 patients and suggest this as a main explanation for the improved LV function. However, the mechanism of reduced external constraint during CRT was not investigated and should be explored. End-diastolic LV volume was not reported explicitly but was presumably increased, implying that 1 or more of the other chamber volume(s) must have decreased because of limited space inside the pericardium. The authors speculate that CRT delayed RV filling relative to LV filling, allowing increased LV filling. This is a possible mechanism because pacing of the LV may in essence disturb RV function, causing delayed and impaired RV filling. When the LV and RV compete for limited space inside the pericardium, increased LV filling and volume may occur at the expense of RV filling. Impaired RV function could be a result of pacing and pacing location. In contrast to electric activation through the Purkinje network, which propagates rapidly to all parts of the ventricular myocardium, pacing causes a slowed propagation of electric activation through the myocardium. Hence, LV pacing or biventricular pacing may produce a situation similar to that in right bundle-branch block, in which RV function is impaired. If RV relaxation and onset of filling are delayed, the LV may fill to a larger volume at a lower pressure while the RV is in a smaller, still contracted state because of the later relaxation. We examined measurements from our experimental dog model to investigate the plausibility of this mechanism. The details of the preparation of the animals have been described previously.13 Intramyocardial electrodes were placed in the RV lateral wall, septum, and LV lateral wall to record timing of regional electric depolarization at these 3 sites. Figure 2 shows that electric activation was essentially synchronous at the 3 locations during baseline, whereas RV lateral wall activation was delayed during early ectopic activation of the LV myocardium, a situation similar to LV pacing. The RV pressure tracing slightly preceded LV pressure during baseline, whereas it was substantially delayed relative to LV pressure when activation of the RV myocardium was delayed compared with the LV. This notion is consistent with the time shift of RV and LV pressures observed in paced dogs with left bundle-branch block.14 Our measurements support the possibility that earlier pacing of the LV myocardium may cause interventricular dyssynchrony that delays the RV relative to the LV and may give LV filling a head start, which could be beneficial in a situation in which LV filling is compromised by the pericardial constraint. A relatively simple investigation of such a mechanism could be performed by echocardiographic examination of the patients in the study by Williams et al3 by analyzing timing of filling and valve opening and closing in the 2 ventricles in addition to volumes and septal position and compare these measures with the pacemaker turned off and on.

As another proposed mechanism of improved LV function, Williams et al3 suggest that the patients may have had “occult”
dyssynchrony, which could have been corrected by CRT. They argue that conventional measures of dysynchrony are suboptimal because they focus mainly on longitudinal function and ignore radial wall motion, ie, shortening of the short-axis cavity diameter by myocardial circumferential shortening and wall thickening, which is perhaps the major contributor to LV ejection. No attempt to quantify radial dysynchrony is reported in the article, and the mechanism of such potential radial dysynchrony is unclear. One possible explanation is that some of the patients with moderately prolonged QRS (∼120 ms) had delayed regional depolarization (ie, electric dysynchrony). However, it is difficult to understand how patients with a nearly normal QRS width would have a sufficient mass of myocardium with delayed depolarization to benefit substantially from CRT.

We may also speculate on other possible mechanisms of improved LV function. CRT has been shown to reduce mitral regurgitation both in patients with left bundle-branch block and in HF patients with narrow QRS. Regurgitation increases atrial volume, and higher atrial end-diastolic volumes will increase pericardial pressure. One may speculate that some of these HF patients had a prolonged atrioventricular delay, which may have caused increased late-diastolic retrograde mitral flow, thereby increasing atrial end-diastolic volumes and hence the external constraint. Williams et al applied a constant 100-ms atrioventricular pacing delay, which may have been a more optimal atrioventricular delay in these patients, thereby decreasing late-diastolic retrograde mitral flow and hence atrial end-diastolic volumes.

Conclusions

The findings by Williams et al of acute hemodynamic improvement together with a reduction of pericardial constraint (in some patients) by CRT in HF patients with narrow QRS are interesting. The article is moving focus toward ventricular interaction and pericardial constraint as important factors in HF patients who could benefit from CRT. However, their study does not answer the question of why CRT reduces pericardial constraint or whether the acute responses persist during long-term treatment. It would be interesting to study whether the degree of pericardial constraint could be an additional factor that predicts long-term success of CRT.

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None.

References


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