EDITORIAL COMMENT

The Importance of Being Synchronous: On the Prognostic Value of Ventricular Conduction Delay in Heart Failure*

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It has long been recognized that prolongation of the QRS complex in the surface electrocardiogram is an independent predictor of an adverse outcome in patients with heart failure (HF) (1,2). In most patients with dilated cardiomyopathy, QRS prolongation presents as a left bundle branch block (LBBB) (3,4). Not only is LBBB a marker of disease progression in cardiomyopathy but the ventricular dyssynchrony associated with ventricular conduction delay may have negative hemodynamic consequences: it can reduce contractility (5) and ejection fraction (6), shorten diastolic filling time (7), and cause functional mitral regurgitation (8). Thus, ventricular conduction disturbance in HF may lead to a vicious circle with further hemodynamic deterioration and left ventricular (LV) dilation. There is experimental evidence that asynchronous LV activation results in a reduced work in early-activated regions (i.e., the septum in LBBB) and increased work in late-activated regions (i.e., the LV free wall) (9) which causes asymmetric LV hypertrophy (10). This may be explained on the basis of regional disparities in the expression of calcium handling and stress proteins (11).

The evaluation of the pathophysiologic consequences of cardiac conduction disturbances, such as LBBB, is an interesting new application for cardiac nuclear imaging. Beyond functional assessment of interventricular and intraventricular dyssynchrony by Fourier phase analysis of equilibrium radionuclide angiography as performed by Fauchier et al. (12), nuclear imaging techniques have also been used to study the effects of LBBB on myocardial perfusion and metabolism. A reduction in septal glucose uptake with preserved myocardial blood flow (13) has been noted in LBBB caused by dilated cardiomyopathy, whereas there is ongoing discussion on the effects on oxidative metabolism (14,15). Cardiac resynchronization therapy (CRT), which aims to correct the hemodynamic disturbances caused by ventricular dyssynchrony in patients with moderate-to-advanced HF and LBBB, has been shown to have some positive impact on the metabolic effects of ventricular dyssynchrony. Preliminary data suggest improved myocardial oxygen consumption during low-dose dobutamine stress with biventricular (BV) pacing as determined by 13C-acetate positron emission tomography (16) and a restoration of a homogeneous myocardial glucose metabolism as shown by 18F-fluorodeoxyglucose positron emission tomography (17).

Acute hemodynamic (18–20) and mid-term functional improvement (21–23) as well as a reverse remodeling effect (24–27) have been demonstrated with CRT. Cardiac resynchronization is usually achieved by atrial triggered BV pacing, but it is unclear whether BV pacing is necessary to achieve optimal ventricular resynchronization or whether it is sufficient to pace only the LV. Currently available evidence suggests that there is no clear advantage of BV over LV pacing, but most studies are limited by small sample sizes (22), nonrandomized study design (28), or no direct comparison of both approaches (29). The real question behind this debate is whether it is necessary to achieve interventricular synchronization or whether it is sufficient to correct LV intraventricular dyssynchrony. Parameters of interventricular dyssynchrony such as the interventricular mechanical delay derived from echocardiography are being used to identify patients suitable for CRT, based on the assumption that correction of interventricular dyssynchrony may be an adequate therapeutic target (30). The data from the study by Fauchier et al. (12) do not support this hypothesis because interventricular dyssynchrony did not prove to be of prognostic importance. In contrast, increased LV intraventricular dyssynchrony is not only relevant for prognosis but has also been shown to predict a positive response to CRT (31,32). If only the LV has to be resynchronized, one may speculate that LV pacing alone, with a critically timed atioventricular delay allowing fusion with intrinsic conduction through the right bundle branch, is enough to achieve optimal hemodynamic support in HF patients with LBBB.

However, the argument that interventricular delay has

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some importance cannot be easily refuted. First, correction of interventricular dyssynchrony may still lead to hemodynamic improvement despite a lack of prognostic importance. A scintigraphic study by Kerwin et al. (33) using similar methodology as in the study presented in this issue of the Journal indicated that BV pacing mainly reduced interventricular but actually increased LV intraventricular dyssynchrony. However, these data were confounded by a heterogeneous patient population studied, including patients with right bundle branch block, ischemic heart disease, and only minor conduction delay. Moreover, LV lead position was not standardized, which is a critical determinant of therapeutic success in CRT. It is now accepted that a lateral or posterior LV lead position, i.e., in the area of the LV that is usually activated with the greatest delay in LBBB, provides optimal ventricular resynchronization and, thus, hemodynamic support (34).

Second, the positive hemodynamic impact of correcting LV intraventricular dyssynchrony by CRT may not necessarily translate into improvement in prognosis. Previous studies with positive inotropic drugs (35–37) have taught us to be cautious with assumptions on prognosis in therapeutic interventions that acutely improve cardiac hemodynamics. However, there is good reason to be optimistic that the hemodynamic benefit achieved by CRT may not be paid for by increased mortality because CRT does not seem to increase myocardial oxygen demand as opposed to positive inotropic drugs (38).

Third, another aspect of the study by Fauchier et al. (12) deserves our attention: there may be a potential hazard of right ventricular (RV) desynchronization caused by CRT as RV intraventricular dyssynchrony was found to be predictive of an adverse outcome at least by univariate analysis; LV pacing alone especially may lead to substantial RV desynchronization. This may not only impair RV hemodynamic performance (39) and promote the occurrence of right-sided HF but may also potentially have a negative prognostic impact. This could be an advantage of BV over LV resynchronization because it does not appear to increase RV dyssynchrony substantially (33). However, in animal studies even BV pacing has been shown to impair RV hemodynamics acutely (40). Moreover, there are only very few long-term data with CRT and no data on RV function after long-term LV or BV pacing to the best of our knowledge.

Currently, there are no prospective data available on the influence of CRT on mortality in patients with HF. Thus, any discussion about the prognostic impact of interventricular versus intraventricular resynchronization remains speculative. Hopefully, the ongoing COMPANION study (41), which analyzes all-cause mortality as the primary study endpoint, and the CARE-HF (30) study, investigating the combined end point of all-cause mortality and unplanned cardiovascular hospitalizations, will answer the question of whether CRT has a positive impact on these significant clinical end points. However, both studies only apply BV pacing and, therefore, the question of whether correction of interventricular dyssynchrony is necessary will not be answered.

Caution needs to be taken when interpreting the data presented by Fauchier et al. (12) on the correlation of interventricular and interventricular dyssynchrony to hemodynamic parameters. Intraventricular dyssynchrony in both ventricles appeared to correlate to echocardiographic measurements of LV function (end-diastolic and end-systolic diameter, ejection fraction) and to cardiac index, whereas only RV dyssynchrony correlated to functional parameters (New York Heart Association [NYHA] functional class, peak oxygen consumption) and RV ejection fraction. Even more surprising, interventricular delay showed an inverse correlation to NYHA functional class, i.e., less interventricular dyssynchrony was associated with functional impairment. It is likely that echocardiograms and radionuclide scans were not taken on the same day and the correlations were confounded by differences in volume status of the patients. No data on drug treatment are provided, which further limits the relevance of the observed correlations. In addition, the assessment of NYHA functional class may be too imprecise to allow for a meaningful correlation with the scintigraphic data. Nevertheless, the data should at least raise our attention to the potential importance of RV dyssynchrony in patients with HF, which has frequently been neglected in the discussion on CRT.

Clearly, more questions are raised than answers provided by the data from the Fauchier et al. (12) study. However, the study sheds some light on the importance of ventricular conduction disturbance in a relevant number of patients with dilated cardiomyopathy, and the authors should be credited for this effort. At present, we can only conclude that for patients suffering from systolic HF it is obviously of prognostic importance that LV contraction is in synchrony. There is great hope that CRT may therefore improve prognosis in HF patients with ventricular conduction delay.

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