

A troubled marriage: When electrical and mechanical dyssynchrony don't go along

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Mechanical contraction of the heart muscle is initiated by electrical activation of myocytes. Left ventricular mechanical dyssynchrony (LVMD) refers to a difference in the timing of mechanical contraction or relaxation between different segments of the left ventricle (LV). It is important to acknowledge that mechanical dyssynchrony does not equal electrical dyssynchrony which is defined by an asynchronous electrical activation of the LV leading to a prolonged QRS duration (> 120 ms) on the ECG, and is usually the result of a left bundle branch block (LBBB). Although electrical and mechanical dyssynchrony often coincide, electrical and mechanical dyssynchrony are commonly not present at the same time in a given patient.^{1,2}

Cardiac resynchronization therapy (CRT) was developed with the goal to treat mechanical dyssynchrony with the hope it will improve cardiac performance and improve outcomes.³⁻⁵ Right at the get-go the simple assumption was made that electrical dyssynchrony and mechanical dyssynchrony track well with each other, and since it is so much easier to mea-

sure and quantify electrical dyssynchrony (presence of absence of a LBBB and QRS width), the electrical dyssynchrony on ECG became the designated target of CRT. Currently, presence of electrical dyssynchrony is among the inclusion criteria for CRT in heart failure (HF) patients. Other criteria include left ventricular ejection fraction (LVEF) $\leq 35\%$ and New York Heart Association class II-IV despite optimal medical therapy. Under those criteria, biventricular pacing has been shown to reduce all-cause mortality.⁶ Nonetheless, among patients who meet the criteria, around 30% to 40% fail to show an improvement in clinical symptoms and cardiac function,⁷ suggesting the need for a more efficient selection of CRT candidates to improve patient outcomes and decrease costs. Today we know that diseased hearts with electrical dyssynchrony do not equally respond to CRT. The two key determinants of treatment response that emerged are QRS width and presence of LBBB. Meta-analysis of three randomized trials suggests that a wide QRS duration > 150 ms, regardless of QRS morphology, is most important for CRT response.⁸ Further, the majority of clinical trials that studied CRT have found that it is mostly efficacious in patients with LBBB.⁹⁻¹¹ More recent work now suggests that LBBB in itself may represent a previously unrecognized cause of LV dysfunction and may impair left ventricular recovery.¹²

In the present analysis the authors set out to investigate the LBBB and its relationship with mechanical dyssynchrony using myocardial perfusion imaging (MPI) and vector electrocardiography (VECG, another surrogate of mechanical myocyte activation, derived from an ECG analysis). In a retrospective analysis the authors selected 45 patients with LBBB and 24 controls out of a cohort of 994 patients. The authors found a large degree of electromechanical dissociation ($\sim 40\%$ of cases). Electromechanical dissociation refers to the fact that patients with LBBB (electrical

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dyssynchrony) can have no evidence of mechanical dyssynchrony on myocardial perfusion imaging. Several ECG/VECG parameters correlated significantly with mechanical dyssynchrony when the whole population was studied. In a multivariate analysis, independent predictors of mechanical dyssynchrony were QRS duration and end diastolic volume (a marker of ventricular dilation/dysfunction). The most significant contribution of this publication is the confirmation of the “etiologic diversity of the LBBB.” In other words, not all LBBB are alike and only a slim majority is accompanied by mechanical dyssynchrony. Whether these findings can be extrapolated to other types of electrical dyssynchrony such as right bundle branch blocks or nonspecific intraventricular conduction delays needs to be determined. It is though worth mentioning that QRS width and end diastolic volume predicted up to 55% of the variation in mechanical dyssynchrony (phase bandwidth).

This study raises several important questions. Do LBBBs with mechanical dyssynchrony have worse outcomes than LBBBs without mechanical dyssynchrony? Does targeting LBBB with mechanical dyssynchrony in patients undergoing CRT going to make a difference?

LVMD was found to have significant prognostic implications in a variety of patient groups. In an earlier study on HF patients with LVEF $\leq 45\%$ and no history of myocardial infarction (MI), those with LVMD as measured by tissue Doppler echocardiography had significantly higher risks of cardiac events irrespective of QRS width and LVEF.¹³ Furthermore, in a large cohort of patients with CAD, a recent study demonstrated that measured LVMD had a stronger relationship with all-cause death and cardiovascular death independent of electrical dyssynchrony.^{14,15}

Several studies suggested that the lack of response to CRT in some patients meeting traditional criteria may be due to the absence of LVMD.^{16,17} Using speckle-tracking strain imaging to assess mechanical dyssynchrony, Hara and colleagues noted that presence of LVMD improves CRT response with more favorable long-term outcomes especially in non-LBBB patients.¹⁸ Moreover, earlier studies assessing LVMD by tissue Doppler echocardiography proposed that reversal of ventricular remodeling by CRT is mainly attributable to an improved mechanical synchrony.^{19,20} Finally, in some patients with HF and no electrical dyssynchrony (i.e., QRS < 120 ms), LVMD might still be present and those patients may benefit from CRT.²¹ The evidence suggests that the benefit of CRT is driven by the presence of LVMD, yet in the clinical setting electrical dyssynchrony (aka. QRS width/presence of LBBB) is used as the primary and only target.¹

The above cited evidence was recently challenged by large randomized trials which found that no echocardiographic parameter of LVMD can predict CRT response accurately.^{22,23} Importantly, those two trials assessed LVMD by tissue Doppler echocardiography limited by reproducibility and standardization in methodology. More recently nuclear imaging techniques were developed to allow for a more accurate measurement of LVMD, eliminating the inter- and intra-observer variability that plagued echocardiography-based techniques.²⁴ Assessment of LVMD by MPI has indeed shown to aid in selecting CRT candidates.^{25,26} Using cut-off values of 72.5° for histogram bandwidth (HBW) and 19.6° for phase standard deviation (SD), Boogers and colleagues found 83% sensitivity and 81% specificity for prediction of CRT response.²⁷ Using cut-off values for MPI dyssynchrony parameters could further aid clinical decision making regarding CRT implantation.²⁸ Recently, new cut-off values for the four dyssynchrony parameters obtained by MPI in CRT candidates were determined, and they could possibly be used as part of an algorithm that includes other variables (clinical information, LVEF, etc.) to help come up with a decision about CRT implantation.^{28,29} Unfortunately, to date we lack prospective randomized trials to show the value of such MPI dyssynchrony parameters on clinical decision making for CRT patient selection and CRT lead positioning. Thus future work will be tremendously important to clarify the significance of MPI-derived dyssynchrony in patients with and without electrical dyssynchrony and whether it is of value in guiding treatment pathways.

Disclosure

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