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Electrocardiographic and echocardiographic dyssynchrony parameters that might better predict the response to cardiac resynchronization therapy than QRS morphology and duration

András Vereckei✉

Department of Medicine and Hematology, Semmelweis University, Budapest, Hungary
✉ Correspondence to: vereckei.andras@med.semmelweis-univ.hu
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Cardiac resynchronization therapy (CRT) is an evidence-based effective therapy of symptomatic heart failure with reduced ejection fraction refractory to optimal medical therapy and associated with intraventricular conduction disturbance, that results in a significant electrical ventricular dyssynchrony. However, the non-response rate to CRT is still 20%–40%.[1] The potential underlying causes of CRT non-response are: (1) suboptimal localization of the left ventricular (LV) electrode, far away from the latest activated LV region; (2) placement of the LV electrode over a transmural scar; (3) absence of significant dyssynchrony; (4) suboptimal A-V, V-V delay settings; and (5) too severe heart disease.[2] The most important way to further reduce the number of CRT non-responders is the optimal patient selection for CRT. The current guidelines[3] recommend the determination of QRS morphology, QRS duration and the measurement of LV ejection fraction for patient selection for CRT. The main determinant of CRT outcome is the presence or absence of significant ventricular dyssynchrony and the ability of the applied CRT technique to eliminate it. Moreover, CRT can only eliminate mechanical dyssynchrony due to primary electrical dyssynchrony, it is ineffective in mechanical dyssynchrony without primary electrical dyssynchrony, such as inflammation, myocardial ischemia and myocardial scar.[4,5] The explanation of the still non-negligible non-response rate to CRT is that QRS morphology and QRS duration are not perfect indicators of electrical ventricular dyssynchrony. Therefore, finding better markers of electrical ventricular dyssynchrony may significantly improve the outcome of CRT. There are some promising methods, which can assess the presence of electrical dyssynchrony before CRT implantation in patients who are already on the operating table for CRT implantation, such as the determination of the QLV interval [the interval from the onset of the QRS from the surface electrocardiogram (ECG) to the first large peak of the LV electrogram], or the determination of the right ventricular electrogram-LV electrogram interval in sinus rhythm reflecting interventricular delay. However, these methods can only be applied in the patient who is already on the operating table with invasive procedures.[6,7] The greatest challenge is to find methods that can assess electrical dyssynchrony before the patient is on the operating table, which can determine, which patient should be selected for CRT implantation. Thus, the main purpose of this Special Issue is to discuss non-invasive (electrocardiographic and echocardiographic) methods that may improve patient selection for CRT, may better indicate the presence of electrical ventricular dyssynchrony than QRS morphology and duration, and can be applied before starting the CRT implantation. Since CRT is only effective in mechanical dyssynchrony due to primary electrical dyssynchrony, this Special Issue is mainly focusing on electrocardiographic methods, but also discusses echocardiographic methods, that can detect dyssynchrony. In this Special Issue, we discuss non-invasive methods that can improve patient selection for the conventional biventricular pacing CRT technique, and we are not dealing with newer CRT techniques, such as endocardial LV pacing, multisite pacing, and conduction system pacing (His-bundle pacing and left bundle branch pacing).

In this Special Issue Ghossein MA, *et al.*[8] summarize the significance of vectorcardiographic QRS area determination as a predictor of response to CRT. Vectorcardiographic QRS area is a promising parameter that identifies LV activation delay more accurately than the current ECG criteria and proved to be a better predictor of echocardiographic response to CRT, heart failure hospitalizations and cardiac mortality after CRT, than the combination of QRS duration and QRS morphology.[9,10]

Tapia-Orihuela RKA, *et al*.[11] in this issue are discussing the usefulness of the measurement of the time to intrinsicoid deflection (ID) onset in lateral ECG leads for the estimation of the LV lateral wall activation delay, which can be used as a predictor for CRT response, particularly in patients with nonspecific intraventricular conduction disturbance (NICD) or in patients with left bundle branch block (LBBB) patterns and a QRS duration < 150 ms. They demonstrated[12] that delayed ID onset in the lateral ECG leads predicted LV reverse remodeling after CRT, while in their study pre-implant QRS duration was not a significant predictor of CRT response.

Katona G, *et al*.[13] in this issue discuss the role of novel ECG dyssynchrony criteria in better patient selection for CRT. Vereckei A, *et al*.[14] devised novel LV intraventricular and interventricular dyssynchrony ECG criteria by calculating the absolute value of the difference between the onset of ID in leads aVL and aVF divided by the QRS duration [(aVLID–aVFID)/QRS duration] (for LV intraventricular dyssynchrony) and of the difference between the onset of ID in leads V5 and V1 divided by the QRS duration [(V5ID–V1ID)/QRS duration] (for interventricular dyssynchrony). These novel ECG criteria proved to be useful predictors of clinical response to CRT, particularly in patients with NICD pattern (the second greatest group of CRT candidates), but not in patients with LBBB pattern, who respond well to CRT anyway, thereby improving patient selection for CRT.

Abu-Alrub S, *et al*.[15] in their article, which was originally planned in this Special Issue, but ultimately was published in the October, 2021 Issue of *Journal of Geriatric Cardiology*, are discussing the application of a very promising technique, the electrocardiographic imaging in the assessment of electrical ventricular dyssynchrony. Electrocardiographic imaging combines body surface mapping, using a vest containing about 250 electrodes, with thoracic non-contrast gated computed tomography, that localizes electrode positions and identifies their relations to the heart-torso geometry, and a special software that solves the inverse problem by computing the epicardial potentials from the recorded body surface potentials. This combination ultimately results in the construction of an epicardial activation map, thus, electrocardiographic imaging corresponds to a high-resolution, non-invasive epicardial electrophysiological examination. Ploux S, *et al*.[16] using electrocardiographic imaging found that ventricular electrical uncoupling calculated as the difference in the mean total LV and right ventricular activation times, which is a measure of both interventricular and LV intraventricular dyssynchrony, similarly to our results,[14] could predict clinical CRT response in patients with NICD pattern, but not in patients with LBBB pattern. In another study,[17] the right to left direction of the activation delay vector determined by electrocardiographic imaging was similar in patients with NICD pattern to that of patients with narrow QRS or LBBB pattern, but the magnitude of activation delay vector was significantly greater in patients with LBBB pattern than in patients with NICD pattern and with narrow QRS, and in patients with NICD pattern compared with patients with narrow QRS. The magnitude of right to left activation delay identified best responders to CRT outperforming QRS duration and morphology.

Satish P, *et al*.[18] in this issue demonstrate the potential role of echocardiography in the improvement of patient selection for CRT. After the disappointing results of the PROSPECT trial[19] investigating the value of the earlier conventional echocardiographic criteria of mechanical dyssynchrony in the prediction of CRT response, the current guidelines[3] do not recommend the use of echocardiographic mechanical dyssynchrony criteria for patient selection for CRT. However, there are some potentially promising newer echocardiographic mechanical dyssynchrony criteria, which were not yet tested in randomized trials, but there are already some favorable results with their application. Such newer potentially promising echocardiographic mechanical dyssynchrony criteria are: the presence of septal flash and apical rocking in patients with LBBB pattern, the difference in time to peak radial strain between the LV anteroseptal and posterior walls, mechanical dispersion, calculated as the standard deviation of time from the QRS onset to the peak longitudinal strain of the 16 LV segments, and myocardial work (negative and positive).[1,3,20] The ongoing EuroCRT trial[21] investigating these newer echocardiographic mechanical dyssynchrony parameters will hopefully elucidate the usefulness of these parameters in patient selection for CRT.

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