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Investigating myocardial work as a CRT response predictor is not a waste of work

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This editorial refers to ‘Targeting septal work and viability identifies responders to cardiac resynchronization therapy’[†], by J.M. Aalen et al., on page 3813.

In this issue of the *European Heart Journal*, Aalen et al. report on a prospective study to explore the use of regional left ventricular (LV) myocardial work differences as a predictor of response to cardiac resynchronization therapy (CRT).¹

The concept behind determination of myocardial work as a predictor of CRT response stems from the characteristic contraction patterns in dyssynchronous hearts. Early-activated regions start to shorten before aortic valve opening, thereby stretching later activated regions (Figure 1, blue arrows). This early systolic stretching makes the late-activated regions contract more forcefully due to the local Frank–Starling effect. This stronger contraction causes mid-systolic stretching of the earlier activated regions² (Figure 1, red arrows). Simultaneous invasive measurement of LV pressure and non-invasive measurement of myocardial strains showed low, and sometimes negative, work in early-activated regions and enhanced myocardial work in late-activated regions in animal models and computer simulations of ventricular pacing^{3,4} and left bundle branch block (LBBB).^{5,6} Later work of the Oslo group redefined the negative work, characterized by a typical clockwise course of the pressure–strain loop (Figure 1, red area), as ‘wasted’ work.⁷ A next important step towards clinical application, i.e. the development of a non-invasive way to assess LV pressure, was developed by the same group.⁸ It was shown that peak systolic arterial pressure, measured using the arm-cuff method, in combination with timing of opening and closure of the cardiac valves, using echo-Doppler, provides a reliable systolic part of the LV pressure curve that can be used to plot strain against, and thus non-invasively determine, regional myocardial work.

The prospective randomized trial,¹ performed in 200 patients recruited in five European centres, is a logical next step to evaluate the clinical usefulness of myocardial work to select patients who

benefit from CRT. The investigators show that the difference between myocardial work performed by the septum (S) and LV lateral wall (LW) predicted CRT response (defined as LV end-systolic volume reduction >15% after 6 months) with an area under the curve (AUC) of 0.77 [95% confidence interval (CI) 0.70–0.84]. The predictive value was further increased by adding information on septal scar as obtained by magnetic resonance imaging (MRI) late enhancement in a subpopulation of patients [AUC 0.88 (95% CI 0.81–0.95)]. Importantly, predictive value was as good in patients with QRS duration 120–150 ms as in the entire cohort. Equally important is the observation that work difference alone and combined with septal viability predicted long-term survival without heart transplantation with a hazard ratio (HR) of 0.36 (95% CI 0.18–0.74) and 0.21 (95% CI 0.072–0.61), respectively. Myocardial work is determined objectively and hardly depends on the user, in contrast to, for example, apical rocking and septal flash. The feasibility of the work analysis is undoubtedly high (98%) due to the use of only the basal and mid-LV S and LW segments in the four-chamber view.

What makes myocardial work such a good predictive measure?

We believe the strongest fundament for the predictive power of the S–LW work difference lies in the fact that it incorporates the intra-ventricular difference in strain morphology. It is the typical pattern of contralateral S–LW interactions that causes the S–LW work difference in a heart with LBBB. Importantly, this mechanical behaviour of contralateral stretching and shortening is not only indicative for an electrical activation delay, it also strongly indicates good contractile function of the myocardium. In other words, the septal wall can only be stretched during systole when the LW is strong enough to do so. As a result, a large S–LW work is indicative of the combination of

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gross S–LW electrical dyssynchrony and good overall myocardial viability and contractile function.

Gross electrical dyssynchrony is typical for LBBB and similar conduction abnormalities, such as considerable fascicular blocks. To this purpose, the ECG can also be used. However, QRS duration provides insufficient information on non-electrical myocardial disease substrates, and criteria for LBBB are complicated, variable, and subjective.⁹ Recently QRSarea obtained with vectorcardiography appeared as a promising electrical indicator, with a HR of 0.50 for survival without heart transplant in an ~1500 patient retrospective study.¹⁰ However, QRSarea can only partially assess the other requirement for large differences in myocardial work: viability. The results from the Aalen study suggest that the S–LW work difference incorporates the involvement of LW scar. However, additional information of septal scar from MRI is needed to improve CRT response prediction. The latter may be explained by the fact that in LBBB hearts, septal strain amplitudes are low, and thus hard to distinguish from scar.

The use of the S–LW work difference as an index for CRT selection fits the paradigm of using parameters of mechanical discoordination rather than of mechanical dyssynchrony. Parameters of mechanical dyssynchrony were initially used for CRT response prediction, but no randomized study was able to show the benefit of measuring time-to-peak shortening or velocity beyond ECG markers for CRT selection. Several studies combining computer simulations with clinical data have shown that S–LW differences in time-to-peak shortening or motion are rather aspecific and unable to differentiate

between electrical and mechanical substrates of mechanical discoordination.^{11,12} The definition of septal peak shortening, in particular, was shown to be sensitive to subjective interpretation.

In their study, Aalen et al compared the predictive power of S–LW work difference with that of other indices of mechanical discoordination, i.e. septal flash, apical rocking, and systolic stretch index (SSI; Figure 1). All these measures are based on very similar mechanistic grounds, so any differences in predictive power are unlikely to originate from their theoretical background. The arrows in the figure illustrate that the two kinds of systolic stretch, making up SSI, are directly related to the widening of the LW workloop and the clockwise S workloop. Although the authors claim that S–LW work difference predicted CRT response better than SSI, it is important to mention that this conclusion is drawn from the analysis with LV reverse remodelling as the CRT response definition. The authors do not report any differences between the associations of S–LW work difference and SSI with clinical outcome after CRT. In a recent study,¹³ SSI analysis was prospectively applied to an existing CRT trial database, including 478 patients from 94 international sites, reflecting a real-world clinical setting. High SSI was strongly associated with good clinical outcome after CRT, in patients with both class I and class II guideline indications for CRT. HRs indicated associations between SSI and clinical outcome of the same order of magnitude, or even better, than those between S–LW work difference and outcome reported by Aalen et al., and it should be noted that in that analysis neither MRI late enhancement nor pressure estimation were required.

While the authors are to be complemented on this study, its limitations should also be recognized. An important limitation is that only 125 of the 200 patients underwent an MRI scan, of whom had 61 any scar. Given the fact that the authors distinguished scar between four regions, the number of patients with septal scar is probably much lower. So the 'added value' of septal scar was established in only a minority of patients. Also, the subanalysis of the patients with QRS duration between 120 and 150 ms is based on analysis of 44 patients (27 for those with late gadolinium enhancement cardiac MRI). Therefore, conclusions should be drawn with care.

What would be the way to go? To convincingly prove the advantage of imaging for CRT response prediction, a prospective study of much larger size is needed. The larger size would allow evaluation of the value of imaging in class I and II patients separately as well as in other subcategories, such as patients with (septal) scar. In such a study, some of the other echocardiographic indicators used, such as septal flash, apical rocking, and SSI, should also be included, as well as ECG markers. Importantly, in order to prove that the approaches tested are effective and have additional value beyond the ECG markers, data should be analysed by an echocardiographic core lab as well as by all individual centres separately. This is because the various echocardiographic markers may differ in user dependency. In the Aalen study, the simpler septal flash and apical rocking turned out to be equally good predictors as S-LW work difference, but this may be related to the fact that the analyses were performed in expert core labs. Only if the analysis by all individual centres also proves that one or more mechanical and/or scar imaging modalities does improve CRT response prediction beyond the use of ECG markers, such measurements may be ready to be included in the guidelines for CRT, which currently do not contain any advice on the assessment of mechanical dyssynchrony or discoordination.

In conclusion, the study reported by Aalen *et al.* provides a strong extension of our understanding of CRT response. It is not a waste of work to perform a larger prospective study to prove the clinical feasibility and benefit of a meaningful measure of LV mechanical discoordination, such as S-LW work difference or SSI, as an important additional selection criterion for CRT in the real-world setting.

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