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DOI: https://doi.org/10.1093/eurheartj/eht364

European Heart Journal (2014) **35**, 13–15
doi:10.1093/eurheartj/eht364

EDITORIAL

Mechanical dyssynchrony in CRT: still searching for the Holy Grail

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Online publish-ahead-of-print 17 September 2013

This editorial refers to 'Dynamic relationship of left-ventricular dyssynchrony and contractile reserve in patients undergoing cardiac resynchronization therapy'†, by I. Stankovic *et al.*, on page 48–55

The challenge of non-response to cardiac resynchronization therapy

Cardiac resynchronization therapy (CRT) is a cornerstone of modern day heart failure therapy due to the consistent reduction in morbidity and mortality observed in large-scale clinical trials in patients with a severely reduced left ventricular ejection fraction (LVEF ≤35%), symptomatic heart failure, and a wide QRS complex.[1–5] The individual benefit derived from CRT, however, may vary considerably, with a significant number of subjects demonstrating good or even excellent clinical and echocardiographic improvement and others showing little to no response.[6] A reliable *a priori* identification of these so-called non-responders represents one of the most important challenges for physicians involved in the care of these patients. Some electrocardiographic as well as clinical parameters have so far been identified as being associated with an increased likelihood for response to CRT, including a very wide QRS complex (≥150 ms), left bundle branch block morphology of the QRS complex, lack of ischaemic cardiomyopathy, and female gender.[1,4,6,7] However, so far, no single parameter has been found to be robust enough to exclude *a priori* otherwise eligible patients from receiving a CRT device. As a result, other methods including echocardiographic assessment of ventricular dyssynchrony were probed to identify these patients as well as, conversely, individuals likely to respond to CRT.

Mechanical dyssynchrony and cardiac resynchronization therapy in narrow QRS: Paradise Lost

As the majority of heart failure patients do not present with a QRS width ≥120 ms,[8] it intuitively appeared reasonable to investigate whether echocardiographic parameters of dyssynchrony would be able to identify subjects with narrow QRS likely to derive a benefit from CRT. Indeed, various small studies were able to identify patients who demonstrated a substantial echocardiographic and clinical improvement following CRT.[6,9,10]

Following these single-centre preliminary studies, however, two small-scale randomized clinical trials showed conflicting results regarding the usefulness of echocardiographic parameters in the selection of CRT candidates with narrow QRS complex. In the recently published single-blind NARROW-CRT trial, 117 patients with ventricular dyssynchrony on tissue Doppler imaging were randomized to either CRT-D or ICD (implantable cadioverter defibrillator) implantation.[11] The heart failure clinical composite response (primary study endpoint) improved more frequently in CRT-D than ICD recipients; furthermore, the composite of heart failure hospitalization, cardiovascular death, and spontaneous ventricular fibrillation occurred less frequently in CRT-D patients. In a similar setting, the randomized Cardiac Resynchronization Therapy in Patients with Heart Failure and Narrow QRS (RethinQ) study previously investigated the effect of CRT in 172 patients with a narrow QRS (≤130 ms) and echocardiographic signs of mechanical dyssynchrony as assessed by tissue Doppler imaging.[12] However, contrary to the other studies mentioned above, the primary endpoint (increase in peak oxygen consumption ≥1 mL/kg during cardiopulmonary exercise testing) occurred to a similar degree in both groups.

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† doi:10.1093/eurheartj/eht294.

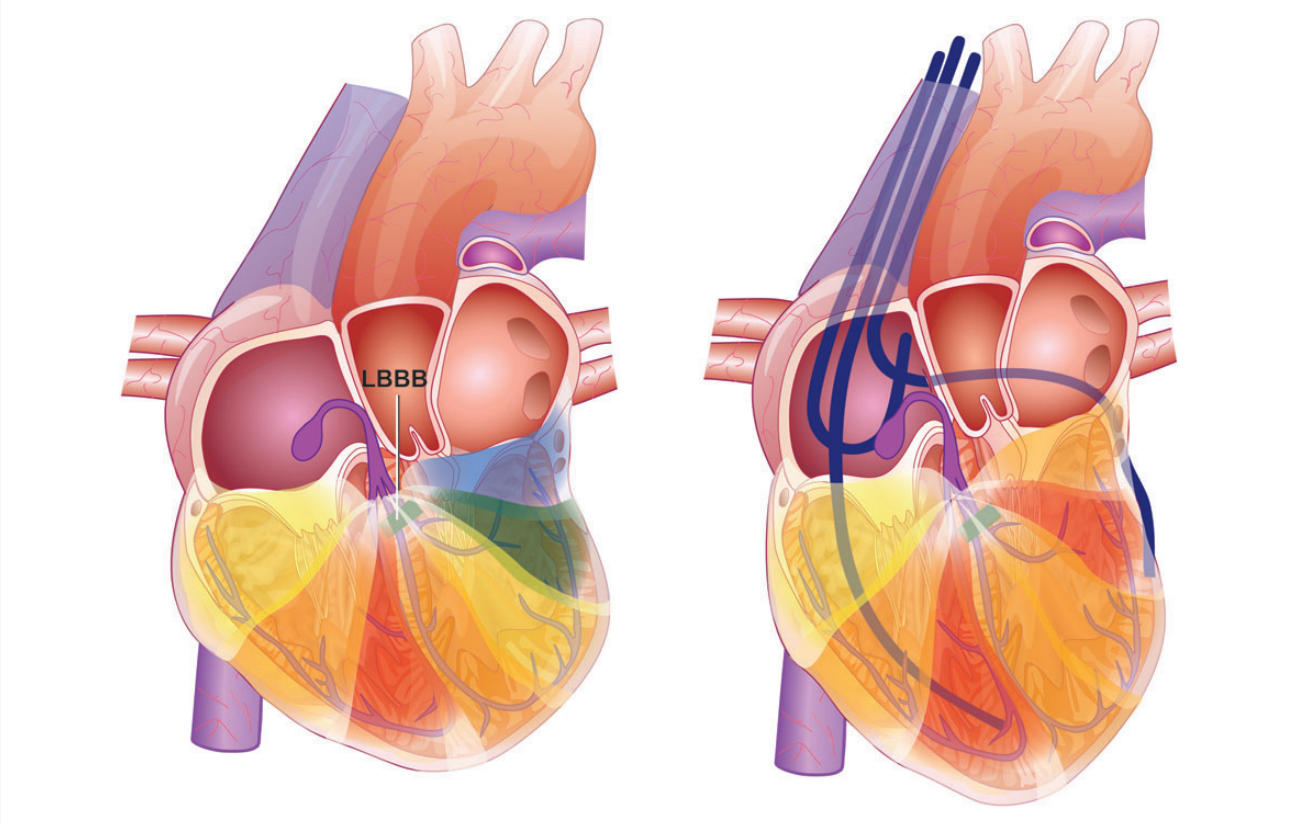

Figure 1 Mechanical dyssynchrony occurs secondary to electrical dyssynchrony [left bundle branch block (LBBB)], which is corrected by cardiac resynchronization therapy. Colours indicate areas of early (red) to late (blue) activation of the ventricles.

Several weaknesses are inherent to both studies, including the low number of patients, a short follow-up period, and, consequently, lack of statistical power for hard clinical endpoints. The recently presented EchoCRT trial was designed to overcome these shortcomings by evaluating the effect of CRT on morbidity and mortality in patients with a narrow QRS complex ($\leq$ 130 ms) and echocardiographic signs of ventricular dyssynchrony in a large randomized double-blind event-driven clinical trial (presented at ESC 2013). The trial was recently terminated early due to futility of CRT in this patient population. Together with the aforementioned studies, one of the most likely although counter-intuitive conclusions may be that correction of mechanical dyssynchrony without electrical dyssynchrony may not be the therapeutic principle behind CRT.

Mechanical dyssynchrony and cardiac resynchronization therapy in wide QRS: more questions than answers

A similar, albeit not as gloomy situation can be encountered regarding the role of dyssynchrony parameters in the (sub-) selection of CRT patients with a wide QRS complex. After various positive small-scale studies had raised considerable hope, the largest prospective multicentre trial (PROSPECT) was unable to find a single echocardiographic measure of dyssynchrony through which patient selection for CRT could be improved.[13] The PROSPECT study enrolled 498 heart failure patients from 53 centres, who fulfilled standard CRT indications (NYHA functional class III or IV, LVEF $\leq$35%, QRS $\geq$130 ms). After 6 months of CRT, the clinical composite score improved in 69% of 426 patients, and LV end-systolic volume was reduced by $\geq$15% in 56% of 286 patients. The investigated 12 (!) echocardiographic parameters, however, demonstrated large variations for the prediction of clinical outcomes (6–74% and 35–91% for sensitivity and specificity, respectively) or reduction in LV end-systolic volume response (9–77% and 31–93%, respectively). Admittedly, the PROSPECT trial has been criticized on several fronts, including the high interobserver variability in echocardiographic assessment, inadequate echocardiographic training, outdated equipment, short follow-up, and residual confounding. Nevertheless, with the only prospective trial being negative, strong evidence for the usefulness of echocardiography for patient selection in CRT is still lacking.

Apical rocking in severely reduced ejection fraction and wide QRS: another marker for mechanical dyssynchrony

Stankovic *et al.*[14] have used apical rocking (ApRock) as a surrogate marker for LV dyssynchrony in patients with wide QRS, which was quantified by measuring the apical transverse motion (ATM), i.e. the motion of the LV apex perpendicular to the LV long axis, in the apical four-chamber view. In their cohort, they prospectively

enrolled 58 CRT candidates according to current guidelines and assessed ApRock as well as LVEF at baseline and during low-dose dobutamine stress echocardiography (DSE). An increase in ApRock during DSE was associated with a pronounced response to CRT (as defined by a decrease in end-systolic volume >10%), but correlated inversely with an improvement in EF after CRT (i.e. the more pronounced the ApRock the less likely was an improvement in EF). Furthermore, and more importantly, a DSE-induced increase in ApRock (but not LVEF) was associated with improved long-term survival during a mean follow-up of 41 ± 13 months after CRT implantation.

The authors are to be congratulated for the careful conduct of their study as well as the meticulous echocardiographic analyses. By doing so, they were able to demonstrate that an increase in dyssynchrony (as assessed by ApRock), but not in LVEF during DSE may predict response to CRT and survival. Mechanistically, this is equally of interest, as it implies that patients with an increase in myocardial contractile reserve resulting in more dyssynchrony may derive a greater benefit from CRT, whereas an increase in LVEF during stress appears to be of lesser value. Differences from similar studies, which did find a positive influence of LVEF augmentation during DSE, may well be, as acknowledged by the authors, due to different definitions of dyssynchrony as well as different definitions of outcome and echocardiographic 'response'.

Implications for daily clinical practice

Despite the well presented data and the convincing results, the ultimate question for clinicians involved in the care of heart failure patients will be: how far do the results of the study of Stankovic *et al.* alter the way we will select patients for CRT? Indeed, certain parallels with the aforementioned hypothesis of CRT in narrow QRS with ventricular dyssynchrony cannot be neglected, with this study equally being rather small scale, single centre, and observational in nature. The importance of the results, as clear and intuitive as they may seem, should hence not be overestimated but should be regarded as 'hypothesis-generating' at best.

Will patients with an absence of ApRock at baseline or during DSE be denied a CRT device, even if they otherwise fulfil current guidelines? Conversely, should a CRT device be implanted in patients just based on ApRock who otherwise would not qualify? In both scenarios, the answer at this point in time clearly is: no. Indeed, the host of positive data from large-scale landmark trials justifies CRT implantation in patients meeting current guideline criteria, irrespective of echocardiographically measured dyssynchrony. Even more importantly, however, CRT implantation cannot be recommended in patients who otherwise do not qualify for it, e.g. patients with preserved EF or narrow QRS complex, just based on positive ApRock on echocardiography. Observational data from the past have indicated that it may indeed be possible not only to have a neutral effect with CRT, but that one may in fact induce harm by biventricular stimulation in certain patients. The latter has just been confirmed with the highest level of evidence, i.e. in the context of the EchoCRT study. These findings impressively demonstrate how a beautiful hypothesis, i.e. a beneficial effect of resynchronization in mechanically dyssynchronous hearts, can be proven wrong by ugly facts. Whether the same is true for ApRock and in which setting, of course, cannot be determined at this point in time. To evaluate this, confirmation in a large-scale randomized trial powered for hard clinical outcome parameters of morbidity and mortality is indispensable, possibly in the sense of a 'PROSPECT-2' trial. The unexpected experience from EchoCRT serves as a clear and present reminder that this highest level of evidence is necessary and needs to be awaited before altering clinical practice according to newly defined selection criteria for CRT.

Conflict of interest: J.S. has received research support from St. Jude Medical and consulting honoraria from Biotronik, Medtronic, Sorin, and St. Jude Medical. C.L. has received research support from St. Jude Medical, Medtronic, Sorin, Biotronik, and Boston Scientific and consulting honoraria from Biotronik, Medtronic, Sorin. and St. Jude Medical.

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