Criteria predicting response to CRT: is more better?

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This editorial refers to ‘Validation of an echocardiographic multiparametric strategy to increase responder patients after cardiac resynchronization: a multicentre study’1, by S. Lafitte et al. on page 2880

The quest for the perfect parameter to predict response to cardiac resynchronization therapy (CRT) suffered a major setback when two prospective trials (PROSPECT and ReTHINQ) demonstrated limitations in the potential clinical value of the much-touted tissue Doppler velocity-based criteria.1,2 Until then there was a steady stream of ‘highly accurate’ predictors of response to CRT.3–5 Notwithstanding the bevy of potential technical issues plaguing these studies, they did successfully raise serious doubts about how the clinical community and vendors were going about identifying patients likely to respond to CRT. We have always been of the opinion that attempting to solve a complex issue such as predicting response to CRT by means of a single binary parameter, such as tissue Doppler velocity-derived delays, is overly simplistic. For what it is worth, several studies over thousands of patients do indicate some value to testing dyssynchrony using tissue velocities.6 In a similar vein, our take on PROSPECT and ReTHINQ is that they do not convincingly repudiate the notion that a dyssynchronous heart is more likely to respond to CRT. In that regard it is heartening to see a study examine the value of using multiple parameters to predict response to CRT.

Lafitte and colleagues examined parameters of dyssynchrony at multiple functional levels including atrioventricular, interventricular and intraventricular.7 The strengths of this study include: size (n = 181), multicentre design, all patients fulfilled standard clinical criteria for CRT (New York Heart Association class II–IV, ejection fraction <35%, and QRS width > 120 ms) and a large proportion of ‘responders’ to CRT (57%). The authors used a relatively well-validated index of response, namely a ≥15% decrease in left ventricular end-systolic volume. Feasibility of measurement was high (~80%) at acceptable variability of ~9%. The primary incremental finding of this study is that false-positive predictive rates decreased from ~14% when using one parameter to ~1% when using four parameters. Using ≥3 parameters resulted in a specificity >90% and a positive predictive value of >65%. Only 4% of patients with no positive criteria responded to CRT. Lastly, the authors noted a relationship between reverse remodelling and number of parameters found to be positive, i.e. patients with more dyssynchrony demonstrated more pronounced reverse remodelling after CRT.

These strengths are tempered by a number of limitations. This is an observational study. Whether this study cohort is representative of the general population or the population enrolled in the large CRT trials is unclear. Non-responder rates were somewhat higher than those previously reported (~50% vs. 30%, respectively).8,9 The proportion of patients with ≥3 echocardiographic parameters was low. Sensitivity rates were low. Some of the parameters in their algorithm, such as septal to posterior wall motion delay by M-mode, may be challenging to obtain and may be ineffectual in an infarct population. Other parameters, such as systo-diastolic overlap, are ill defined and not well validated. The authors also use tissue velocity-based indices that have been much maligned (with or without good cause) after PROSPECT. Indeed, some work suggests even visual assessment of dyssynchrony is superior to tissue velocity-based analysis.10 Other echocardiographic parameters such as severity of mitral regurgitation, global diastolic function, or regional diastolic dyssynchrony were not assessed. This paper also does not inform the readers as to whether the parameters tested provide independent and/or incremental value over each other. It may be more informative to test multiple independent parameters of dyssynchrony. Atrioventricular delay is optimized using an unconventional and unvalidated method. The value of strain is not evaluated, although there is recent and increasing evidence that regional strain may be superior to tissue velocity in assessing dyssynchrony.10,11

This study is rather echo-centric; however, the general concept of more is better can be extended to be more patient-centric. The authors indicate that ischaemic heart disease and shorter QRS duration were more likely to be associated with lack of response to CRT. Yet they did not include these or other previously described parameters in their multiple parameter model to improve response to CRT. The authors nudge the concept of the multiparametric approach but restrict themselves to echo parameters.

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We fully endorse a patient-centric, multiparametric approach to assessing likelihood of response to CRT. Such an approach would take into consideration several factors with potential influence on the outcome post-CRT. We summarize our proposal in Figure 1. This approach is based on our premise that response to CRT is not a dichotomous phenomenon although almost all echo-based publications to date seem to treat it as such. Instead we suggest that the likelihood of response to CRT is a continuum that ranges from a low likelihood of response to a high likelihood of response to CRT. Such a model would take into consideration a multitude of clinical, electrocardiographic, echocardiographic, electrophysiologic, and haemodynamic parameters. These parameters would be classified into salutary and adverse, with the notion that a preponderance of salutary factors or the absence of adverse factors would trend the patient towards the ‘high likelihood of response’ end of the continuum, while the converse, i.e. several adverse elements and few salutary factors, would put the patient at the ‘low likelihood of response’ end of the spectrum.

In such an analysis, presence or absence of mechanical dyssynchrony would be important but not the sole parameter of interest. The presence of significant dyssynchrony in the setting of a large scar burden may be clinically meaningless. Similarly, borderline or no dyssynchrony by current criteria may suggest a higher likelihood of response to CRT. Such a model would take into consideration a multitude of clinical, electrocardiographic, echocardiographic, electrophysiologic, and haemodynamic parameters. These parameters would be classified into salutary and adverse, with the notion that a preponderance of salutary factors or the absence of adverse factors would trend the patient towards the ‘high likelihood of response’ end of the continuum, while the converse, i.e. several adverse elements and few salutary factors, would put the patient at the ‘low likelihood of response’ end of the spectrum.

indices have some value, should prompt us to consider adding strain analysis to the assessment of dysynchrony. \[10,11\] Although the focus has generally been on displacement and deformational indices of dysynchrony, three-dimensional echocardiography-based assessment of regional volumetric changes may also be of value. \[12\] Lafitte et al. do not test or discuss the rationale or potential inaccuracies of tissue velocity analysis except to say that they had better reproducibility. Is that because observers at all institutions measured the same peak but that particular peak has nothing to do with regional mechanics? A degree of concordance among observers does not always imply that they are all measuring the correct mechanical phenomenon. What peak to measure and when in the cardiac cycle will probably need more sophisticated physiological studies. We have previously suggested that noisy or unreliable signals should not be used for analysis of dysynchrony. \[13\]

Taking a highly contrarian view, one could suggest that this study has very limited value since almost all patients fulfilled clinical criteria justifying CRT, namely heart failure symptoms, low ejection fraction, and prolonged QRS duration. One could argue that this particular population may not need additional analysis prior to proceeding to CRT. In this regard it would have been more informative if the authors had tested their criteria on patients with borderline criteria, in particular those with narrow QRS complexes, i.e. the ReTHINQ population.

Lastly, how would we use this study in a routine clinical practice? The only way for the general community to know how this multiparametric approach works is actually to test it. We hope to implement it in our patients to ascertain feasibility and efficacy in our population. We agree with the authors that a larger study would offer more rigorous evaluation of this approach. However, their current study does point us in a new, and hopefully, more effective direction with regards to predicting response to CRT.
A 58-year-old female presented with severe chest pain following news of bereavement. ECG suggested myocardial ischaemia, and troponin-I (2.19 μg/mL) was raised. Left ventricular (LV) echocardiogram (Panel 1) showed apico-midventricular akinesia and basal hyperkinesia. Forty-eight hours later, coronary arteries were normal (Panel 2a and 2b) and LV angiogram (Panel 3a and 3b) showed mid-ventricular ballooning and apico-basal hyperkinesia. Twenty-four-hour urinary catecholamines were normal. The LV recovered in 4 weeks (Panel 4a and 4b). Stress-induced cardiomyopathy (SCM) was diagnosed.

The two patterns of LV dysfunction (tako-tsubo and reverse tako-tsubo) in SCM may occur in the same patient during two different episodes of stress separated by long durations. This case, for the first time, demonstrates that SCM that may start as apical-midventricular dysfunction may evolve into mid-ventricular dysfunction over hours before recovering completely over weeks.

This may explain the different patterns of myocardial dysfunction seen in SCM. The initial pattern of injury is reportedly apical, as in our patient. The temporal variation in the hitherto unknown evolution of the LV dysfunction, which has never been examined, may range from few minutes to weeks. The pattern of LV dysfunction may thus depend on the timing of the angiography in relation to speed of this evolution.

"^{125}I"-meta-iodobenzylguanidine myocardial scintigraphy suggests that a base-to-apex incremental abnormality in myocardial sympathetic innervation may be a primary defect in tako-tsubo cardiomyopathy. This provokes a graded myocardial stunning, worst affecting the apex, during a catecholamine surge. The ebb in catecholamine level may interact with this gradient in a manner leading to a quicker apical recovery compared with the mid-ventricular myocardium giving rise to the reverse tako-tsubo pattern.

Supplementary material is available at European Heart Journal online.