Mechanical dyssynchrony and super-response to CRT

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Cardiac resynchronisation therapy (CRT) is a well-established and important treatment option for patients in heart failure, which improves survival, morbidity, and quality of life.[1–3] However, CRT is not an effective treatment for all patients and despite all the research that the selection criteria is based on,[4] approximately 30% of patients who undergo CRT therapy are classified as non-responders.[5] CRT is costly and not without risk; therefore, finding ways to predict responders to CRT is of clinical interest.

CRT aims to improve cardiac output and promote reverse modeling by improving mechanical synchrony. The current ESC guidelines recommend CRT for symptomatic heart failure patients in sinus rhythm, with an LVEF $\leq 35\%$ and LBBB with a QRS duration of > 130 ms.[4] However, a wide QRS indicates electrical dyssynchrony, but not necessarily mechanical dyssynchrony. Previously assessed markers of mechanical dyssynchrony are not included in the current selection criteria.

There have been many studies published investigating imaging parameters as predictors to CRT response with varying degrees of success. However, comparing the studies is complex due to the varying definition of a CRT responder. Definitions used include an increase in LVEF, change in end-systolic volume, and change in New York Heart Association Symptom Class, with many studies using a combination of all these parameters. In general, the patients labeled as non-responders have no measurable improvement, but it is unknown if CRT has prevented further deterioration in this group.

Another issue when using imaging parameters as a marker of response is the associated reproducibility of the technique, which is often not addressed. For example, some studies use an improvement in Simpsons biplane LVEF of 5% as the definition of response to CRT, even though the reproducibility of this technique is approximately 10%.[6]

Mechanical dyssynchrony can be measured by different cardiac imaging techniques, including echo (2D M-mode, spectral Doppler, and tissue Doppler imaging parameters), gated single photon emission computed tomography myocardial perfusion imaging (gSPECT MPI), radionuclide ventriculography (RNVG), and magnetic resonance imaging (MRI). However, for measures of dyssynchrony to be used routinely in clinical practice, it is clear that standardization and a normal cut-off will need to be established for each parameter.

Echo dyssynchrony parameters have been widely investigated for predicting CRT response. Small echo studies suggest there is a significant difference in dyssynchrony between responders and non-responders before CRT implantation, as described in the review by Hawkins et al[7]. Despite promising results in single center studies, the results have not been reproduced in larger multi-center trials. For example, in the PROSPECT trial,[5] a number of dyssynchrony measurements derived from echo were investigated as predictors of CRT response. The study concluded that none of the parameters could accurately predict response. This result may be partly due to high inter- and intra-operator variability. However, newer echo parameters such as apical rocking, septal flash, systolic stretch, work difference between septal and lateral wall, and septal deformation patterns have produced some promising

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results for predicting CRT response, even in terms of mortality and hospital admissions.[8–11]

Mechanical dyssynchrony can also be measured using cardiac MRI. However, Cardiac MRI remains expensive and time-consuming, with limited access in some centers for cardiac indications, and is unsuitable for some patients who have an older pacemaker.

In nuclear cardiology, dyssynchrony can be measured using RNVG or gSPECT MPI. It is measured from the average of many cardiac cycles, unlike echo where it is measured from a single beat. Dyssynchrony studies using RNVG imaging have demonstrated some interesting results for predicting CRT response.[12,13] Chen et al proposed using phase SD and bandwidth of the phase histogram as measures of dyssynchrony using gSPECT MPI.[14] Mean phase, phase SD, and phase bandwidth can be easily measured from gSPECT MPI, although the normal range may be software dependant. To create the phase image, a Fourier transform is applied to the time-activity curve from each voxel of the gSPECT MPI image over the cardiac cycle, with the resulting phase values relating to the time of myocardial contraction. Using this technique has the added advantage of providing a measure of myocardial perfusion, as well as LVEF and dyssynchrony. Furthermore, gSPECT MPI is a well-established, low cost, reproducible, and readily available technique. Although there is the disadvantage of the radiation dose when compared to echo and MRI, the development and increased use of solid-state gamma cameras in nuclear cardiology has resulted in a significantly lower radiation dose to the patient compared to the conventional gamma camera. Results from the Vision-CRT trial[15] demonstrated that improvement in gSPECT MPI dyssynchrony parameters predict clinical outcome for patients undergoing CRT.

Some patients, known as ‘super-responders’, experience dramatic improvements after CRT, including the normalization of LVEF in some cases.[16] From the MADIT-CRT trial cohort,[17] predictors of super-response to CRT were investigated for patients with mildly symptomatic heart failure. The results of the trial suggested that super-response to CRT, defined as the top quartile of patients with LVEF improvement at the 12 month follow-up, was associated with a reduced risk of subsequent cardiac events. They also found six predictors of super-response, including QRS duration and left atrial volume. There was no relation between left ventricular volumes and super-response in this patient cohort.

In the current edition of this journal, the paper published by Mesquita et al[18] expands on the results of the Vision-CRT trial[15] and investigates clinical parameters and phase SD to determine if there is an association with super-response following CRT. Several studies have investigated gSPECT dyssynchrony parameters for predicting response to CRT,[15,19] but this is the first published work investigating these parameters for super-response to CRT. One of the strengths of this study is that it is a multi-center trial carried out across ten sites from eight countries. The gSPECT images were also processed in a centralized core lab, removing the issue of variability between software vendors.

In this study, super-response was defined as an improvement of LVEF $> 15\%$ and NYHA class I/II, or reduction in LV end-systolic volume $> 30\%$. As expected, the presence of diabetes, history of CAD, and previous myocardial infarction were significantly less common in the super-responder group compared to the other groups. At baseline, QRS duration, LVEF, LV end-systolic volume, and phase SD were not significantly different among the groups. This research suggests that phase SD after CRT is associated with super-response, but baseline phase SD from gSPECT MPI is not an independent predictor of super-response.

Interestingly, the findings differ from the MADIT trial results[17] where QRS duration was found to be a predictor of super-response. One potential explanation for the difference in results is the differing proportion of patients with ischemia included in each trial, as it’s known that patients with ischemic etiology are less likely to be super-responders.[20] There are also differences in the patient selection criteria, average patient age, time to follow-up assessment, and definition of super-responder that could partly explain the difference in results. Future follow-up of this patient group with survival analysis will be of interest.

At present, there is not enough evidence to suggest that CRT selection criteria should include mechanical dyssynchrony. The literature to date suggests that there may not be one single predictor of CRT response. Instead, a multi-faceted approach may be the best way to optimize the selection criteria. Combining phase parameters and more novel approaches, for example, contraction patterns, image texture, and more advanced dyssynchrony measurements, with known predictors such as scarring and lead placement, may have potential to improve the success rate for CRT.

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