Mechanical Dyssynchrony with Gated Myocardial Perfusion SPECT: Reproducibility is the Key

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The benefits of cardiac resynchronization therapy (CRT) for patients with heart failure with a reduced left ventricular ejection fraction (LVEF) and coinciding interventricular dyssynchrony are long standing. CRT modifies the electromechanical delay associated with heart failure and improves ventricular function and patient outcomes. Multiple trials have demonstrated benefit with CRT in this population. Landmark trials including MADIT-CRT,[1] RAFT,[2] and MIRACLE-ICD[3] all demonstrate the positive effects of CRT in appropriate patients.

Currently, the ACC/AHA/HRS guidelines identify patients who benefit from CRT based on evidence of moderate to severe systolic dysfunction with LVEF $\leq$ 35%, NYHA class III or IV symptoms, and ECG demonstrating left bundle branch block (LBBB) morphology with QRS duration of >150 ms.[4] The ECG findings of QRS duration and LBBB morphology are directly correlated with severity and prognosis of heart failure. QRS durations of $>$ 150 ms are correlated with systolic dysfunction in 75.7% of patients and QRS durations of $>$ 160 ms are associated with 58% mortality over 3 years.[5] Additionally, QRS duration is a quantitative surrogate of LV systolic function and mortality risk as studies indicate worse function and outcomes coincide with progressive lengthening of the QRS duration. The QRS duration also demonstrates the likelihood to respond to CRT therapy as multiple studies demonstrate maximal benefit with therapy associated with QRS durations of $>$ 150 ms compared to those with QRS durations 120 to 140 ms.[4]

The morphology of interventricular delay as seen in the ECG is also correlated with physiologic mechanical disruption. Conduction in the setting of LBBB activates the interventricular septum followed later by contraction in the lateral walls while the septum is subsequently relaxed. This dyssynchrony of LV contraction between the septal and lateral walls leads to decreased contraction efficiency.[6] In fact, the LBBB pattern compared to the RBBB pattern is associated with improved survival, LV function, and symptom improvement following resynchronization.[7] Also, this benefit comes directly from CRT as studies demonstrate a significant reduction in heart failure exacerbations and mortality compared for patients with LBBB with ICD implantation alone.[1]

The ECG is also useful in evaluation improvement following CRT. The post-CRT ECG demonstrates usually significant change in bundle branch morphology with conversion to RBBB morphology associated with biventricular pacing as well as some narrowing in the QRS. These findings can also predict response to therapy. Demonstration of R wave in V1 and S wave in lead I following CRT was shown to be associated with fewer deaths, heart failure exacerbations, LV assist device

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implants, or transplants in a year compared to those who did not demonstrate these ECG findings following CRT.[8]

However, and despite its proven benefits, approximately one third of patients who undergo CRT do not improve their heart failure symptoms and are, thus, considered non-responders. In this sense, there are data that assessment of mechanical dyssynchrony by echocardiography can potentially improve patient selection and lead to an overall reduction in the non-responder rate in observational studies.[9]

Importantly, phase analysis of gated myocardial perfusion imaging (MPI) with single-photon emission computed tomography (SPECT) is a validated tool for the evaluation of LV dyssynchrony, and especially, the histogram bandwidth and phase standard deviation (PSD) have been shown to correlate well with tissue Doppler imaging (TDI) in patients with heart failure, reduced LV systolic function, and wide QRS complex.[10,11] SPECT is an attractive method for this indication because additionally, it can provide assessment of the location and extent of LV scarring. This is potentially clinically relevant as patients with replacement fibrosis are known to benefit less from CRT, in particular when the scar tissue is in the vicinity of the LV lead.[12]Therefore, knowing this information ahead of time may aid in positioning the LV lead in a viable segment with the latest mechanical activation to yield optimal CRT results.

Consequently, gated MPI with phase analysis has been the subject of a number of research studies, including the ongoing VISION CRT trial, a non-randomized, multicenter study, sponsored by the International Atomic Energy Agency (IAEA) aiming at investigating whether gated MPI techniques could improve the clinical response of heart failure patients to CRT.[13] In their preliminary results that included 195 patients with ischemic (N = 60) and non-ischemic (N = 135) cardiomyopathy (LVEF $\leq$ 35%), the authors observed that change in LV PSD from baseline was the main predictor of CRT response, whereas on-target LV lead placement was not a significant predictor.[13] However, one important limitation of this study is that LV lead positioning was not SPECT-guided at the time of CRT.

Nevertheless, these preliminary results are important and highlight the potential prognostic value of PSD for further investigation in randomized trials. In this issue, the investigators of VISION CRT evaluated the inter-site agreement (compared to the core lab) for LV volumes, EF and PSD using the Emory Cardiac Toolbox Version 4.0 (Emory Cardiac Toolbox, Atlanta, GA) from the gated MPI SPECT before and after CRT, an important next step to assure the reproducibility of imaging findings, which is key when it comes to important clinical decision-making.[14] Overall, compared to the core lab, the authors observed strong correlations of LV end-systolic volumes ($r = 0.95$; $P < 0.001$), LVEF ($r = 0.81$; $P < 0.001$), and even LVPSD ($r = 0.73$; $P < 0.001$) obtained by the individual sites. However, the mean difference for LVPSD in the Bland–Altman plot was 5.08° (SD 18.2°), whereas the median values of LVPSD between sites and the core lab was $\sim$ 12% different (55.0 IQR [33.3 to 71.5] vs 48.5 IQR [27.3 to 66.8]; $P < 0.001$). Moreover, the correlation of LVPSD change pre- and post-CRT was moderately strong only ($r = 0.47$; $P < 0.001$).

This is an important limitation because implementation of this measurement will require more accurate assessments. For example, in their previous work, LV dyssynchrony was defined by the authors as LVPSD > 43°,[13] thus, if this cutoff were to guide CRT in future trials, inevitably a proportion of patients will have significantly different results depending on the site. Obviously, this drawback is not unique to PSD and also applies to LVEF assessment.

Fortunately, the authors have already identified this as an issue, and pointed out to the need for improving this important measurement, which seems to be related to a mixture of technical, post-processing, and operator-dependent issues. However, of these proposed workarounds, adjustment of post-processing parameters and manual definition of the valve plane seem to be the only ones that might be subject to improvement of the technique, whereas other factors related to the limited spatial and temporal resolution of gated SPECT imaging might be more challenging to overcome.

Another limitation of the study is that the fact only patients in sinus rhythm were included in the trial per protocol; thus, it will be important to assess the effect of arrhythmias in future studies, particularly atrial fibrillation and/or frequent ventricular ectopy, as dysrhythmias can result in a reduction of counts in the late frames, and potentially cause errors in the measurement of LV dyssynchrony.[15]

In summary, improvement of inter-site reproducibility will be key for future studies, including addressing the main question of whether phase analysis from gated SPECT (especially at baseline) can improve CRT results beyond the well-established ECG-defined dyssynchrony and clinical criteria assessments.

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