Quantitative Radionuclide Assessment of Cardiac Dyssynchrony: Breakthrough in Patient Selection for Cardiac Resynchronization Therapy for Refractory Heart Failure?

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An estimated 5.7 million adults with heart failure (HF) currently burden the human, medical and financial resources of the United States. By 2030, this number is expected to increase to more than 8 million. In 2012, the total cost of HF in the United States was estimated at $30.7 billion which is expected to increase to $69.7 billion by 2030. HF contributes substantially to mortality and is documented on 1 in 9 death certificates in the United States. [1] HF mortality 1 year after diagnosis appears to be declining in the 21st century according to Medicare data: 31.7% in 1999 to 29.6% in 2008. [2] These improvements have been attributed to evidence-based approaches in the management of HF, including guideline-directed medical therapy, coronary revascularization, implantable cardioverter-defibrillators, and cardiac resynchronization therapy (CRT) in which both the right and left ventricles are paced synchronously to augment cardiac output. [1]

With a reported NNT of 24, CRT substantially reduces HF mortality at 1 year. [3] The MIRACLE trial (2002) was the first double blinded CRT trial, and showed improvement in New York Heart Association (NYHA) functional class, quality of life, and ejection fraction as well as reduced HF hospitalizations in patients with HF, LVEF <=35%, and QRS duration >= 130 msec. [4] Several landmark trials followed, including COMPANION, CARE-HF, RAFT, and MADIT-CRT which demonstrated improvements in pathophysiologic HF indicators, HF admissions, and all-cause mortality. [5–8] These trials included patients with markers of dyssynchrony including prolonged QRS duration, with the CARE-HF trial requiring echocardiographic evidence of dyssynchrony for those with QRS duration 120 to 150 msec. [6] Society guidelines accordingly began recommending CRT for select patients in 2008. The American College of Cardiology, the American Heart Association, and the Heart Rhythm Society currently recommend CRT for patients with LVEF <=35%, NYHA class II, III, and ambulatory class IV symptoms, and evidence of dyssynchrony with QRS duration of >= 120 msec with stronger recommendation for QRS duration >=150 msec and those with LBBB. [9–11]
Unfortunately, 30-40% of CRT treated patients are reported to have either no response or worsened HF. Limitations of patient selection technique and definition of CRT response likely contribute to high non-response rates. [12–14] In this issue of the Journal of Nuclear Medicine, Badwhar et al present a novel and effective approach to determining which patients most likely benefit from CRT using new measures of both intra-LV and inter-ventricular dyssynchrony by planar equilibrium radionuclide angiography (ERNA). [15] This cardiac blood pool based approach utilizes the first harmonic curve fit by phase and amplitude for each ERNA pixel as a surrogate for the timing and magnitude of regional contraction relative to the ECG R wave gating signal. In a previous report [16], ERNA derived phase angle (Ø), and amplitude quantitate regional contraction timing and magnitude and are the basis for synchrony and entropy parameters. Synchrony is the vector sum of all amplitudes based on the angular distribution of Ø divided by the scalar sum of the length of all vectors, and Entropy measures the disorder in the region of interest. These parameters were previously reported to be superior to SD of Ø to distinguish hearts with normal, aneurysmal, diffuse dysfunction and severe regional dysfunction. [16]

In the current study, ERNA measurements of LV synchrony (LVS) and interventricular synchrony (IVS, the difference between mean LVS and RV synchrony), were strongly predictive of response to CRT of NYHA symptom class. Lower baseline LVS and higher baseline IVS predicted greater response to CRT with larger improvements in NYHA functional class. These findings are particularly relevant in patients with QRS duration of 120-150 msec with LBBB and those with QRS duration >=150 msec with non-LBBB morphology, in whom CRT is less strongly recommended.

Badwhar’s planar ERNA approach has several advantages compared with other imaging techniques used to evaluate dyssynchrony and predict CRT response. In the past, numerous echocardiographic approaches have attempted to identify patients most likely to benefit from CRT. A major weakness of echocardiographic techniques is the lack of reproducibility. While echocardiographic techniques assess dyssynchrony in either longitudinal or circumferential direction, the lack of a composite 3D echocardiographic assessment of ventricular dyssynchrony limits its effectiveness.
Although 3D echocardiography reportedly enhances accuracy and reproducibility of the assessment of LV volumes and EF as well as assessment of myocardial dyssynchrony of the cardiac ultrasound approach [17,18], its use in contemporary practice remains limited. Thus, an effective echocardiographic strategy for predicting CRT response remains elusive, and the American Society of Echocardiography recommends strongly against withholding CRT based on lack of echocardiographic evidence of dyssynchrony. [19] Cardiac MRI is another strategy to evaluate dyssynchrony; however, widespread use is limited by cost, access issues, and incompatibility of many pacemaker and ICD devices with MRI. [20] By contrast, radionuclide imaging techniques such as planar ERNA can be safely performed in patients with pacemaker and ICD devices, and are highly reproducible, semi-automated with limited operator intervention.

Radionuclide–based dyssynchrony assessment utilizing phase analysis of gated SPECT myocardial perfusion image (MPI) data [21] has gained widespread recognition since its initial report of clinical utility for of acute CRT response predictive of long term HF outcome [22,23]. Both blood pool and MPI techniques offer the advantage of excellent statistical sampling of up to hundreds of beats for quantitative assessment of dyssynchrony. Distinct from the ERNA blood pool based approach utilizing the first harmonic curve fit by phase and amplitude for each ERNA pixel as a surrogate for the timing and magnitude of regional contraction relative to the ECG R wave gating signal, as reported in this issue of the Journal by Badwahr, ECG-gated SPECT MPI assessment of dyssynchrony relies on quantifying regional temporal differences in myocardial thickening of 600 myocardial voxels of myocardial count density during the summated cardiac cycle [21,22]. With this approach, acute change in synchrony pre- and post-CRT with a single injection technique with Tc-99m sestamibi has been prospectively studied and the highly predictive markers of improved short-term clinical outcomes include presence of baseline dyssynchrony, scar burden of < 40% and concordance of LV lead with the site of latest activation. [22] The presence of baseline dyssynchrony on gated SPECT as a predictor of CRT response is similar to the predictive value of low LVS by planar ERNA noted in the current study. We now understand assessment of dyssynchrony alone as a predictor of CRT response patients with medically refractory HF will be futile, as evidenced by Echo-CRT. [24] In addition to
dyssynchrony, the major predictors of CRT response include scar burden and LV lead concordance with the site of latest activation. [25,26] The lack of assessment of these important determinants of CRT response from an ERNA based approach appears disadvantageous. However, a limitation SPECT MPI based techniques for prediction of HF response to CRT includes attenuation and perfusion abnormalities that could result in under sampling of the myocardium, especially in the basal segments. The lack of dependency on geometric boundaries and the greater temporal resolution inherent to ERNA are advantages compared to MPI techniques for assessing dyssynchrony, especially interventricular dyssynchrony which is poorly assessed by SPECT due to low RV count density. Additionally, ERNA is the most reproducible technique for assessment of the gatekeeper variable LV EF in patients with HF.

The incremental value of these radionuclide approaches to assess HR response to CRT of new measures of biventricular and inter-ventricular dyssynchrony and the value of the acute response of these radionuclide indices of dyssynchrony by serial studies of ERNA or gated SPECT MPI are important hypotheses which will require large confirmatory clinical trials. Further research should include additional heart failure indicators such as LVEF, LV and RV volume indices by SPECT ERNA, MIBG neurohormonal activation [27,28], on the 6 minute walk, HF hospitalizations, the quality of life, and mortality.

A new window of opportunity confronts us as we grapple with the massive, looming clinical and economic burdens of HF in the 21st century. Carefully planned large confirmatory clinical trials are warranted to evaluate the available evidence which suggests quantitative radionuclide methods to measure cardiac dyssynchrony and the acute quantitative responses to CRT with ERNA and / or ECG-gated SPECT MPI are effective strategies to predict long term response of HF to CRT. Application of these techniques has the potential to prevent or limit futile CRT device implantations, expand access to CRT to those most likely to benefit, and improve the clinical and cost effectiveness of CRT for medically and surgically refractory heart failure.
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