EDITORIAL

Cardiac dyssynchrony: We have the tools. It is time to use them

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It has now been over a decade since the appearance of the first clinical report demonstrating improvement in symptoms after cardiac resynchronization therapy (CRT).[1] CRT was initially applied to patients with depressed left ventricular systolic function, severe congestive heart failure (CHF) and a wide QRS on the electrocardiogram. Much has been learned since then.

As additional reports filtered in, it became apparent that not only did symptoms improve but also measurable changes in left ventricular volumes, i.e., reverse remodeling, increases in left ventricular ejection fraction (LVEF), reduction in the severity of mitral regurgitation, decreases in the occurrence of severe heart failure, and most notably, improved survival were documented.[2-5]

Standard criteria for the application of CRT initially included an LVEF <35% or 30% (depending on the study), Class III or Class IV CHF and a QRS duration of 120 or 130 mseconds, again depending on the study. More recently, clinical trials have shown that the benefit of CRT can be extended to patients with Class II CHF. Although the initial trial in patients with class II CHF only showed a reduction in the subsequent recurrence of CHF requiring hospitalization, more recent data have also demonstrated a mortality benefit of CRT in patients with class II CHF.[6] When first introduced, CRT was added to both maximum medical therapy and defibrillator (ICD) therapy. Interestingly, there are data that show that CRT reduces or delays mortality even in the absence of an ICD.[7] Furthermore, the benefits of therapy have been indistinguishable between patients with ischemic and non-ischemic cardiomyopathies.

Clearly, this is a robust therapy.

However, as with ICD therapy, itself, not all recipients of the therapy enjoy the anticipated benefit. The rate of improvement after CRT varies considerably. Many authors quote an approximate 65%-70% improvement rate with the widely held notion that fully 1/3 of patients do not experience any benefit. The truth may not even be that good because, benefit has typically included quality of life measures assessed by either or both patient and physician and physicians may not be easily blinded to the therapy due to the knowledge of the lead insertion or to the effect of biventricular pacing on the QRS. And while subjective improvement may be as important as more objective benefit, when we focus on harder events such as mortality and the adjudicated recurrence of severe CHF, the absolute differences between patients treated with or without CRT are much more modest. For example, in Class II/III heart failure, the RAFT investigators reported a 28.6% 5-year actuarial mortality rate in their ICD-CRT group compared to 34.6% in the ICD-only group, an absolute difference of 6%. The authors of that report pointed out that 14 patients would have to be treated with CRT for 5 years to prevent one death. Similarly, the rehospitalization rate for recurrent CHF was 19.5% in the ICD-CRT group compared to 26.1% in the ICD-only group. Again, the authors pointed out that the 11 patients would have to be treated for 5 years with CRT to prevent 1 hospitalization for CHF. Disappointingly, the rate of overall re-hospitalization was no different between the groups because of an 8% higher re-hospitalization rate in the CRT-ICD group secondary to device-related complications, including pneumothorax, serious pocket hematomas and pocket infections.[6]

And so, as with ICD therapy, investigators are searching for better screening algorithms to identify responders and non-responders to CRT therapy. At the core of the problem is the very premise of the therapy, i.e., dyssynchrony. Indeed, it is for the correction of left ventricular mechanical dyssynchrony that pacing strategies have been advocated and applied. If we are to correct mechanical dyssynchrony, then it is incumbent upon us to be able to detect it, measure it, and track serial changes in it. And therein lies a part of the rub. In lieu of reliable tools to measure and track mechanical dyssynchrony, all studies have used an electrical surrogate, i.e., the QRS. And as a reasonable broad brush, QRS has brought us to the current state of the art. The quintessential example of mechanical dyssynchrony resulting from electrical dyssynchrony is left bundle branch. In 2011, the

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MADIT-CRT investigators reported that the risk of ventricular tachycardia, ventricular fibrillation or death was only reduced by CRT in those patients with LBBB morphology on their ECG. The hazard ratio for the primary endpoint of the study was 0.47 in patients with LBBB compared to 1.24 for the non-LBBB group.[8] Furthermore, the MADIT-CRT investigators reported a hazard ratio for the primary outcome of 0.48 in those with a QRS of 150 mseconds compared to a hazard ratio of 1.06 in patients with <150-msecond QRS. Those results certainly support the hypothesis that the type and degree of dyssynchrony are directly related to the magnitude of benefit to be expected from CRT therapy.

If that is the case, it seems intuitive that a direct measurement of mechanical dyssynchrony would prove a better marker of CRT success than the broad brush ECG. What, then, are the tools available to the clinician to make such measurements and what do we know about their applicability in this clinical arena?

Echocardiographic approaches to the measurement of dyssynchrony have taken center stage in the major trials of CRT. Tissue doppler imaging (TDI) was initially advocated for the determination of the time to peak regional wall velocity, the difference between the time to peak velocity of the septum and lateral walls, and the standard deviation of the time to peak velocity among multiple ventricular segments. TDI measurements are constrained by the need for the ultrasound beam to be parallel to the axis of motion of the segment being assessed. With the distorted shapes of abnormal ventricles and the limitations of ultrasonic windows, that could often be a major constraint. After a number of small, single-center studies suggested that TDI velocity measurements could be used to distinguish responders from non-responders to CRT, Chung et al[9] reporting on the multicenter, prospective but non-randomized, PROSPECT trial, showed that TDI velocity measurements could not satisfactorily predict the outcome of CRT. While that was going on, other investigators were pursuing the so-called speckle tracking approach to myocardial thickening and shortening. The major advantage of speckle tracking is its independence of the axis of the ultrasound beam. In the multicenter, Speckle Tracking and Resynchronization (STAR) trial, speckle tracking radial strain, and transverse strain were associated with the response to CRT.[10] The absence of dyssynchrony prior to CRT, as measured by speckle tracking radial strain, predicted a poor outcome in patients with intermediate QRS durations of 120-150 mseconds. In addition, Delgado et al showed that when dyssynchrony by speckle tracking time-to-peak radial strain was <130 mseconds, 3-year outcome was inferior (65% vs 82%) to outcome with >130 mseconds of dyssynchrony. In addition, outcome was better if a pacing lead could be delivered to the site of latest mechanical activation and also better if peak radial strain in the targeted segment exceeded 16.5%.[11] In the MADIT-CRT trial, transverse strain and longitudinal strain were both associated with outcome following CRT. Each 20 mseconds decrease in dyssynchrony that occurred after CRT resulted in a 7% reduction in the primary endpoint of death or CHF.[12]

Radionuclide approaches to dyssynchrony antedated echocardiographic approaches literally by many years. Early applications of phase analysis to equilibrium radionuclide angiographic data appeared as early as 1980. The ability to accurately detect the sites of earliest mechanical activation in the ventricle led to the analysis of arrhythmias, conduction abnormalities, and regional ventricular dysfunction. However, after initial excitement and technical explorations, the clinical use of phase analysis lay fallow for lack of an identifiable clinical niche and because of the migration of the field away from blood pool imaging to perfusion imaging. CRT therapy rekindled interest in the application of phase analysis. Some investigators explored alternative approaches to the radionuclide assessment of ventricular dyssynchrony, proposing that the relatively ''simplistic'' reliance on the phase angle and the standard deviation of phase angles would not sufficiently characterize the various permutations of mechanical dyssynchrony.

O'Connell, representing the UCSF group reported on the parameters of Synchrony and Entropy which, when applied to planar ERNA, were able to better distinguish different disturbances of both timing and magnitude of contraction than did the phase standard deviation.[13] Expanding on that study, the group from Ottawa, using planar ERNA, compared the standard deviation of phase to Synchrony and Entropy in normals and in patients with LBBB. In this electrocardiographically and mechanically fairly homogeneous population, all three variables performed equally well by ROC analysis.[14] Harel et al[15] developed their own Contraction Heterogeneity Index (CHI) which was another effort at incorporating both timing and amplitude signals in a single parameter.

Others have focused on SPECT ERNA, including Courtehoux et al who recently showed that regional differences in wall motion could influence the results of CRT even in patients with non-ischemic cardiomyopathies. They were unable to show any change in phase angle after pacing in areas whose peak amplitude was <20% of the maximum amplitude in the ventricle.[16]

However, neither large single center nor any multicenter trials of such alternative approaches to ERNA applied to the CRT population ever materialized. Instead, the field took a different turn as others focused on the feasibility of applying phase analysis to gated SPECT myocardial perfusion imaging (SPECT MPI).

The partial volume effect had already been put to good use for the quantitation of the magnitude of wall thickening in gated SPECT perfusion data and the extension of that approach to quantify the timing of onset of wall thickening seemed intuitive. Largely through the efforts of the team at Emory University, that approach has been well documented and made available for routine clinical application. Using the parameters of mean phase angle, standard deviation of phase angles (SDθ) and the so-called bandwidth which quantifies the width of the histogram of phase angles, left ventricular dyssynchrony can be reliably detected and quantified.[17] In a subsequent study of 42 patients by Henneman et al,[18] the same group reported that the outcome following CRT was related to the baseline bandwidth and SDθ. Bandwidth was 175° and SDθ 56° in responders compared to 117° and 37° in non-responders. One particularly appealing aspect of this approach is that SPECT MPI can also be used to accurately localize and quantify the extent of scarred myocardium, a variable that seems to be of importance in predicting the likelihood of a response to CRT.[19]

In this issue of the *Journal*, Cheung et al,[20] from the Emory group, present the results of a simulation study that examines the accuracy of phase analysis as applied to SPECT MPI through a spectrum of count densities and statistical image noise. The results show that single-harmonic Fourier analysis, in this setting, is robust enough to remain accurate down to very low signal strength and to fairly high noise ratios. Not until count density dropped to <10% of ''normal'' activity or until the signal-to-noise ratio dropped below 12, was the phase measurement distinguishable from baseline. That is good news for nuclear cardiologists, because it tells us that the technique remains viable even when the myocardium may not be or when the data are relatively noisy. It also provides a convenient yardstick to use for quality control when reporting the results of phase analysis. Of course, simulation studies do not necessarily completely reflect ''real-world'' imaging but the data offer the promise of clinical success across a wide range of study quality and should be of particular interest to those who are working with low-dose, ultra-fast SPECT acquisitions using newer detectors.

The success or failure of CRT depends on several variables. At a minimum, they appear to include the presence and the magnitude of left ventricular dyssynchrony, the extent of infarction in the left ventricle, in particular in the target segment for pacing, and the successful delivery of a pacing electrode to a site with markedly delayed contraction that has adequate contractile reserve. There may also be some importance to the optimization of atrioventricular and/or RV-LV pacing intervals. Both the gated SPECT ERNA and the gated SPECT MPI provide important data that are related to all those variables and small, single-center studies continue to hold promise for the role of radionuclide techniques in this arena.

But, it has now been a decade since this area of nuclear cardiology has been explored. The current paper by Cheung et al[20] is one more step in assuring us of the durability of the radionuclide measurement of dyssynchrony even under the adverse conditions of low counts and excess noise. What more does the clinician need to know about measuring dyssynchrony at this point?

The clinician needs to know whether any of the radionuclide or speckle-tracking echo methods will withstand the scrutiny of a prospective, randomized trial in patients undergoing CRT. Based on single-center data, it seemed intuitive to the PROSPECT[9] investigators that TDI indices of dyssynchrony would help to distinguish responders from non-responders. But, in a multicenter, prospective trial, they did not. We have been at that point in nuclear cardiology since I wrote an editorial on phase analysis for the *Journal* in 2005.[21] And as I think about the technical progress since then, I do get that somewhat uncomfortable ''dejas vu all over again'' feeling. I think we have enough small single-center trials. Unless there is some major technical or conceptual innovation in this area that is currently cooking in someone's nuclear cardiology laboratory, it is high time, to cease the tweaking and go for it.

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