Single photon emission computed tomography (SPECT) techniques for resynchronization: Phase analysis and equilibrium radionuclide angiocardiology

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Although cardiac resynchronization therapy (CRT) has been shown to improve heart failure (HF) symptoms and survival in selected patients,^{1,2} questions remain about optimal patient selection and implementation of this therapy. Efforts to improve patient selection have focused on the cardiac substrate for resynchronization, including assessment of mechanical discoordination, or dyssynchrony, of the left ventricle (LV)^{3,4} and other structural characteristics such as scar or volumes that may be associated with the likelihood of response. This issue of the *Journal* contains papers on two distinct applications of nuclear imaging for patients who may be candidates for CRT or who have received CRT. In the study by Samad et al,⁵ phase analysis was performed retrospectively in a series of patients with LVEF ≤ 0.35 who had undergone single photon emission computed tomography (SPECT) myocardial perfusion imaging (MPI) at a single center for evaluation of coronary heart disease (CHD), whereas the study by Clements et al⁶ presents an analysis of right ventricular (RV) and LV structure and function in a series of patients referred for biventricular pacemaker upgrades.

The interesting study by Samad et al provides needed insights into baseline predictors of an abnormal SPECT phase analysis based on a retrospective series of 260 patients with SPECT MPI. Patients in this study were not referred for CRT, and no data on CRT response are available based on the study design. The authors

found that significant multivariate predictors of phase SD $\geq 43^\circ$ included greater QRS duration (QRSd), lower LVEF, and greater summed rest perfusion score (SRS). The influence of resting perfusion abnormalities on phase SD and the distribution of abnormal phase SD based on QRSd are of particular interest and will be explored further in this editorial. Overall, abnormal phase SD was present in 39% with QRS < 100 ms, 41% with QRS 100–119 ms, 61% with QRSd 120–149 ms, and 80% with QRSd greater than 150 ms.

The principle of phase analysis, as pioneered by Chen and colleagues,^{7,8} is that the phase extracted from the regional LV count changes throughout the cardiac cycle is related to regional variability in the time to onset of mechanical contraction. The standard deviation of the phase distribution may then be calculated as the phase SD (the more commonly used parameter), while the phase bandwidth represents the phase range during which 95% of the LV is initiating contraction. From a physiological standpoint, the phase SD, with its characterization of regional timing in *onset* of LV strain, contrasts with other dyssynchrony parameters based on regional differences in time to *peak* strain,⁹ although a good correlation ($r = 0.80$, $P < .0001$) has been found between phase SD and difference in time to peak velocity in opposing walls by echocardiographic tissue Doppler imaging (TDI).¹⁰ Of note, quantification of timing either to peak onset or to peak strain is difficult and less meaningful in regions with akinesis due to myocardial infarction since strain remains close to zero throughout systole. Of note, this highlights a role for other types of metrics in these patients.¹¹

The rationale for using phase SD in patients referred for CRT is based largely on the well-designed but relatively small prospective study by Henneman et al.¹² The 42 patients included had New York Heart Association (NYHA) Class III–IV HF, LVEF < 0.35 , and QRSd > 120 ms. Overall, the mean QRSd, LV end-diastolic volume (LVEDV), LVEF, and NYHA Class were 153 ± 32 ms, 251 ± 87 mL, $24 \pm 7\%$, and 2.9 ± 0.4 , respectively. The overall response rate to CRT, defined as an improvement of at least one NYHA class, was 71% at

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6 months. In this study, ROC analysis showed that phase SD $\geq 43^\circ$ had a sensitivity and specificity of 74% to identify CRT responders. Based on this study, 43° is generally considered the cutoff for phase SD.

In contrast, Samad et al⁵ present a larger but retrospective study in patients with CHD but with no information or follow-up regarding CRT. The high prevalence of abnormal phase SD in patients with narrow QRS complexes is curious and consistent with the findings of another recent study of phase analysis by Aljaroudi et al in patients with a broad range of QRS complexes and implantable cardioverter defibrillators (ICDs).¹³ In the latter study, there was a weak but statistically significant correlation between phase SD and QRSd for QRSd ranging from 80 to 250 ms ($r = 0.25$; $P = .04$), and a significant number of patients with QRSd < 120 ms had phase SD $\geq 43^\circ$. It was also uncommon to have a normal phase SD in patients with a QRSd > 150 ms.

In the study by Samad et al, it should be emphasized that the prevalence of phase SD was high not only in patients with QRSd 100–119 ms, but also in patients with QRSd < 100 . If phase analysis truly identified narrow QRS patients with a cardiac substrate likely to benefit from CRT, the implications for CRT implantation would be highly significant. It would imply that two out of five patients with narrow QRS complexes and even very narrow QRS complexes (< 100 ms) referred for single- or dual-chamber ICDs should now also get CRT. However, this study was not a CRT response study, so we do not have data to support that conclusion. Furthermore, it would be inappropriate to apply the results of the previously discussed prospective study of phase SD¹² in patients meeting standard CRT implant criteria¹⁴ to this population who did not all meet these criteria.

Nevertheless, there has been significant interest regarding whether selected patients with narrow QRS complexes should be targeted for CRT based on the identification of mechanical dyssynchrony,^{15,16} and the study by Samad et al⁵ provides useful insights into this issue. Most of the TDI studies investigating mechanical dyssynchrony in patients with narrow QRS complexes were done prior to the large multicenter echocardiographic PROSPECT study that unfortunately showed significant inter-observer variability for TDI parameters and limited predictive ability for these parameters in predicting CRT response.¹⁷ One such study by Bleeker et al¹⁵ compared the TDI septal-lateral delay and QRSd in 90 patients with QRSd ranging from less than 100 to greater than 200 ms and found only a weak correlation ($r = 0.48$, $P < .05$) in nonischemic cardiomyopathy patients but no correlation overall between QRSd and the septal-lateral delay. Although 27% of the patients with QRSd < 120 ms were noted to have an abnormal TDI dyssynchrony parameter, the patients with QRSd

less than about 100 ms had timing delays close to zero. In contrast, 39% of patients with QRSd < 100 ms had phase SD $\geq 43^\circ$ in Samad et al.⁵

A few early efficacy series of CRT in patients with narrow QRS complexes and positive TDI criteria for mechanical dyssynchrony showed mixed results, and interpretation was limited by various factors including a small number of patients enrolled with narrow QRS complexes in one study,¹⁸ lack of a control group without CRT in another,¹⁹ and absence of any difference in response parameters between the CRT-on and CRT-off states in the third.²⁰ The one multicenter randomized clinical trial to address this issue was the RETHINQ study,²¹ which randomized patients with QRSd less than 130 ms and positive TDI evaluations to CRT or standard therapy. Unfortunately, this study found that none of VO_{2max}, quality of life, or the 6-minute walk was improved with CRT in patients with narrow QRS complexes. The authors concluded that “CRT did not improve peak oxygen consumption [primary endpoint] in patients with moderate heart failure, a QRS interval of less than 130 ms, and mechanical dyssynchrony,” although those with QRSd 120–130 ms (but not those with QRSd < 120 ms) had a significant improvement in the percent change from baseline of the primary endpoint. Interestingly, there was a significant rate of improvement in patients assigned to the control group that may have been due to background improvements in medical therapy. This highlights the importance of an adequate control group in these studies.

Returning to Samad et al,⁵ the meaning of an abnormal phase SD in these patients, particularly those with narrow QRS complexes, may be influenced by the ischemic cardiomyopathy substrate. In addition to the QRSd, the SRS also predicted an abnormal phase SD in the multivariate analysis. Of note, phase SD is intended to characterize regional variation in the onset of mechanical contraction, and myocardium with infarction or other perfusion abnormalities may have abnormal timing to onset of contraction, or onset of contraction may be difficult to determine in the absence of significant myocardial contraction. Based on this, the authors have provided a potential mechanism for abnormal phase SD in CHD that perhaps explains the significant prevalence of phase SD $\geq 43^\circ$, particularly in patients with narrow QRS complexes.

Unfortunately, this association between infarction/scar and phase SD $\geq 43^\circ$ makes the relationship between phase SD and CRT response more complex, since extensive scar by cardiac magnetic resonance (CMR) late gadolinium enhancement has been shown to make CRT response less likely.^{4,22} In fact, both LV percent scar volume of at least 15%²² and significant posterolateral scar²³ as assessed by CMR have been

shown to predict CRT nonresponse. The rationale for this is that it is more difficult to resynchronize scar than viable myocardium, particularly when that scar is located in the late-activated region of the LV where left ventricular pacing usually occurs in CRT systems. In summary, the authors have shown that the SRS predicts an elevated phase SD (associated with CRT response in patients meeting standard CRT implant criteria), even though increased scar burden has been associated with CRT nonresponse. Based on these results, some further refinement of this phase analysis may be required to separate the contributions of true mechanical dyssynchrony and wall motion abnormalities associated with CHD to increased phase SD.

A paper based on a different SPECT application, equilibrium radionuclide angiocardigraphy (ERNA), is presented by Clements et al.⁶ This technique was used to evaluate RV and LV structure and function after upgrade to a CRT system. SPECT ERNA is well suited to evaluation of patients with preexisting devices. Although CMR may be the gold standard for evaluating mechanical dyssynchrony in HF²⁴ and several studies have suggested safety of CMR in patients with recent pacemaker and ICD systems,²⁵ CMR is presently not approved by the U.S. Food and Drug Administration (FDA) for this purpose. CT is associated with contrast administration, and some patients may favor the open design of the SPECT ERNA camera. Echocardiography may be used in patients with devices, but may not be the optimal imaging modality to quantify RV volumes and ejection fraction.²⁶ In this study, overall 94% of SPECT ERNA studies yielded reasonable data.⁶

CRT upgrades may be indicated in patients with standard pacing systems due to worsening HF in the setting of frequent RV pacing or chronic left bundle branch block (LBBB). With RV pacing, left ventricular activation is similar to that with LBBB. Early septal contraction with lateral wall stretch followed by late lateral wall contraction with septal stretch leads to decreased stroke work and cardiac output.²⁷ The DAVID trial²⁸ showed increased rates of HF in patients with LVEF less than 0.40 and increasing amounts of RV pacing, and current ICD guidelines now recommend CRT for selected patients with HF and frequent dependence on RV pacing.¹⁴

In the study by Clements et al.,⁶ the overall clinical response rate based on NYHA class was on the lower end (47%) of what has been reported in the literature. Possible explanations for this include limitations of NYHA class in identifying CRT responders, issues related to CRT implementation such as lead placement, or other patient-specific factors that decrease CRT response rates. Of note, despite some variability, there was a reasonable concordance rate between clinical response and structural

LV remodeling after CRT, consistent with the 75% concordance rate between clinical and echocardiographic responses reported in the literature.²⁹

A significant finding was that a pre-upgrade LVEDV of 174 mL had a sensitivity of 78% and specificity of 80% for predicting CRT response. Most of the major CRT clinical trials^{1,2,30,31} required that patients have dilated LVs in the entry criteria, although current guidelines do not have a specific requirement for LV size.¹⁴ The usual criterion in the trials was an echocardiographic LV end-diastolic dimension ≥ 55 -60 mm or a cutoff indexed by height. Based on this, it makes physiologic sense that a larger end-diastolic volume was predictive of CRT response. In the long run, SPECT ERNA may prove to be a good method for LV volume assessment prior to CRT, particularly in patients with preexisting devices, and merits further evaluation in larger series of CRT upgrades in order to facilitate inclusion of additional factors such as phase SD in the predictive model for CRT response.

It is interesting that the authors did not find evidence of RV remodeling after resynchronization by 3-6 months despite the improvements in LV remodeling. Although the beneficial effects of resynchronization on LV remodeling in patients with HF and LBBB have been well studied, the effects of resynchronization on RV remodeling are not as well studied. Biventricular pacing results in dual-site pacing of the LV, but RV activation still proceeds from the RV apex. RV multisite pacing has been shown to be beneficial in selected patients with congenital heart disease and systemic ventricles at risk for HF,³² but the RV is not resynchronized in a standard CRT system. From a physiologic perspective, even without RV resynchronization, RV function could still improve with LV resynchronization due to ventricular interdependent mechanisms.

With respect to LV remodeling, CRT responders usually have significant improvements in LV function and volumes by 3 months that are predicted by baseline LV mechanical dyssynchrony.³³ With respect to RV remodeling, Bleeker et al.³⁴ have demonstrated improvements in RV remodeling in patients with substantial baseline TDI-based dyssynchrony by 6 months, including a decrease in the RV annulus from 37 ± 9 to 32 ± 10 mm, RV short-axis from 29 ± 11 to 26 ± 7 mm, and RV long-axis from 89 ± 11 to 82 ± 10 mm. It is remarkable that these changes in RV remodeling were not observed immediately after CRT and that the changes were only demonstrated in patients who met TDI criteria for LV dyssynchrony at baseline. This suggests that the mechanism of RV remodeling after CRT is dependent on LV remodeling.

With this in mind, explanations for the lack of significant RV remodeling in this series could be related

to differences in RV remodeling after CRT upgrades as opposed to RV remodeling after new CRT implants or the need for longer periods of follow-up after CRT. Another likely possibility is that a larger sample size is necessary to demonstrate these benefits, particularly if the magnitude of these RV remodeling changes is smaller than those observed for LV remodeling or present in only a subset of patients. Larger series with longer follow-up would help to further elucidate the nature of RV remodeling after CRT using this advanced SPECT technique for volume assessments.

In summary, the original contributions by Samad et al⁵ and Clements et al⁶ in this issue of the *Journal* present interesting applications of phase analysis and SPECT ERNA in patients with HF who may be considered for CRT. The first paper demonstrates the influence of the resting perfusion abnormalities on SPECT phase analysis for mechanical dyssynchrony and provides further data on the prevalence of an abnormal phase SD with narrow and wide QRS complexes. The second paper demonstrates the feasibility of LV and RV volume analysis with SPECT ERNA in patients referred for an upgrade to a CRT device and provides data on LV remodeling and lack of RV remodeling after implantation, albeit with a small sample size. Perhaps these two techniques could be combined for a more complete SPECT assessment in future patient series. Overall, these papers highlight the strengths and limitations of SPECT analysis for patients with HF referred for resynchronization, as well as the need for further investigation with respect to the application of these techniques to these patients.

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