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EDITORIAL COMMENT

# Cardiac Imaging and Cardiac Resynchronization Therapy

## Time to Get in Phase*

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In this issue of *iJACC (JACC: Cardiovascular Imaging)*, Botvinick et al. (1) perform a complex study involving the performance of equilibrium radionuclide myocardiography with phase analysis during ventricular tachycardia. The authors identify specific characteristics that define tolerability of the arrhythmia in individual patients. Most of these discriminating factors in the 2 patient groups involve changes in classic hemodynamic measurements such as ejection fraction, stroke volume, cardiac output, and end-diastolic volume during the arrhythmia when compared with the basal state. Heterogeneity in regional contraction, as defined by phase analysis, was discriminating between groups only in the resting state. The exit site of the ventricular tachycardia could be defined in approximately 80% of arrhythmias. The authors conclude that this type of image analysis offers substantial physiologic information concerning the ability of a patient to tolerate a rhythm disturbance.

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In addition, with respect to clinical relevance, they posit that such an imaging approach could provide clinical insight in heart failure patients considered for cardiac resynchronization therapy (CRT), with a view toward defining which individuals would benefit from this procedure. It is this potential that appears to excite the authors with respect to the future application of the imaging technique.

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Cardiac resynchronization is a relatively recent major advance in the treatment of advanced congestive heart failure, specifically those with significant symptoms, depression of ejection fraction, and prolonged QRS duration on the surface electrocardiogram (2). Recent clinical trials have demonstrated that CRT can lead to major symptom improvement as well as provide a mortality benefit in patients with severe congestive heart failure (3–8). However, these previous studies also have demonstrated that 20% to 30% of patients who were deemed suitable for CRT will not receive benefit from this therapy.

The definition of these 20% to 30% of patients receiving CRT with no clinical improvement but considerable clinical cost presents an immediate clinical need. Major attempts in the imaging community have centered on developing appropriate noninvasive surrogate markers that might enrich the selection process of those suitable for this expensive therapy. The magnitude of the problem is very significant when one considers that the incidence of congestive heart failure continues to grow dramatically within the U.S. (9). Currently there are more than 5 million patients afflicted by this condition, with approximately 550,000 new cases annually. Hospitalization for congestive heart failure involves more than 1 million admissions per year.

Comparable with the case of patient selection for implantable defibrillators, a more accurate and precise definition of those who will benefit is both a clinical and economic necessity. As in most instances of clinical medicine and evidence-based algorithms, extracting data derived from large populations, despite their statistical significance, and applying them to the individual patient, remains a major challenge. It behooves all of us who care for patients to become more precise in our therapeutic decision matrix and to rely on more than generalized criteria or intuition in the use of new, extremely important, potentially beneficial but yet extremely expensive procedures. It is in exactly this circumstance that noninvasive imaging can potentially prove exceedingly valuable.

The application of phase analysis to equilibrium radionuclide angiography is extremely appealing. Although the technique has been around for almost 30 years, it has not yet achieved wide clinical use (10,11). The technology basically involves application of the fundamental Fourier harmonic to generate phase and amplitude images. Quantitative data are generated as right ventricular and left ventricular phase histograms, which allow the definition of heterogeneity of contraction patterns both within each ventricle and between the ventricles (12). This approach would seem a good one for application to the study of CRT.

At this point in time, it is important to assess where this technique stands with respect to use in patient selection for CRT. The work of Botvinick et al. (1) addresses the issue of the hemodynamic relevance of ventricular tachycardia. Although it is obvious that the technique is also suitable for application to the study of patients considered for CRT, there are no clinical data, let alone clinical trials, to support this application. Such studies would be extremely welcome and potentially quite valuable. However, the imaging community has not been standing still on the issue. A number of other approaches have been offered to address this particular problem.

Currently, the most commonly used imaging modality for the study of CRT is echocardiography. A number of echocardiographic parameters relating to ventricular desynchronization have been proposed (13). However, at this time, no major prospective trial incorporating echocardiography that addresses clinical utility has been undertaken. In addition, there appears to be a lack of standardization for many, if not all, of the proposed echocardiographic parameters.

In a recent review, Anderson et al. (13) highlighted this particular problem. Despite a plethora of publications on the subject, the authors advised not to routinely incorporate echocardiographic parameters into the selection of candidates for CRT. This recommendation was based upon the absence of clinical trial data and the conflicting results concerning value emanating from smaller studies. As the authors pointed out, from a clinical standpoint, it would be more important to identify nonresponders to CRT by using various parameters with a high degree of accuracy. However, as stated, the ideal parameters have yet to be unequivocally defined. Whether there will be a single echocardiographic parameter or multiple parameters that will provide the requisite selection remains to be determined at this time.

In the light of these considerations, the current 2005 American College of Cardiology/American Heart Association Guidelines indicate a Class IA indication for CRT in patients with left ventricular ejection fraction <35%, normal sinus rhythm, and New York Heart Association functional class 3 to 4 despite optimal medical therapy who manifest cardiac desynchronization as defined only by a QRS duration >120 ms (14). Note the absence of incorporation of specific imaging parameters of desynchronization, by whatever technique, in this recommendation. This recommendation exists despite the recognition that using the surface electrocardiography alone to detect mechanical asynchrony is imperfect (15,16).

Much fewer studies evaluating desynchronization have been performed in nuclear cardiology. Interestingly, the principles of phase analysis have been similarly applied to electrocardiogram-gated single-photon emission computed tomography myocardial perfusion imaging (17,18). In a recent report by Trimble et al. (18) involving 120 patients with left ventricular dysfunction, several indices indicating the phase dispersion of the onset of mechanical contraction were determined. When compared with normal controls, there were significant differences noted in these 5 parameters. The authors demonstrated proof of principle concerning potential for studying CRT but by no means proceeded to the next step, namely using the technology to assess patient's suitability for therapy or response to therapy.

In addition, iodine-123 metaiodobenzylguanidine (MIBG) also has been studied in a cohort of 30 patients before and at least 3 months after CRT (19). The authors noted that MIBG imaging, defined as an abnormality in MIBG heart/mediastinum ratio, could be helpful in defining patients suitable for CRT. Nonresponders to CRT could be identified with a sensitivity of 75% and specificity of 71%.

Consequently, the search for the appropriate noninvasive imaging desynchronization surrogates for CRT patients continues. There are several players on the field. None, to my mind, has provided the requisite scientific data to mandate clinical prime time. The appropriate clinical trial to define which technique should play a role in clinical decision making has not as yet been performed. Until that time, both clinical electrophysiology and cardiac imaging will continue to be presented with a number of approaches, all with interest, all with potential, but none with hard data to justify a proposed clinical role.

This case study is an important one for cardiac imaging. There is a defined clinical need. There are candidate technologies that appear to offer appropriate information that could satisfy that clinical need. Specific prospective clinical trials either primarily designed to address the value of imaging strategies in CRT or the addition of imaging protocols to other CRT clinical trials is the all too obvious answer. Appropriate funding for such studies must be forthcoming. There is little time to tarry. If this does not occur, cardiac imaging in CRT will continue to provide physiologically meaningful investigations that set a beautiful table but do not deliver the main course.

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**Key Words:** cardiac resynchronization ■ patient selection.