The handle http://hdl.handle.net/1887/19082 holds various files of this Leiden University dissertation.

Author: Boogers, Johannes Maria Josephus
Title: Novel insights into cardiac imaging in cardiovascular disease
Date: 2012-06-14
Chapter 6

Role of Nuclear Imaging in Cardiac Resynchronization Therapy

Mark M. Boogers, MD1, 2, Ji Chen, PhD3, Jeroen J. Bax, MD, PhD1.

1Department of Cardiology, Leiden University Medical Center, Leiden, the Netherlands; 2The Interuniversity Cardiology Institute of the Netherlands, Utrecht, the Netherlands; 3Department of Radiology, Emory University School of Medicine, Atlanta, Georgia.
Abstract

Cardiac resynchronization therapy (CRT) has become an integrated treatment option for patients with drug-refractory heart failure. Selection of patients for CRT is based on moderate to severe heart failure (New York Heart Association, NYHA functional class III-IV), depressed left ventricular (LV) systolic function ≤35% and prolonged QRS interval ≥120 ms. However, 30-40% of selected patients do not exhibit improvement in heart failure symptoms or LV systolic performance.

Efforts have been made to improve patient selection criteria and several studies using echocardiography have demonstrated the significance of LV dyssynchrony for prediction of CRT response as an additional selection criterium. In addition, (location and extent of) viability and scar tissue are important for outcome after CRT. Nuclear imaging with ECG-gated myocardial perfusion SPECT (GMPS) permits assessment of viability, scar tissue and LV dyssynchrony from 1 dataset. The potential value of GMPS in CRT patients is discussed in this review. In addition, the use of nuclear imaging (and particularly positron emission tomography, PET) for evaluation of changes in blood flow, metabolism and innervation after CRT is addressed.
Introduction

Heart failure represents a major problem in the Western health care system. In the United States, heart failure affects 5.3 million patients and each year approximately 660,000 patients are diagnosed with heart failure. Furthermore, (decompensated) heart failure is responsible for more than one million hospital admissions per year and direct and indirect costs accounted for $34.8 billion in 2008. Despite advanced treatment options for heart failure, the 5-year mortality rate still exceeds 50%.

In recent years, cardiac resynchronization therapy (CRT) has been integrated in the treatment of patients with drug-refractory heart failure. The evidence for success of CRT in heart failure patients is mainly based on results of eight large clinical trials that have demonstrated beneficial effects of CRT on heart failure symptoms, quality of life, and exercise capacity. In addition, a reduction in left ventricular (LV) volumes (indicating reverse remodeling) along with an improvement in LV ejection fraction (LVEF) and mitral regurgitation were observed in patients undergoing CRT. Besides clinical and echocardiographic end-points, two large clinical trials have demonstrated an improvement in survival with a reduction in morbidity in patients undergoing CRT as compared to patients on optimal medical therapy.

Current ACC/AHA/ESC guidelines recommend CRT in patients with advanced heart failure (NYHA class III or IV), prolonged QRS duration (≥120 ms), depressed LV systolic function (LVEF ≤35%) and sinus rhythm. However, multiple clinical trials have demonstrated that a substantial group of patients (30-40%), who were selected according to current criteria on CRT, did not show significant improvement in heart failure symptoms or LV systolic performance. Hence, refinement of selection criteria is needed and several studies have emphasized the importance of cardiac dyssynchrony for response to CRT. Cardiac dyssynchrony includes atrioventricular dyssynchrony, interventricular dyssynchrony and intraventricular (LV) dyssynchrony, and most studies suggested that the latter may be most powerful for prediction of response to CRT. In this regard, QRS duration is of limited value for prediction of response to CRT, mainly since QRS duration reflects interventricular rather than intraventricular dyssynchrony.

At present, detection of LV dyssynchrony can be performed with several cardiac imaging techniques, including echocardiography, magnetic resonance imaging and nuclear imaging. The majority of clinical studies on LV dyssynchrony and the prediction of response to CRT used echocardiography. These predominantly single-center studies have clearly demonstrated that LV dyssynchrony has additional value in selection of patients for CRT. Since all studies used different echocardiographic techniques and different criteria for LV dyssynchrony, it is currently unclear which are the precise cut-off values that could be used for prediction of CRT response. This issue has been addressed in the Predictors of Response to Cardiac Resynchronization Therapy (PROSPECT) trial, which was the first multi-center prospective trial using echocardiography for identification of predictors of response.
The study has shown only a modest value of echocardiography to predict response to CRT, and an important problem posed the limited intra- and interobserver variability. Another aspect that may have influenced the study results is the heterogeneous study population included. A substantial cohort of patients included had a LV ejection fraction >35% without severe LV dilatation. These patients were not able to demonstrate cardiac remodeling, one of major endpoints of the study. In addition, other issues could have contributed to the disappointing results, including myocardial scar tissue, LV lead positioning and accessibility of the venous anatomy.

Accordingly, more sophisticated and reproducible imaging techniques are needed for assessment of LV dyssynchrony for selection of CRT candidates.

One of these techniques may be nuclear imaging. Particularly, ECG-gated myocardial perfusion SPECT (GMPS) has emerged as a reasonable technique to determine LV dyssynchrony. Moreover, nuclear imaging is already used extensively in heart failure patients to detect LVEF, LV volumes, ischemia, viability and scar tissue. Accordingly, the addition of LV dyssynchrony to previously mentioned clinical data, provides heart failure clinicians tools to direct therapeutic strategy in the individual heart failure patient (medical therapy, revascularization or CRT). Beyond LV dyssynchrony, viability and scar tissue are particularly important in CRT patients, since the location and extent of scar tissue is also predictive of (non-) response to CRT.

In this review, the potential role of GMPS for prediction of response to CRT is addressed. Moreover, nuclear imaging (and particularly positron emission tomography, PET) is also important in the evaluation of changes in perfusion, metabolism and innervation after CRT, which is also discussed in this review.

**Nuclear Imaging to Assess Left Ventricular Dyssynchrony**

Several nuclear imaging techniques can be used for detection of cardiac dyssynchrony, including multi-gated equilibrium blood-pool scintigraphy, gated blood-pool SPECT, and GMPS.

Initially, gated blood-pool scintigraphy was used for assessment of the myocardial contraction pattern. In gated blood-pool imaging, labeled erythrocytes are used for generating count-based volume-time curves. Images are obtained from one left-anterior oblique view (LAO) in 16 to 64 frames per cardiac cycle and can be smoothed with spatial and temporal filtering in order to reduce noise. Subsequently, regions of interest (ROI) are drawn automatically or manually on the left and right ventricles respectively. For each pixel in the ROI, a time-activity curve is generated by approximation of discrete sample points into a continuous curve using the first Fourier Harmonic (FFH) function. The phase angle of the first FFH function corresponds to the timing of contraction at the particular region. The standard deviation (SD) of phase angles over the ventricle represents the intra-ventricular dyssynchrony, and the difference between the means of the phase angles of the two
ventricles represents inter-ventricular dyssynchrony. The major limitation of this method is that determination of ROI from planar images is less accurate due to overlap of non-cardiac structures. Gated blood-pool SPECT, with the similar principles of phase analysis as gated blood-pool scintigraphy, allows assessment of inter- and intraventricular dyssynchrony in 3 dimensions (3D).26, 27 The major limitation of this method is that it lacks standard processing procedures due to the complexity of generation time-activity curves from gated blood-pool SPECT images.

Recently, phase analysis of GMPS has attracted considerable attention. GMPS is frequently applied in heart failure patients to evaluate for ischemia, viability and scar tissue to direct patient management (revascularization or medical therapy), and the current possibility to derive information on cardiac dyssynchrony from the same dataset has emerged as an appropriate alternative to assess cardiac dyssynchrony.28-30, 33, 34

The phase analysis of GMPS studies is based on the partial-volume effect in which changes in segmental maximal counts is proportional to cardiac wall thickening.36, 37 Phase analysis is performed on standard GMPS images without any additional acquisition. For each frame of the gated short-axis image, a 3D sampling algorithm is used to search for regional maximal counts. Next, a count-based wall-thickening curve is generated for each segment and then approximated using the FFH function. The phase angle of the FFH function represents the onset of mechanical activation of the region. Hetero- or homogeneity of the phase distribution over the entire LV represents LV dys- or synchrony. Peak phase (maximum of phase histogram), phase standard deviation (standard deviation (SD) of phase distribution), histogram bandwidth (bandwidth which includes 95% of phase angles), kurtosis (degree of peakedness of histogram) and skewness (symmetry of histogram) are used to quantify the phase distribution. In Figure 1, an example of a patient with a synchronous

![Phase Polarmap and Phase Histogram](image)

**Figure 1A.** Heart failure patient with minimal left ventricular (LV) dyssynchrony as evidenced by the homogeneous phase angle distribution (polar map, left panel) and a narrow phase histogram (right panel). This patient did not improve in symptoms or LV systolic function after 6 months of cardiac resynchronization therapy (CRT); particularly, LV ejection fraction did not improve (30% at baseline vs. 29% at follow-up).
LV contraction pattern is illustrated in upper panel, whereas an example of a patient with extensive LV dyssynchrony is illustrated in the lower panel.

In general, GMPS studies are perceived with poor temporal resolution since data acquisition is based on 8 or 16 frames per cardiac cycle. However, phase analysis on GMPS is able to improve temporal resolution by replacing 8 or 16 discrete points into a continuous FFH curve. It has been shown that in clinical settings (≥10 counts per pixel) phase analysis using either first, second or third harmonics, phase analysis was able to detect phase difference of 5.6 degrees, reflecting 1/64 of the cardiac cycle. GMPS has been validated against echocardiography for assessment of LV dyssynchrony. Henneman and coworkers have published on the agreement between echocardiography with tissue Doppler imaging (TDI) and GMPS. Good correlations between LV dyssynchrony as measured by TDI and histogram bandwidth (r=0.89, P<0.0001) or phase SD (r=0.80, P<0.0001) as measured by phase analysis of GMPS were presented. Moreover, good correlations between LV dyssynchrony indices on 3D echocardiography and GMPS were recently reported. The systolic dyssynchrony index (derived from real-time 3D echocardiography) correlated well with histogram bandwidth (r=0.76, P<0.0001) and phase SD (r=0.80, P<0.0001) as illustrated in Figure 2.

Henneman and colleagues have evaluated 42 heart failure patients who underwent CRT with GMPS. After 6 months of CRT, a significant improvement in NYHA class, quality of life score and exercise capacity was noted. The authors demonstrated that LV dyssynchrony derived from GMPS was related to CRT response. Particularly, histogram bandwidth (175±63 versus 117±51, P<0.05) and phase SD (56.3±19.9 versus 37.1±14.4, P<0.05) were significantly larger in responders as compared to non-responders to CRT. Receiver operating characteristic curve analysis revealed good predictive values for CRT response using histogram bandwidth (AUC 0.78) or phase SD (AUC 0.81) as markers of LV dyssynchrony (Figure 3). For histogram bandwidth, a cut-off value of 135° had a sensitivity and specificity...
Figure 2A. Comparison between left ventricular (LV) dyssynchrony derived from real-time 3 dimensional echocardiography (RT3DE) and gated myocardial perfusion single photon emission computed tomography (SPECT) (GMPS). The systolic dyssynchrony index (SDI) from RT3DE correlated well with histogram bandwidth derived from GMPS. Reprinted with permission from reference 20.

Figure 2B. Comparison between left ventricular (LV) dyssynchrony derived from real-time 3 dimensional echocardiography (RT3DE) and gated myocardial perfusion single photon emission computed tomography (SPECT) (GMPS). Good correlation was observed between systolic dyssynchrony index (SDI) from RT3DE and phase standard deviation (SD) derived from GMPS. Reprinted with permission from reference 20.
Figure 3A. Receiver operating characteristic curve analysis on histogram bandwidth demonstrated a good predictive value (AUC 0.78) for response to cardiac resynchronization therapy (CRT). A cut-off value of 135° for histogram bandwidth showed a sensitivity and specificity of 70%. Reprinted with permission from reference 40.

Figure 3B. Receiver operating characteristic curve analysis on phase standard deviation (SD) showed a good predictive value (AUC 0.81) for response to cardiac resynchronization therapy (CRT). A cut-off value of 43° for phase SD yielded a sensitivity and specificity of 74%. Reprinted with permission from reference 40.
of 70%; for phase SD, a threshold of 43° yielded a sensitivity and specificity of 74% for prediction of CRT response.

One important advantage of phase analysis of GMPS for assessment of LV dyssynchrony is that this method is largely automatic and has superior reproducibility to echocardiography. Trimble and colleagues\(^\text{33}\) have evaluated phase analysis of GMPS with 10 normal subjects and 10 patients with LV dysfunction and showed that intra-observer and inter-observer reproducibility of phase analysis of GMPS is very robust with correlation coefficients of 1.00 and 0.99 respectively.

**Nuclear Imaging to Assess Viability and Scar Tissue**

It appears that viability and scar tissue are important for response to CRT. In particular, the presence of scar tissue in the region where the LV pacing lead is positioned is of importance. Bleeker et al.\(^\text{41}\) have demonstrated in an elegant study with contrast-enhanced magnetic resonance imaging that patients with scar tissue in the posterolateral region (where the LV lead was positioned in these patients) was associated with non-response to CRT\(^\text{41}\); the authors hypothesized that transmural scar tissue in the LV pacing region resulted in ineffective pacing prohibiting LV resynchronization. Another important issue in patients considered for CRT is identification of the region of latest activation for optimal LV lead positioning.\(^\text{42-44}\) Recently, Ypenburg and colleagues\(^\text{44}\) have evaluated echocardiographic response to CRT in patients with LV lead positioned at the region of latest activation (concordant) and in patients with LV lead positioned at other regions than the area of latest activation (discordant). Patients with concordant LV lead positioning (n=153) showed significant reduction in LV end-systolic volume, whereas patients with discordant LV lead position (n=91) demonstrated no significant reduction in LV end-systolic volume.

In addition to the area of latest activation and its viability, the balance between the total extent of viable myocardium and scar tissue in the left ventricle is important.\(^\text{45-47}\) In 61 patients with ischemic cardiomyopathy, Ypenburg and colleagues\(^\text{45}\) have shown that the extent of viable myocardium (assessed with F18-fluorodeoxyglucose, FDG) and SPECT) was directly related to improvement in LVEF (r=0.56, P<0.05) after 6 months of CRT, whereas the extent of scar tissue was inversely related to change in LVEF (r=-0.56, P<0.05) at 6 months follow-up. Also, responders to CRT had significantly more viable segments as compared to non-responders (12±3 vs. 7±3 viable segments respectively, P<0.01). Based on these data, receiver operating characteristic curve analysis was performed, and a cutoff value of 11 viable segments was defined to predict CRT response with a sensitivity of 74% and a specificity of 87%.

Adelstein et al.\(^\text{48}\) have reported similar findings in 50 heart failure patients undergoing SPECT. Larger extent of scar tissue and the presence of scar tissue in the region where the LV pacing lead was positioned were inversely related to improvement in LVEF after CRT.
Similar findings were reported with FDG PET in 39 patients with ischemic cardiomyopathy undergoing CRT, confirming a direct relation between the extent of viable tissue and cardiac performance after CRT \( (r=0.64, P<0.001) \).\(^4^9\) The optimal threshold for prediction of hemodynamic response (improvement in cardiac index >15%) after LV pacing was defined at 3 viable segments, yielding a sensitivity of 72% with a specificity of 71% \( (\text{AUC} \ 0.80) \) to predict hemodynamic improvement after CRT.

Of note, these studies found different cutoff values for prediction of response to CRT. One of potential explanations for the observed discrepancy is the fact that different scoring models were used. In the study by Ypenburg and colleagues\(^4^5\), the 17-segment model was used for assessment of the number of viable and infarcted segments, whereas Van Campen et al.\(^4^9\) used a 13-segment model. Moreover, different definitions for response to CRT were used in these studies. Patients with an improvement in \( \geq 1 \) NYHA class were considered responders to CRT in the study by Ypenburg et al.\(^4^5\), while Van Campen and colleagues\(^4^9\) considered patients as responders to CRT in the presence of >15% improvement in cardiac index.

**Nuclear Imaging to Evaluate CRT Effects on Blood Flow, Metabolism and Innervation**

The effects of CRT on myocardial blood flow, metabolism and sympathetic innervation have been studied using nuclear imaging.\(^5^0-6^1\) To evaluate the beneficial effects of CRT, particularly correction of LV dyssynchrony, the etiology of heart failure plays an important role as different mechanism may be involved. In this regard, two concepts are important, including cardiac dyssynchrony and cardiac dyssynergy; cardiac dyssynchrony results from different timing of contraction between cardiac segments, whereas cardiac dyssynergy refers to heterogeneous contractile capacity (contractile disparity) between cardiac segments with similar contraction timing. The former may play an important role in patients with congestive heart failure and left bundle branch block, whereas cardiac dyssynergy may play a more evident role in ischemic heart failure patients. The effect of CRT in patients with cardiac dyssynchrony based on disparity in activation timing can be expected, however, the precise mechanisms of effects of CRT in patients with cardiac contractile disparity are less clear. Several studies on nuclear imaging have been performed to evaluate the beneficial effects of CRT on myocardial blood flow, oxidative metabolism, glucose utilization and sympathetic innervation. Particularly the effects of CRT on myocardial blood flow have been extensively studied with PET.\(^5^0-5^7\) Different studies demonstrated that global blood flow did not change after CRT.\(^5^0-5^7\) However, an inhomogeneous distribution of blood flow was observed in heart failure patients, with lower values in the septum as compared to the lateral wall. After CRT a more homogeneous distribution of blood flow was detected. Knaapen and coworkers\(^5^4\) have evaluated 14 heart failure patients who underwent CRT with O15-labeled water and PET. Myocardial blood flow was inhomogeneously distributed as reflected by a
baseline septal-to-lateral blood flow ratio of 0.77±0.27, which increased to 0.97±0.34 after 3 months of CRT. Similarly, a heterogeneous distribution of glucose utilization was observed in heart failure patients, with lower glucose utilization in the septum as compared to the lateral wall. Nowak and colleagues have used FDG PET in 15 patients with dilated cardiomyopathy and left bundle branch block configuration on the ECG, and demonstrated low FDG uptake in the septum as compared to the lateral wall (56±12% versus 89±6%, P<0.001). The septal-to-lateral FDG ratio improved significantly after CRT (0.62±0.12 versus 0.91±0.26, P<0.001) indicating more homogeneous tracer uptake.

The effect of CRT on myocardial efficiency has been evaluated by Ukkonen and colleagues. The authors used C11-acetate with PET and showed an improvement in cardiac efficiency after CRT.

Finally, sympathetic innervation has been evaluated with 123-I-metaiodobenzylguanidine (MIBG) and SPECT in patients undergoing CRT, suggesting that patients with more preserved innervation had better response to CRT.

**Conclusions**

In heart failure patients, nuclear imaging with GMPS can provide information on myocardial ischemia, viability and scar tissue; in addition, precise information on LV function and LV volumes can be derived. With current technology of phase analysis, assessment of LV dysynchrony is possible from the same dataset. It provides a comprehensive overview for the heart failure specialist, permitting therapeutic decision making. At present, large trials are needed to determine the precise role of GMPS for assessment of LV dyssynchrony and outcome after CRT.

**Future Perspectives**

Accurate prediction of response to CRT remains challenging. Different issues need to be concerned for appropriate patient selection for CRT, in particular the assessment of LV dysynchrony. Most frequently, echocardiography has been proposed to provide information on LV dyssynchrony, however the results from the PROSPECT trial are disappointing; a major issue was the reproducibility of echo analyses, with large inter- and intraobserver variability of dyssynchrony measurements. GMPS has the potential to provide objective, reproducible parameters on LV dyssynchrony. In clinical cardiology, many heart failure patients undergo nuclear imaging for assessment of myocardial perfusion state and simultaneous detection of mechanical dyssynchrony will add important information for therapeutic strategies. Although GMPS is promising, limited data are available on the use of GMPS for selection of CRT candidates and larger trials are needed to define to final role of GMPS in CRT. As a consequence, echocardiography remains the first choice for patient selection to CRT,
however, depending on upcoming studies GMPS may be incorporated in the clinical workup of patient selection for CRT.
Reference List


