LV Dyssynchrony Assessed With Phase Analysis on Gated Myocardial Perfusion SPECT Can Predict Response to CRT in Patients With End-Stage Heart Failure

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Background: Cardiac resynchronization therapy (CRT) is an established treatment in patients with end-stage heart failure and wide QRS complex. However, about 30% of patients do not benefit from CRT (non-responder). Recent studies with tissue Doppler imaging yielded disappointing results in predicting CRT responders. Phase analysis was developed to allow assessment of LV dyssynchrony by gated single photon emission computed tomography (SPECT) myocardial perfusion imaging (GMPS).

Objectives: The aim of present study was to investigate the role of quantitative GMPS-derived LV dyssynchrony data to predict CRT responder.

Patients and Methods: Thirty eligible patients for CRT implantation underwent GMPS and echocardiography. Response to CRT was evaluated six months after the device implantation. Clinical response to CRT was defined as 50 meters increase in 6-minute walking test (6-MWT) distance. Echocardiographic response to CRT was defined as ≥ 15% decrease in left ventricular end-systolic volume (LVESV). The lead position was considered concordant if it was positioned at the area of latest mechanical activation, and discordant if located outside the area of latest mechanical activation.

Results: Clinical response to CRT was observed in 74% of patients. However, only 57% of patients were responder according to the echo criteria. There were statistically significant differences between CRT responders and non-responders for GMPS-derived variables, including phased histogram bandwidth (PHB), phase SD (PSD), and Entropy. Moreover, a cutoff value of 112° for PHB with a sensitivity of 72% and specificity of 70%, a cutoff value of 21° for PSD with a sensitivity of 90% and specificity of 74%, and a cutoff of 52% for Entropy with a sensitivity of 90% and a specificity of 80% were considered to discriminate responders and non-responders. CRT response was more likely in patients with concordant LV lead position compared to those with discordant LV lead position.

Conclusions: GMPS-derived LV dyssynchrony variables can predict response to CRT with good sensitivity and specificity.

Keywords: Cardiac Resynchronization Therapy; left ventricular dyssynchrony; Heart Failure; gated single photon emission computed tomography

1. Background

In the recent years, cardiac resynchronization therapy (CRT) has been emerged as a new treatment strategy for a subgroup of patients with end-stage heart failure (HF) with severely depressed left ventricular (LV) ejection fraction ≤ 35%, wide QRS complex on electrocardiogram (≥ 120 ms) and the New York Heart Association (NYHA) class III and early class IV. However, 30% of patients who meet the above criteria fail to respond CRT (1-3). In search for better selection criteria, it was found that presence of mechanical LV dyssynchrony increased the likelihood of a positive CRT response. During the past few years, a variety of echo techniques have been developed to determine mechanical LV dyssynchrony (4-6). However, current echocardiography techniques are not ready to pre-dict the response of CRT due to high intra-observer and inter-observer variability (5). These results prompted the search for a new method of measuring LV dyssynchrony. In 2005, assessment of LV mechanical dyssynchrony using phase analysis of gated myocardial perfusion single-photon emission tomography (SPECT) (GMPS) was introduced, allowing for simultaneous assessment of LV perfusion, function and mechanical dyssynchrony (7). Compared to other imaging modalities, phase analysis of GMPS has shown several advantages such as simplicity, widespread availability, applicability to retrospective data and ability to simultaneously assess myocardial scar location and severity for optimizing cardiac resynchronization therapy (CRT) in patients with HF.

2. Objectives

Considering several advantages of GMPS-derived LV dyssynchrony, the aim of the present study was to explore clinical use of GMPS-derived phase analysis data to predict CRT response.

3. Patients and Methods

3.1. Study Population

The study population consisted of 30 patients with heart failure who were prospectively included for implantation of a CRT device. Selection criteria for CRT were severe HF (NYHA class III or early IV), LVEF $\leq 35\%$, sinus rhythm and wide QRS complex (≥ 120 ms). Patients with previous CRT, implantable cardiac defibrillator (ICD) or pacemaker were excluded.

3.2. Study Protocol

Before the device implantation, enrolled patients underwent LV dyssynchrony assessment by phase analysis of GMPS, assessment of NYHA functional class and 6-minute walking test (6-MWT). Moreover, 2-dimentional (2D) echocardiography was performed to assess LV volumes (end-diastolic and end systolic volumes) and function. Both clinical assessment (NYHA class and 6-MWT) and echocardiographic study were repeated at 6-month follow-up. Clinical response to CRT was defined as 50 meters increase in 6-MWT distance. Echocardiographic response to CRT was defined as $\geq 15\%$ decrease in left ventricular end-systolic volume (LVESV).

3.3. Gated SPECT Myocardial Perfusion Imaging

Details of the GMPS protocol was described previously (8). Briefly, resting gated-SPECT MPI study was performed 45-60 minutes after intravenous administration of 15-20 mCi (555-740 MBq) of 99 mTc-sestamibi with a dual-head gamma camera (Symbia T2, Siemens Healthcare). ECG-gated data acquisition was performed with 16 frames per cardiac cycle and 30% acceptance window for R-R interval length using forward-backward gating method. Then phase of regional count changes in the left ventricle throughout the cardiac cycle was analyzed by software package from Cedars-Sinai medical center (Quantitative Gated SPECT-QGS; version 0.4; May 2009). The phase analysis tool extracts a phase distribution from a gated SPECT study representing the regional LV onset of mechanical contraction in 3D. Because it has an association with the time interval when a region in the 3D LV myocardial wall starts to contract (onset of mechanical contraction), it provides some information on uniformity of distribution of these time intervals for the entire LV, which is a measure of ventricular dyssynchrony. The phase distribution could be displayed in a polar map or in 3D and used to generate a phase histogram. The following quantitative indices were calculated from the phase arrays of

all 30 patients (1). Phase histogram bandwidth (PHB) includes 95% of the elements of the phase distribution and (2) phase standard deviation (PSD) is the SD of the phase distribution (3). The QGS software also provides another index of dyssynchrony, entropy, which is normalized to its maximum value and reported as a percentage. The site of latest activation was revealed by phase polar maps (including anterior, inferior, lateral and septal walls). The color scale had been used in the polar map (as regions with larger phases could appear either brighter or darker according to the color scale). In a healthy individual, ventricles contract with coordination and most myocardial segments have similar phases. Therefore, the phase distribution is approximately uniform and the phase histogram is a highly peaked narrow distribution. PSD, PHB, and Entropy increase as the LV mechanical synchrony worsens.

3.4. Standard Two-Dimensional Echocardiography

Two-dimensional echocardiography was performed before the CRT implantation and at 6-month follow-up. Patients were imaged in the left lateral decubitus position. Imaging was performed in the parasternal view and apical 2- and 4-chamber views. LVESV and LV end-diastolic volume (LVEDV) were derived from apical 2- and 4-chamber views.

3.5. CRT Implantation

Our technique of CRT implantation was described previously (9). In brief, a coronary sinus venogram was obtained using a balloon catheter, followed by the insertion of LV pacing lead. The preferred position was a lateral or posterolateral vein. All leads were connected to a biventricular implantable cardioverter defibrillator (ICD). LV pacing lead was implanted by an electrophysiologist blinded to other data. LV lead position was determined empirically by electrophysiologist. Using the six-segment model, LV lead site was secured as anterior, lateral, posterior or inferior. LV lead position was considered concordant if the lead was positioned at the area of latest mechanical activation and considered discordant if the lead was located outside the area of latest mechanical activation.

3.6. Statistical Analysis

Results were considered as mean ± SD. Continuous data were compared using the paired student T-test. Categorical data were compared with Mann-Whitney test. The fisher exact test was used for proportions. P < 0.05 was considered statistically significant in all the analyses.

4. Results

4.1. Baseline Characteristics

Baseline characteristics of the study patients (19 men; a

mean age of 61 ± 10 years) are summarized in Table 1. Underlying heart disease was ischemic cardiomyopathy in 26 (86%) patients and idiopathic dilated cardiomyopathy in remainder. Echocardiography examination showed a mean LVEDV of 241 ± 48 mL, a mean LVESV of 181 ± 45 mL and a mean LVEF of 19 ± 4%. Before CRT implantation, mean values of GMPS variables were as follows: PHB: 128 ± 50°, PSD: 32 ± 14°, and Entropy: 65 ± 10%. CRT implantation was successful in all patients without any complications. The most common location for latest mechanical activation was the lateral wall. Of 30 patients, LV lead position was concordant in 23 (77%) patients and discordant in 7 (23%).

4.2. Clinical and Echocardiographic Responses to CRT

At 6-month follow-up, CRT implantation resulted in significant improvements in the NYHA functional class (2.8 ± 0.4 *vs.* 1.7 ± 0.6, P = 0.0001) and the 6-MWT distance (253 ± 127 *vs.* 357 ± 97 meter, P = 0.0001). In addition, a significant improvement in echocardiographic variables was observed in the responders. LVESV decreased from 181 ± 45 to 113 ± 43 mL (P = 0.001), LVEDV decreased from 241 ± 48 to 140 ± 49 mL (P = 0.0001), and LVEF improved from 19 ± 4 to 29 ± 10% (P = 0.0001). There was no mortality in this cohort.

At 6-month follow up, clinical response to CRT (≥ 1 NYHA class improvement) was observed in 74% of patients. However, only 57% of patients were responders according to echocardiographic criteria (≥ 15% decrease in LVESV). There were no significant differences in baseline clinical and echocardiographic characteristics between the responders and non-responders; however, GMPS-derived LV dyssynchrony data were significantly different between the responders and non-responders; PHB (151 ± 55° *vs.* 102 ± 42°, P = 0.01), PSD (40 ± 14° *vs.* 27 ± 14°, P = 0.01), and Entropy (70 ± 10% *vs.* 63 ± 8%, P = 0.045) were significantly greater in responders (Table 2). Seventy-five percent of responders and 12% of non-responders were concordant (P = 0.04).

4.3. GMPS-Derived Predictors of CRT Response

To define the optimal cutoff value for PHB, PSD, and Entropy to predict response to CRT, receiver-operating curve (ROC) analysis was performed, while defining responders as those exhibiting an improvement in NYHA functional class of ≥ 1 score. A cutoff value of 112° for PHB can predict the clinical response to CRT with a sensitivity of 72% and specificity of 70%. The area under the curve was 0.76, which indicates good predictive value (Figure 1). Similarly, ROC analysis was performed to determine the optimal cutoffs for PSD and Entropy. A cutoff value of 21° for PSD (area under curve: 0.72) yielded sensitivity of 90% and specificity of 74% for prediction of clinical response (Figure 1). Optimal cutoff for Entropy was determined as 52% (area under curve: 0.73) with a sensitivity of 90% and a specificity of 80%.

Table 1. Baseline Characteristics of the Study Population (n = 30) [a,b]

Clinical characteristics	Value
Age, mean ± SD, y	61 ± 10
Men, No. (%)	19 (63)
Ischemic cardiomyopathy, No. (%)	26 (86)
Idiopathic dilated cardiomyopathy, No. (%)	4 (14)
QRS duration, ms	156 ± 22
Two-dimensional echo variables	
Left ventricular end-diastolic volume, mL	241 ± 48
Left ventricular end-systolic volume, mL	181 ± 45
Left ventricular ejection fraction, %	19 ± 4
6-min walk test distance, m	253 ± 127
NYHA class before CRT	2.8 ± 0.40
Gated SPECT variables	
Phase histogram bandwidth, °	128 ± 50
Phase standard deviation, °	32 ± 14
Entropy, %	65 ± 10

[a] Abbreviations: CRT, cardiac resynchronization therapy; NYHA, new york heart association; SPECT, single-photon emission computed tomography.
[b] Data are presented as No (%) or mean ± SD.

Table 2. Baseline Characteristics of Responders and Nonresponders [a, b]

Baseline characteristics	Responders	Nonre-sponders	P Value
Age, mean ± SD, y	62 ± 12	60 ± 8.0	0.65
Men, No.	12	7	0.98
Ischemic cardiomyopathy, No. (%)	16	10	0.60
QRS width, ms	154 ± 21	160 ± 25	0.55
Two-dimensional echo variables			
Left ventricular end-diastolic volume, mL	212 ± 52	292 ± 45	0.15
Left ventricular end-systolic volume, mL	152 ± 46	230 ± 40	0.12
Left ventricular ejection fraction, %	19.7 ± 3.8	19.0 ± 3.7	0.66
6-min walk test distance, m	260 ± 126	247 ± 128	0.55
NYHA class before CRT	2.9 ± 0.30	2.6 ± 0.50	0.15
Gated SPECT variables			
Phase histogram bandwidth, °	151 ± 55	102 ± 42	0.011
Phase standard deviation, °	40 ± 14	27 ± 14	0.012
Entropy, %	70 ± 10	63 ± 8	0.045

[a] Abbreviations: CRT, cardiac resynchronization therapy; NYHA, new york heart association; SPECT, single-photon emission computed tomography.
[b] Data are presented as No. (%) or Mean ± SD.
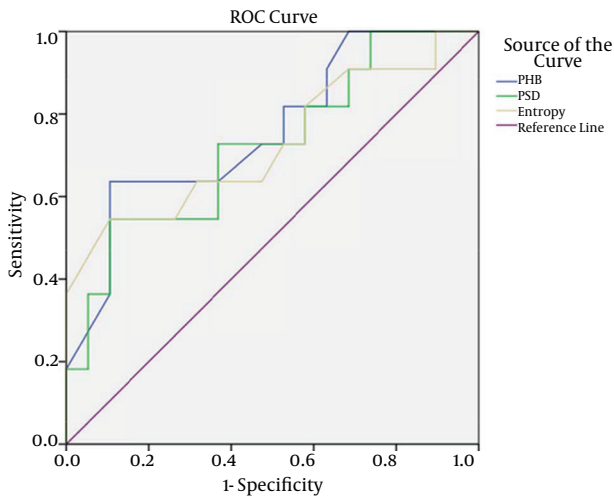
Abbreviations: GMPS, Gated Myocardial Perfusion Single-Photon Emission Tomography; PHB, Phase Histogram Bandwidth; PSD, Phase Standard Deviation.

5. Discussion

The major findings of the present study were as follows: (1) LV dyssynchrony assessed with phase analysis on GMPS could predict clinical response to CRT; (2) Three values in GMPS were able to discriminate responders and nonresponders. PHB cutoff value of 112° (sensitivity of 72% and specificity of 70%), PSD cutoff of 21° (sensitivity of 90% and specificity of 74%), and Entropy cutoff of 52% (sensitivity of 90% and specificity of 80%) are recommended to select CRT responders.

Nuclear imaging has been used to evaluate ventricular dyssynchrony since 1980s. Tsurugaya and colleagues (10) showed significant improvement in LV dyssynchrony in responders. After a follow-up of 18 ± 6 months, patients were classified as responders or nonresponders according to their clinical status and echocardiographic parameters. Sciagra et al. (11) evaluated the use of gated perfusion SPECT to predict response of HF patients to CRT. Patients with extensive resting perfusion defect had a poor response to CRT. Recent analysis of cardiac resynchronization in heart failure (CARE-HF) trial showed that patients with LV dyssynchrony had a long term outcome superior to patients without substantial LV dyssynchrony (12).

5.1. GMPS as a Predictor of CRT Response

Predictive role of echo-derived LV dyssynchrony parameters has been demonstrated in several studies; however, to the best of our knowledge only two studies investigated the predictive power of GMPS-derive LV dyssynchrony in predicting CRT response. In the first study, Henneman et al. (13) evaluated LV dyssynchrony from GMPS using the software from the Emory university (Emory cardiac toolbox-ECTb, Emory University/Syntermed, Atlanta, Ga). In this study, 42 patients with advanced HF (NYHA class III and IV), an LVEF $\leq 35\%$ and a QRS width ≥ 120 ms underwent GMPS before CRT implantation. They found that LV dyssynchrony measures (PHB and PSD) were independent predictors of CRT response six months after device implantation. In this study, a cutoff value of 43° for PSD yielded a sensitivity and specificity of 74% to predict response to CRT; a cutoff value of 135° for histogram bandwidth had a sensitivity and specificity of 70%. In the second study, Boogers et al. (14) investigated feasibility of LV dyssynchrony assessment with phase analysis on GMPS using the Quantitative Gated SPECT (QGS) software (Cedars-Sinai). For this purpose, they enrolled 40 patients with severe HF (NYHA class III-IV), LVEF $\leq 35\%$ and a QRS width ≥ 120 ms. They showed that QGS phase analysis on GMPS correlated significantly with TDI for the assessment of LV dyssynchrony. Moreover, they reported a high accuracy to predict response to CRT using either PHB (cutoff value of 72.5°, sensitivity of 83% and specificity of 81%) or PSD (cutoff value of 19.6°, sensitivity of 83% and specificity of 81%). Overall, it appears that GMPS-derive LV dyssynchrony measures can predict response to CRT; however, different cutoffs should be used for different software. There is limited information on the value of concordant lead position in long-term outcome of patients after CRT implantation. In a study by Zhang et al. (15), 134 patients with heart failure were treated with CRT and followed up for a mean of 39 ± 24 months. Posterolateral LV lead position predicted lower cardiovascular mortality (21% versus 41% P = 0.009). Although, positioning the LV pacing lead at the latest active site may provide the greatest benefit of CRT as previously demonstrated (15-17). The present study showed that appropriate location of LV pacing lead could be a good predictor of CRT response.

5.2. Limitations

Some study limitations need to be acknowledged. First, the study findings were based on a relatively small number of patients referred for CRT. Another limitation of GMPS is the radiation burden, which makes this technique less proper for follow-up study. Although, other techniques such as MRI and TDI can be used to provide information about LV dyssynchrony, they all provide useful information and choosing one of these techniques is determined by local expertise and availability.

Clinical response to CRT is related to LV dyssynchrony assessed by phase analysis from GMPS. PHB, PSD, and Entropy can predict response to CRT; however, the present results need to be confirmed in a larger patient population.

Authors' Contributions

Dr. Haghjoo: design of study, study supervisor and revised the manuscript. Dr. Rastgou: observer and study

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