Multimodality imaging in chronic coronary artery disease

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Chapter 9

Phase analysis of gated myocardial perfusion single photon emission computed tomography compared to tissue Doppler imaging for the assessment of left ventricular dyssynchrony

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Abstract

Introduction: The aim of the study was to compare left ventricular (LV) dyssynchrony assessment by gated myocardial perfusion SPECT (GMPS) and tissue Doppler imaging (TDI). Recently, it has been suggested that LV dyssynchrony is an important predictor of response to cardiac resynchronization therapy (CRT); dyssynchrony is predominantly assessed by TDI with echocardiography. Information on LV dyssynchrony can also be provided by GMPS with phase analysis of regional LV maximal count changes throughout the cardiac cycle which tracks the onset of LV thickening.

Methods: In 75 patients with heart failure, depressed LV function and wide QRS complex, GMPS and 2D echocardiography, including TDI, were performed as part of clinical screening for eligibility for CRT. Clinical status was evaluated using NYHA classification, 6-minute walk distance and quality-of-life score. Different parameters (histogram bandwidth, phase standard deviation (SD), histogram skewness and histogram kurtosis) of LV dyssynchrony were assessed from GMPS and compared with LV dyssynchrony on TDI using Pearson's correlation analyses.

Results: Histogram bandwidth and phase SD correlated well with LV dyssynchrony assessed with TDI ($r=0.89$, $P<0.0001$ and $r=0.80$, $P<0.0001$ respectively). Histogram skewness and kurtosis correlated less well with LV dyssynchrony on TDI ($r=-0.52$, $P<0.0001$ and $r=-0.45$, $P<0.0001$ respectively).

Conclusions: LV dyssynchrony assessed from GMPS correlated well with dyssynchrony assessed by TDI; histogram bandwidth and phase SD showed the best correlation with LV dyssynchrony on TDI. These parameters appear most optimal for assessment of LV dyssynchrony with gated SPECT. Outcome studies after CRT are needed to further validate the use of GMPS for assessment of LV dyssynchrony.

Introduction

Several studies have demonstrated the potential benefit of cardiac resynchronization therapy (CRT) in the treatment of end-stage heart failure.[1-3] Recently, it has been suggested that left ventricular (LV) dyssynchrony is an important predictor of response to CRT, which can be assessed with echocardiography, in particular with tissue Doppler imaging (TDI).[4] TDI permits assessment of segmental myocardial velocities and comparison of the timing of these different segmental velocities allows assessment of LV synchrony or dyssynchrony.[4-6] Specifically, the presence of LV dyssynchrony of 65 ms or more has been demonstrated to adequately predict response to CRT.[4]

Gated single photon emission computed tomography (SPECT) is used for assessment of myocardial perfusion but also provides information on regional wall thickening.[7-9] A count-based method has been developed to extract amplitude (systolic wall thickening) and phase from the regional LV count changes throughout the cardiac cycle. The phase information is related to the time interval when a region in the 3D LV myocardial wall starts to contract. It provides information as to how uniform or inhomogeneous is the distribution of these time intervals for the entire LV, i.e. a measure of LV (dys)synchrony. Recently, this technique has been implemented to the Emory Cardiac Toolbox as a diagnostic tool for assessment of the LV mechanical (dys)synchrony.[10]

The purpose of the present study was to compare the degree of LV dyssynchrony as assessed with phase analysis from gated myocardial perfusion SPECT (GMPS), to the degree of LV dyssynchrony as assessed with TDI in patients with heart failure, depressed LV ejection fraction (LVEF) and wide QRS complex.

Methods

Patients and study protocol

The study population consisted of 75 consecutive patients with heart failure who were clinically referred for evaluation of potential eligibility for CRT. Selection criteria for CRT included severe heart failure (NYHA III or IV), LVEF <35%, and prolonged QRS duration (>120 ms). Medication included diuretics in 92% of patients, ACE inhibitors in 91%, and beta-blockers in 71%. The clinical status of the patients was evaluated, using the NYHA functional class, 6-minute walk distance[11] and quality-of-life score (with the Minnesota Quality of Life Questionnaire).[12]

Resting GMPS with technetium-99m tetrofosmin was clinically performed to exclude extensive ischemia and/or viability, in order to refer patients to revascularization if indicated.[7 8] Extensive echocardiographic analysis, including tissue Doppler imaging (TDI), was performed to evaluate LV function, size and LV dyssynchrony, as previously described.[4] The potential to derive LV dyssynchrony from GMPS was then evaluated. Various parameters (details see below) were obtained from phase analysis using the Emory Cardiac Toolbox software[10], aiming to evaluate LV dyssynchrony. Echocardiographic data obtained with TDI, assessing LV dyssynchrony, were used for comparison.[4]

Gated Myocardial Perfusion SPECT

Resting GMPS with technetium-99m tetrofosmin (500 MBq, injected at rest) was performed using a triple head SPECT camera system (GCA 9300/HG, Toshiba Corp.) equipped with low energy high resolution collimators. Around the 140-KeV energy peak of technetium-99m tetrofosmin, a 20% window was used. A total of 90 projections (step and shoot mode, 35 seconds per projection, imaging time 23 minutes) were obtained over a 360-degree circular orbit. GMPS acquisition involved 16 frames per cardiac cycle. Data were stored in a 64x64 matrix. Data were reconstructed by filtered backprojection and then reoriented to yield gated short-axis images. The reconstruction was performed over 360 degrees. These images were then submitted to the Emory Cardiac Toolbox for phase analysis. All SPECT images were analyzed at the department of radiology of Emory University School of Medicine by J.C. and E.V.G., who were blinded to the echocardiographic and clinical data. A phase distribution was extracted from a GMPS study to represent the regional onset of mechanical contraction of the left ventricle. It can be displayed in a polar map or in 3D, and used to generate a phase histogram. Examples are shown in **Figure 1.**

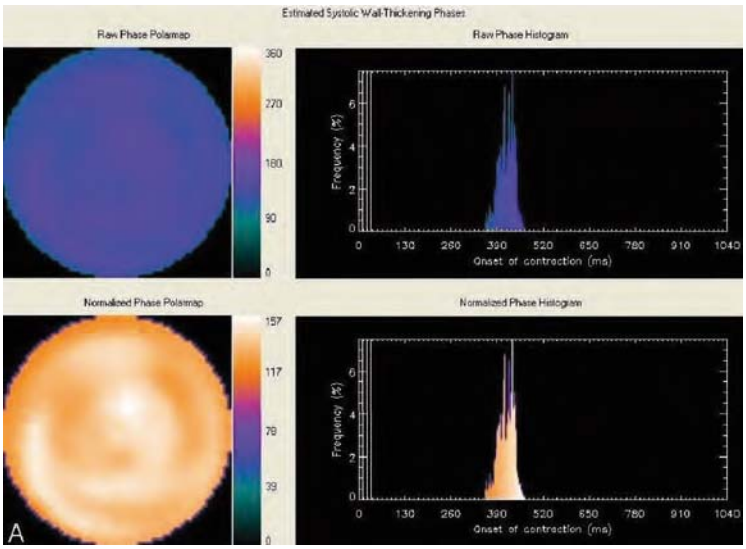

Figure 1A. Example of a patient without LV dyssynchrony on GMPS. The non-normalized (upper panel) and normalized (lower panel) phase distributions are nearly uniform and the corresponding phase histograms are highly-peaked, narrow distributions.

The following 4 quantitative indices were obtained from the phase analysis of all patients: 1. histogram bandwidth, which includes 95% of the elements of the phase distribution; 2. phase SD, which is the SD of the phase distribution; 3. phase histogram skewness, which indicates the symmetry of the histogram; and 4. histogram kurtosis, which indicates the degree to which the histogram is peaked.[10] Preliminary normal databases for these quantitative indices have been created.[10] From the phase polar maps the site of latest activation was identified (4 regions were evaluated including anterior, inferior, lateral, septal). The region with the latest activation had larger phases and appeared in the phase polar map as a brighter region. In a healthy individual, the LV contracts in a coordinated manner and most of the myocardial segments have the same or similar phases. Thus, the phase distribution is nearly uniform and the phase histogram is a highly peaked, narrow distribution (**Figure 1A**). As the LV mechanical synchrony worsens (becoming dyssynchronous), the phase SD and histogram bandwidth are expected to increase (**Figure 1B**).

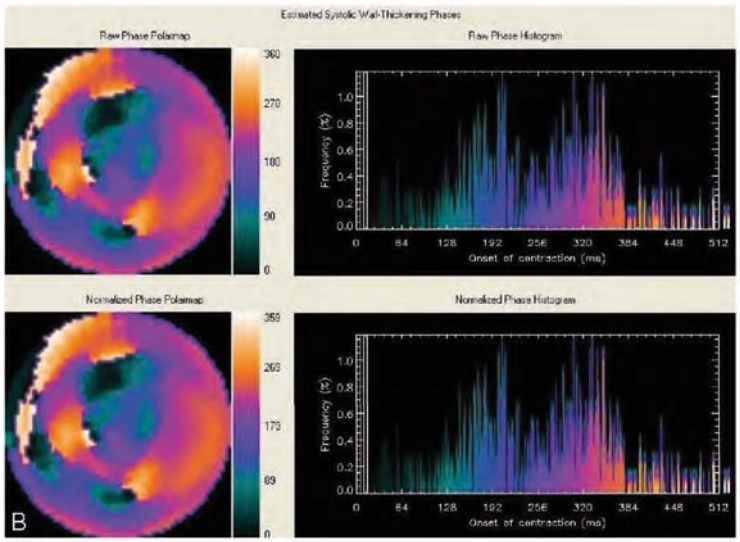

Figure 1B. Example of a patient with LV dyssynchrony derived from GMPS. The non-normalized (upper panel) and normalized (lower panel) phase distributions show significant non-uniformity and the corresponding phase histograms are widely-spread distributions.

2D Echocardiography and TDI

Patients were imaged in the left lateral decubitus position with a commercially available system (Vingmed Vivid Seven, GE-Vingmed, Milwaukee Wisconsin, USA). In all patients the acoustic window was adequate, yielding good image quality.

Images were acquired using 3.5-MHz transducer at a depth of 16 cm in the parasternal view and apical 2- and 4-chamber views. Standard 2D and color Doppler data, triggered to the QRS complex, were saved in cineloop format. All echocardiographic examinations were performed by the same experienced echocardiographist, and all examinations were evaluated by consensus by

2 experienced cardiologists, blinded to the SPECT and clinical data in Leiden University Medical Center. LV volumes (end-systolic and end-diastolic) were derived from the conventional apical 2- and 4-chamber views, and LVEF was calculated using the biplane Simpson's rule.[13] In addition to the conventional 2D echocardiographic examination, TDI was performed to assess LV dyssynchrony. For TDI, color Doppler frame rates varied from 80 to 115 frames/s, depending on the sector width of the region of interest. Pulse repetition frequencies ranged from 500 Hz to 1 kHz, resulting in aliasing velocities of 16 to 32 cm/s. TDI parameters were measured from color-coded images from 3 consecutive heart beats by off-line analysis. Data were analyzed using commercially available software (Echopac 6.1, GE-Vingmed).

To determine LV dyssynchrony, the sample volume was placed in the basal portions of the septum, inferior, anterior and lateral wall (using the 2- and 4-chamber images); peak systolic velocities and time-to-peak systolic velocities were obtained. The delay in peak velocity between the earliest and latest activated segments was calculated as indicator of LV dyssynchrony.[4]

Statistical Analysis

Continuous data are expressed as mean±SD. Pearson's correlation analysis was performed to evaluate the relation between histogram bandwidth, phase SD, histogram skewness and histogram kurtosis by the phase analysis of GMPS and LV dyssynchrony by TDI. Multivariable linear regression analysis was performed to determine the relation between LV dyssynchrony assessed with TDI as dependent variable and histogram bandwidth, phase SD, histogram skewness, histogram kurtosis, etiology of heart failure, gender, age, LVEF, LVEDV, LVESV and NYHA as independent variables. A P-value <0.05 was considered statistically significant.

Results

The study population consisted of 54 men and 21 women, with a mean age of 66±9 years. Patient characteristics are summarized in **Table 1**. Mean NYHA functional class was 2.9±0.3 and mean LVEF was 25±8%. In all patients histogram bandwidth, phase SD, histogram skewness and histogram kurtosis were assessed with the phase analysis of GMPS and compared to the LV dyssynchrony as evaluated with TDI.

Table 1. Clinical characteristics of the study population (n=75).

Characteristic	
Age (yrs)	66±9
Men	54(72%)
Ischemic cardiomyopathy	49(65%)
Idiopathic dilated cardiomyopathy	26(35%)
Previous infarction	41(55%)
Q wave on electrocardiogram	24(32%)
2D echo parameters	
LVEDV (ml)	241±84
LVESV (ml)	185±79
LVEF (%)	25±8
6-MWT (m)	320±107
QoL	35±17
NYHA functional class	2.9±0.3

6-MWT=6-minute walk test; NYHA=New York Heart Association; QoL=quality-of-life score according to the Minnesota living with heart failure questionnaire

Histogram bandwidth

The mean histogram bandwidth was 149±70° (range 31° to 304°), while the normal value of histogram bandwidth is 38.7±11.8° for men, and 30.6±9.6° for women.[10] Pearson's correlation showed a good correlation with LV dyssynchrony as assessed with TDI (r=0.89, P <0.0001, **Figure 2**).

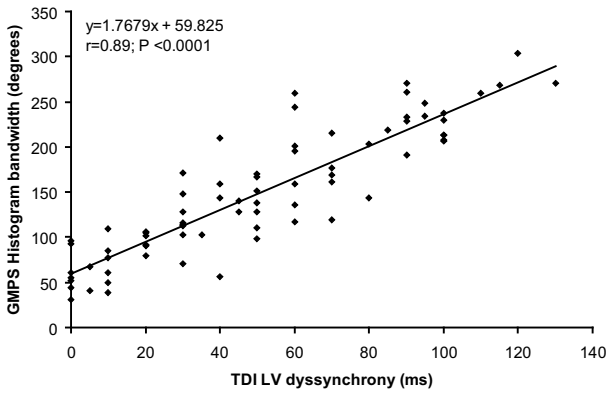

Figure 2. Histogram bandwidth derived from GMPS vs. LV dyssynchrony assessed with TDI. Linear regression plot shows correlation between histogram bandwidth assessed from GMPS and LV dyssynchrony assessed with TDI.

Phase SD

The mean phase SD was 48.6±21.3° (range 10.2° to 98.8°), while the normal value of phase SD is 14.2±5.1° for men, and 11.8±5.2° for women.[10] Pearson's correlation demonstrated a good correlation with LV dyssynchrony as measured with TDI (r=0.80, P <0.0001, **Figure 3**).

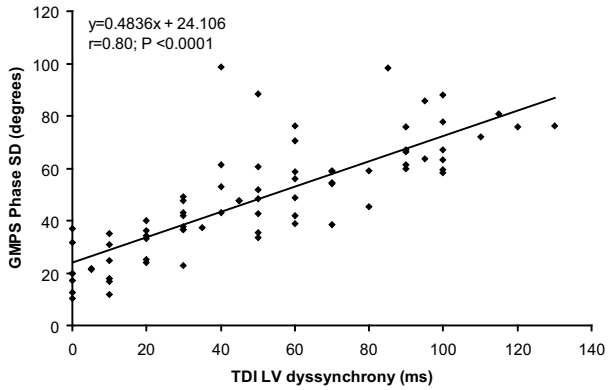

Figure 3. Phase SD derived from GMPS vs. LV dyssynchrony assessed with TDI. Linear regression plot shows correlation between phase SD assessed from GMPS and LV dyssynchrony assessed with TDI.

Histogram skewness

The mean skewness was 2.24±0.71 (range 1.15 to 4.57), while the normal value of histogram skewness is 4.19±0.68 for men, and 4.60±0.72 for women.[10] A fair correlation with LV dyssynchrony as assessed with TDI was demonstrated by Pearson's correlation, with a correlation coefficient r=-0.52, P <0.0001 (**Figure 4**) .

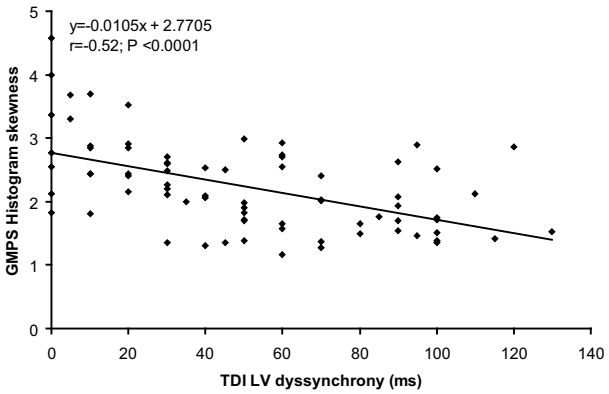

Figure 4. Histogram skewness derived from GMPS vs. LV dyssynchrony assessed with TDI. Linear regression plot shows correlation between histogram skewness assessed from GMPS and LV dyssynchrony assessed with TDI.

Histogram kurtosis

The mean kurtosis was 5.81±4.31 (range 0.53 to 23.08), while the normal value of histogram kurtosis is 19.72±7.68 for men, and 23.21±8.16 for women.[10] A fair correlation with LV dyssynchrony as evaluated with TDI was shown by Pearson's correlation, with correlation coefficient r=-0.45, P <0.0001 (**Figure 5**).

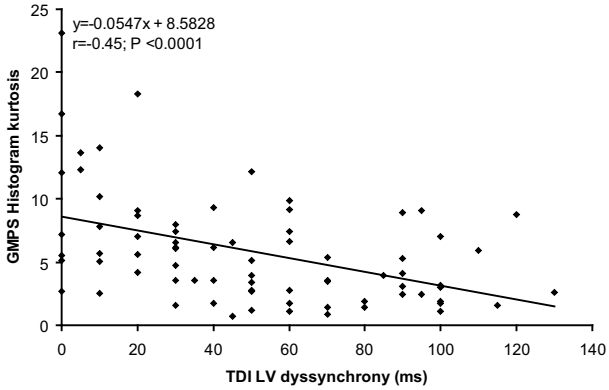

Figure 5. Histogram kurtosis derived from GMPS vs. LV dyssynchrony with TDI. Linear regression plot shows correlation between histogram kurtosis assessed from GMPS and LV dyssynchrony assessed with TDI.

Idiopathic dilated cardiomyopathy vs. ischemic cardiomyopathy

In total, 26 patients had idiopathic dilated cardiomyopathy, whereas 49 patients had ischemic cardiomyopathy. Correlation coefficients for histogram bandwidth, phase SD and histogram skewness were higher in patients with idiopathic dilated cardiomyopathy, whereas the correlation coefficient for histogram kurtosis was lower (**Table 2**). This difference was statistically significant for phase SD (P=0.03).

Table 2. Correlation coefficients of LV dyssynchrony, assessed with TDI, vs. the different LV dyssynchrony parameters, derived from phase analysis of GMPS (idiopathic dilated cardiomyopathy vs. ischemic cardiomyopathy).

	Idiopathic dilated cardiomyopathy (n=26)	Ischemic cardiomyopathy (n=49)	P-value
Histogram Bandwidth	r=0.90	r=0.89	0.40
Phase SD	r=0.87	r=0.77	0.03
Histogram skewness	r=-0.53	r=-0.52	0.72
Histogram kurtosis	r=-0.43	r=-0.45	0.54

Impact of histogram bandwidth and other variables on LV dyssynchrony assessed with TDI

Histogram bandwidth and phase SD showed strongest correlation with LV dyssynchrony assessed with TDI (**Table 3**).

Table 3. Regression model: TDI dependent variable, independent variables histogram bandwidth, phase SD, skewness, kurtosis, etiology, gender, age, LVEF, LVEDV, LVESV and NYHA functional class

Variable	Regression coefficients (confidence interval)	P-value
Histogram bandwidth	0.36 (0.26 – 0.46)	0.000
Phase SD	0.52 (0.10 – 0.95)	0.02
Histogram skewness	22.02 (-3.37 – 47.40)	0.09
Histogram kurtosis	-3.18 (-6.85 – 0.49)	0.09
Etiology	-1.26 (-9.93 – 7.40)	0.77
Gender	-4.12 (-13.03 – 4.79)	0.36
Age	0.01 (-0.42 – 0.44)	0.96
LVEF	-1.06 (-2.19 – 0.08)	0.07
LVEDV	0.17 (-0.20 – 0.54)	0.35
LVESV	-0.29 (-0.74 – 0.16)	0.20
NYHA	0.67 (-10.20 – 11.54)	0.90

Discussion

With the introduction of CRT, a new therapeutic option for patients with end-stage heart failure has emerged. Long-term benefit from CRT has been shown in large trials, demonstrating an improvement in NYHA functional class, 6-minute walk distance, and quality-of-life score.[1 2] In addition, echocardiographic studies have shown improvement in LVEF with a reduction in LV volumes (reverse remodeling).[14 15]

Since not all patients respond equally well to CRT, selection criteria have been defined in the ACC/AHA/NASPE guidelines; these selection criteria include end-stage, drug-refractory heart failure, severe LV dysfunction and wide QRS complex.[16] Still 20% to 30% of the selected patients do not benefit from CRT.[2 17] Better identification of these patients is needed and echocardiographic studies have shown that so-called responders and nonresponders can be distinguished based on the presence or absence of LV dyssynchrony.[5 18 19] In particular, TDI has been shown useful to detect LV dyssynchrony and predict response to CRT.[4]

In the current study, the value of phase analysis derived from GMPS to assess LV dyssynchrony was evaluated. The phase analysis tool in the Emory Cardiac Toolbox extracts a phase distribution from a GMPS study representing the regional LV onset of mechanical contraction. Quantitative indices such as phase SD and histogram bandwidth are then calculated from the phase distribution to assess the LV mechanical (dys)synchrony. In the present study, this technique was compared to TDI for assessment of LV dyssynchrony. Good correlations were noted for histogram bandwidth and LV dyssynchrony assessed with TDI, and for phase SD and LV dyssynchrony assessed with TDI (r=0.89 and r=0.80, respectively). These correlations support the hypothesis that the phase analysis of GMPS can be used to assess LV dyssynchrony. Furthermore, histogram bandwidth and phase SD

best correlated with LV dyssynchrony assessed with TDI.

In total, 49 patients had ischemic cardiomyopathy, whereas 26 patients had idiopathic dilated cardiomyopathy. Correlation coefficients for histogram bandwidth, phase SD and histogram skewness were higher in patients with idiopathic dilated cardiomyopathy, whereas the correlation coefficient for histogram kurtosis was lower. This difference was statistically significant for phase SD (P=0.03). This observation could imply that LV dyssynchrony as assessed with GMPS relates better with LV dyssynchrony as evaluated with TDI in patients with idiopathic dilated cardiomyopathy. However, taken in consideration the relatively small patient population in the present study, this conclusion would be premature.

Recently, a cutoff value of ≥65 ms for LV dyssynchrony has been proposed for the prediction of response to CRT. Using this cutoff value, the sensitivity as well as the specificity for predicting clinical improvement was 80%, whereas the sensitivity and specificity for reverse LV remodeling were both 92%.[4] For the usefulness of the phase analysis of GMPS in daily clinical practice, it would be desirable to determine cutoff values for the parameters given by the phase analysis. However, in the current study only the correlations between the different parameters derived from GMPS and LV dyssynchrony derived from TDI, were evaluated. Future studies comparing TDI and GMPS in patients undergoing CRT are needed to determine on potential cutoff values from GMPS.

Several limitations need to be acknowledged. First of all, follow-up data after CRT implantation were not available; therefore it remains to be determined what the value of GMPS is, for prediction of response to CRT. Another limitation of GMPS in general, is that GMPS is less suitable than echocardiography for follow-up after CRT implantation, due to the radiation burden.

Conclusions

In summary, the current findings demonstrate the feasibility to evaluate LV dyssynchrony with GMPS, and its applicability in a clinical setting. The phase analysis from GMPS was compared with TDI for assessment of LV dyssynchrony and the results demonstrate that the histogram bandwidth and phase SD may be the preferred parameters from GMPS to assess LV dyssynchrony, since these parameters correlated best with LV dyssynchrony as derived from TDI. Outcome studies after CRT are needed to further validate the use of GMPS for assessment of LV dyssynchrony.

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