Cardiac resynchronization therapy : determinants of patient outcome and emerging indications

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Chapter 14

Optimal left ventricular lead position assessed with phase analysis on gated myocardial perfusion SPECT

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ABSTRACT

Background: The current study aimed to evaluate the relation between the site of latest mechanical activation as assessed with gated myocardial perfusion SPECT (GMPS), left ventricular (LV) lead position and response to cardiac resynchronization therapy (CRT).

Methods: The patient population consisted of consecutive advanced heart failure patients currently indicated for CRT. Before implantation, 2D echocardiography and GMPS were performed. 2D echocardiography was performed to assess LV end-systolic volume (LVESV), LV end-diastolic volume (LVEDV) and LV ejection fraction (LVEF). The site of latest mechanical activation was assessed by phase analysis on GMPS and related to LV lead position on fluoroscopy. Echocardiography was repeated after 6 months of CRT. CRT response was defined as >15% decrease in LVESV.

Results: Ninety patients (72% men, 67±10 yrs) with advanced heart failure were enrolled. In 52 (58%) patients, the LV lead was positioned at the site of latest mechanical activation (concordant), whereas the LV lead was positioned outside the site of latest mechanical activation (discordant) in 38 (42%) patients. CRT response was significantly more often documented in patients with concordant LV lead position than in patients with discordant LV lead position (79% vs. 26%, $p<0.01$). After 6 months, patients with concordant LV lead position showed significant improvement in LVEF, LVESV and LVEDV ($p<0.05$), whereas patients with discordant LV lead position showed no significant improvement in these variables.

Conclusions: Patients with concordant LV lead position showed significant improvement in LV volumes and LV systolic function, whereas patients with discordant LV lead position showed no significant improvements.

INTRODUCTION

Cardiac resynchronization therapy (CRT) represents an established therapeutic option for patients with drug-refractory advanced heart failure and ventricular conduction delay.[1, 2] The merits of CRT have been demonstrated for morbidity and mortality in several randomized clinical trials which have currently included more than 4,000 patients diagnosed with moderate-to-severe heart failure.[3-6] Even though promising results have been reported, individual response to CRT varies with up to one-third of the heart failure patients showing no success to CRT.[5, 7]

Different mechanisms play an important role in the response to CRT, such as pre-existent mechanical dyssynchrony, location and extent of scarred myocardium and the position of the left ventricular (LV) pacing lead.[7, 8] The region of LV pacing and the area of latest mechanical activation, seem to be important factors in the prediction of outcome to CRT.[9-14] To date, the LV pacing lead is usually positioned in the lateral or posterolateral vein of the coronary sinus, since the largest hemodynamic response was observed when pacing the free lateral wall.[9] However, recent studies have also demonstrated that the region of latest mechanical activation may vary significantly in patients eligible for CRT.[10, 14-16] Previous studies using echocardiography have reported that patients with the LV lead positioned at the site of latest mechanical activation (concordant LV lead) showed superior response to CRT when compared to patients with the LV lead positioned outside the area of latest mechanical activation (discordant LV lead).[10, 14-16]

Phase analysis on gated myocardial perfusion single photon emission computed tomography (SPECT) (GMPS) has been developed to evaluate the presence and extent of mechanical dyssynchrony using an automatic and standardized approach.[17, 18] Recent developments have resulted in an integrated evaluation of mechanical dyssynchrony, regional mechanical activation pattern and the site of latest mechanical activation using the same SPECT data set. Hence, GMPS with phase analysis may provide important information for assessment of optimal LV lead position in patients referred for CRT. Currently, no study has been performed evaluating the use of GMPS to assess the preferred LV lead position. Moreover, the relation between the site of latest mechanical activation as derived from GMPS, LV lead position and CRT response is unknown. Accordingly, the current study sought to evaluate the feasibility of GMPS to assess the preferred LV lead position. In addition, the study aimed to evaluate the relation between the site of latest mechanical activation, LV lead position and CRT response in patients with CRT.

METHODS

Patient population and protocol

Patients with advanced drug-refractory heart failure (New York Heart Association (NYHA) functional class III-IV), reduced LV systolic function (left ventricular ejection fraction (LVEF) ≤35%), prolonged QRS interval (≥120 ms) and sinus rhythm were consecutively included for implantation of a CRT device.[1, 2] Patients with decompensated heart failure, recent myocardial infarction (within 3 months of CRT device implantation) or who died during 6-months follow-up were excluded. Ischemic cardiomyopathy was defined as the presence of ≥50% stenosis in one or more of the major epicardial coronary arteries and/or previous myocardial infarction or percutaneous coronary intervention.

Prior to CRT device implantation, resting GMPS with ^{99m}technetium tetrofosmin and transthoracic 2D echocardiography were performed in all patients. Clinical status was evaluated by assessment of NYHA functional class. Resting myocardial perfusion imaging was performed to assess the presence and extent of myocardial infarction, whereas phase analyses of GMPS studies was used to assess the site of latest mechanical activation. Resting transthoracic 2D echocardiography was performed to measure LVEF and LV volumes. Additionally, speckle-tracking radial strain analysis on 2D echocardiography was performed in a subset of 50 patients to validate the assessment of the site of latest mechanical activation as derived from GMPS.

After 6 months of CRT, assessment of clinical status and resting 2D transthoracic echocardiography were repeated. Patients with a decrease of >15% in LV end-systolic volume (LVESV) were classified as responders to CRT, whereas patients without <15% decrease in LVESV were classified as non-responders to CRT.[19] Consecutively, the relation between the site of latest mechanical activation on GMPS, LV lead position and CRT response was evaluated.

Gated myocardial perfusion SPECT: acquisition

GMPS imaging with ^{99m}technetium tetrofosmin (500 MBq, MYOVIEW, General Electric Healthcare, United Kingdom) was performed at rest using a triple-head SPECT camera system (GCA 9300/HG; Toshiba Corporation, Tokyo, Japan) equipped with low-energy high-resolution collimators. A 20% window was used around the 140-KeV energy peak of ^{99m}technetium tetrofosmin and 90 projections (step and shoot method, 35 s/projection, 64 x 64 matrix, total imaging time 23 minutes) were obtained over a 360° circular orbit. Acquisition involved 16 frames per cardiac cycle. Data were reconstructed by filtered back projection and reoriented into long- and short-axis projections perpendicular to the heart axis.[20] The short-axis slices were displayed in polar map format and they were normalized for maximal myocardial activity (100%). No attenuation correction was used in this study. Two experienced observers who were blinded to other study data evaluated the SPECT studies. Cardiac segments with <50% tracer uptake were considered as segments with a perfusion defect. The extent of myocardial perfusion defects (<50% tracer uptake) was expressed as a percentage of the myocardium. Consecutively, reoriented gated short-axis images were submitted to the Emory Cardiac Toolbox (Emory University, Atlanta, Georgia, USA) for phase analysis processing. Phase analysis measurements were performed at the Emory University (blinded to echocardiographic and clinical data).

Phase analysis

Phase analysis on GMPS was used to obtain the site of latest mechanical activation. Phase analysis of GMPS studies is based on the partial-volume effect wherein alterations in regional maximum counts are relative to myocardial wall thickening.[21, 22] A 3D sampling algorithm is used to determine regional maximal counts per cardiac frame and is used to generate count-based wall thickening curves by approximation of first Fourier harmonics (FFH) function. The phase angle represents the onset of mechanical activation per segment. The distribution of phase angles within the LV can be displayed in polar map or histogram format and provides quantitative parameters of global LV dyssynchrony; histogram bandwidth (includes 95% of the phase angles) and phase standard deviation (SD) (standard deviation of phase distribution).[17, 18] In addition, phase analysis provides information on regional mechanical activation. For the current study, the area of latest mechanical activation was determined on GMPS studies using the 6-segment model (septal, anteroseptal, anterior, lateral, posterior and inferior).[23] Regions of interests (ROI) corresponding to the 6-segment model were automatically placed on the phase polar map as shown in Figure 1. Each ROI covered 45° and 6 short-axis slices starting from the middle slice toward the base. As the 3D sampling algorithm collected one sample for every 9°, each ROI contains 5 x 6 = 30 samples. The mean phases of the 6 segments were calculated by averaging the phases of their 30 samples and then compared. The latest mechanically activated segment had the largest phase angles.

The intra- and interobserver reproducibility of phase analysis for assessment of the site of latest mechanical activation was determined in a subset of 30 patients, randomly selected from the patient population.

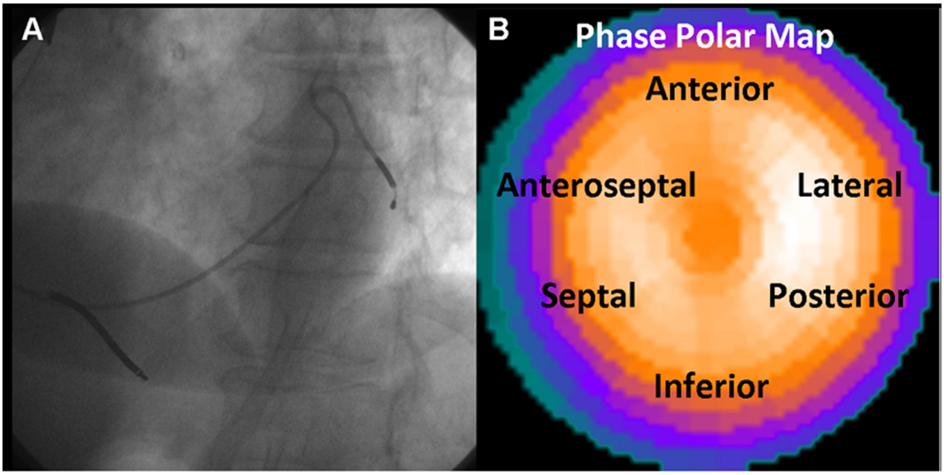

Figure 1. The site of latest mechanical activation was assessed on gated myocardial perfusion single photon emission computed tomography (SPECT) (GMPS) (panel B) and related to the left ventricular (LV) lead position on fluoroscopy (panel A).
A. Panel A shows an example of a patient with the LV lead positioned in the lateral cardiac region.
B. The region of latest mechanical activation was automatically calculated using phase analysis on GMPS. The region of latest mechanical activation was located on the phase polar map using the 6-segment model.

Resting transthoracic echocardiography: acquisition

Echocardiographic images were obtained with a commercially available system (Vivid Seven, General Electric-Vingmed, Milwaukee, Wisconsin, USA) in patients lying in left lateral decubitus position. With a 3.5 MHz transducer data acquisition was performed at a depth of 16 cm in the parasternal and apical views (standard long- and short-axis, 2- and 4-chamber images). Conventional 2D images were obtained during breath hold and saved in cine-loop format from three consecutive beats for offline analysis (EchoPac version 7.0.0, General Electric-Vingmed, Milwaukee, Wisconsin, USA). From apical 2- and 4-chamber views, LVESV and LV end-diastolic volume (LVEDV) along with LVEF were measured using the biplane Simpson's approach.[24] Semi-quantitative assessment of mitral regurgitation was performed from color-flow Doppler images using the apical 4-chamber views. The severity was scored according to the following scale: (1) mild jet (area/left atrial area <20%), (2) moderate (jet area/left atrial area 20-45%) and (3) severe (jet area/left atrial area >45%).[25]

In 50 patients, the site of latest mechanical activation was assessed using 2D speckle-tracking radial strain analysis on baseline mid-ventricular short-axis images. Images were recorded at a frame rate of at least 30 frames/sec and time-frame curves were generated for 6 cardiac segments (EchoPac version 7.0.0, General Electric-Vingmed, Milwaukee, Wisconsin, USA) similar as for GMPS studies. Finally, the time between QRS onset and peak radial strain of the cardiac segments was used to assess the site of latest mechanical activation.[23]

CRT implantation

All leads were placed via the subclavian route and the right atrial and ventricular lead were placed conventionally.[26] With the use of a balloon catheter, a sinus venogram was obtained after occlusion of the coronary sinus. Subsequently, the LV pacing lead was inserted with an 8 Fr guiding catheter in the coronary sinus, preferably in the lateral or posterolateral vein. The positioning of the LV pacing lead was performed by an electrophysiologist who was blinded to other data. The V-V interval was not adjusted during the first 6 months of CRT.

LV lead position and the site of latest activation

LV lead positions were determined by an independent observer who was blinded to other data. The LV lead position was assessed on biplane fluoroscopy (which was obtained during implantation procedure) using the left anterior oblique (LAO 60˚) and right anterior oblique (RAO 30˚) view. For this analysis, LV pacing leads that were positioned in the basal or mid-region of the LV were included and LV leads positioned at the cardiac apex were excluded from further analysis. Using the 6-segment model[23], the LV lead positions were scored as anterior, lateral, posterior or inferior. Subsequently, the LV lead positions were related to the area of latest activation (6-segment model) as assessed with GMPS using phase analysis.

The LV lead position was considered concordant if the LV lead was positioned at the area of latest activation, whereas the LV lead position was considered discordant if the LV lead was positioned outside the area of latest activation.

Intra- and interobserver reproducibility for assessment of LV lead position was evaluated in a randomly selected subset of 30 patients. To assess intraobserver reproducibility, the position of the LV lead on biplane fluoroscopy was assessed twice by the same observer. To assess interobserver reproducibility, a second blinded observer assessed the LV lead position on biplane fluoroscopy.

Statistical analysis

Continuous data are presented as mean±SD and categorical data are presented as numbers and percentages. Differences in baseline characteristics between patients with concordant or discordant LV lead positions were studied with the unpaired Student's *t* test (continuous data) and Chi-square or Fisher exact tests (categorical data). During follow-up, changes in continuous data were studied using the paired Student's *t* test for both study groups. Agreement between GMPS with phase analysis and 2D speckle-tracking radial strain analysis for assessment of the site of latest mechanical activation was evaluated using Cohen's Kappa statistics, and *k* values were qualified as poor (<0.40), moderate (0.40-0.75) or good (>0.75) agreement. In addition, Cohen's Kappa statistics were used to evaluate intra- and interobserver reproducibility for assessment of the site of latest mechanical activation using phase analysis in a subset of 30 randomly selected patients. Similarly, Cohen's Kappa statistics were used to evaluate the intra- and interobserver reproducibility for assessment of the LV lead position on biplane fluoroscopy in 30 randomly selected patients. All tests were two-sided and for all analyses a p-value <0.05 was considered statistically significant. Statistical analyses were performed with SPSS software package, version 16.0 (SPSS Inc., Chicago, Illinois, USA).

RESULTS

Patient population

A total of 95 consecutive patients were derived from our ongoing clinical heart failure registry, of which 50 patients were part of previous work. Five patients were excluded because of (1) apical LV lead position (n = 3) or (2) cardiac death during 6-months follow-up (n = 2). The baseline characteristics of 90 heart failure patients (72% men, mean age 67±10 yrs) are listed in Table 1. The mean NYHA functional class was 3.0±0.4. Sixty-two (69%) patients were diagnosed with ischemic cardiomyopathy, whereas 28 (31%) patients had non-ischemic cardiomyopathy. Patients showed reduced LV systolic function, with a mean LVEF of 26±8%. The extent of myocardial perfusion defect was 26±16% on average. Medication consisted of diuretics (90% of patients), angiotensin-converting enzyme (ACE) inhibitors or angiotensin (AT) II antagonists (88% of patients) or beta-blockers (69% of patients).

Table 1. Baseline characteristics of the patient population (n = 90)

Age (years)	67 ± 10
Male	65 (72)
Ischemic heart failure	62 (69)
NYHA functional class	3.0 ± 0.4
QRS duration (ms)	161 ± 36
Echocardiographic parameters	
LVEDV (ml)	214 ± 64
LVESV (ml)	160 ± 57
LVEF (%)	26 ± 8
Scintigraphic parameters	
Perfusion defect in LV pacing region	17 (19)
Extent of perfusion defect (%)	26 ± 16
Histogram bandwidth (°)	139 ± 77
Phase SD (°)	41 ± 21
Medication	
Diuretics	81 (90)
ACE inhibitors / AT II antagonists	79 (88)
Beta-blockers	62 (69)
Spironolactone	40 (44)
Statins	55 (61)

NYHA = New York Heart Association; LVEDV = left ventricular end-diastolic volume; LVESV = left ventricular end-systolic volume; LVEF = left ventricular ejection fraction; GMPS = gated myocardial perfusion single photon emission computed tomography; SD = standard deviation; ACE = angiotensin-converting enzyme; AT II = angiotensin II

GMPS with phase analysis and LV lead position

The mean value of histogram bandwidth and phase SD was 139±77° and 41±21°. The region of latest mechanical activation as assessed with GMPS was located in the posterior (42.2%), lateral (23.3%), inferior (13.3%), anterior (15.6%), anteroseptal (3%) or septal (2.3%) region. Furthermore, a good agreement was found between GMPS and 2D speckle-tracking radial strain analysis for assessment of the site of latest mechanical activation (total agreement of 86%, k value = 0.79).A good intraobserver (k = 0.96, total agreement of 93%) and interobserver (k = 0.92, total agreement of 87%) reproducibility of phase analysis was observed for assessment of the site of latest mechanical activation. CRT device and LV lead implantation were successful in all patients without major complications. The LV pacing lead was positioned in the lateral (44.4% of patients), posterior (50.0% of patients) or anterior (5.6% of patients) region. A good intraobserver (k = 0.82, total agreement of 90%) and interobserver (k = 0.76, total agreement of 87%) reproducibility for assessment of LV lead position on fluoroscopy was observed. Fifty-two (58%) patients showed a concordant LV lead position and 38 (42%) patients showed a discordant LV lead position, as shown in Table 2. No significant differences were observed for demographic, clinical and echocardiographic variables between patients with concordant or discordant LV lead position. In addition, no difference was found for histogram bandwidth and phase SD between both groups. Patients with concordant and discordant LV lead position showed no significant difference in perfusion defects located in the LV pacing region (13% vs. 26%, p = NS). Additionally, no difference was found between patients with concordant and discordant LV lead position in the extent of myocardial perfusion defects (22.9±14.1% vs. 29.3±18.1%, p = NS). The extent of myocardial perfusion defects was significantly smaller in patients with CRT response as compared to patients without CRT response (21.1±12.3% vs. 31.6±18.7%, p<0.05). Furthermore, the percentage CRT responders was significantly higher in patients with concordant LV lead position when compared to patients with discordant LV lead position (79% vs. 26%, p<0.01). Patient examples with a concordant and discordant LV lead position are shown in Figure 2. Of note, 11 patients with concordant LV lead position showed no response to CRT after 6 months. In these patients, 7 patients showed severe perfusion defects at the region of LV pacing.

Table 2. Baseline characteristics between patients with concordant and discordant LV lead positions

Baseline characteristics	**Concordant LV lead position (n = 52)**	**Discordant LV lead position (n = 38)**	p-value
Age (years)	68 ± 10	66 ± 11	0.5
Gender (male)	37 (71)	28 (74)	0.8
Ischemic heart failure	38 (73)	24 (63)	0.4
NYHA functional class	3.0 ± 0.4	3.0 ± 0.4	1.0
QRS duration (ms)	168 ± 35	153 ± 33	0.1
LVEDV (ml)	214 ± 67	213 ± 62	1.0
LVESV (ml)	160 ± 57	161 ± 57	0.9
LVEF (%)	27 ± 8	26 ± 8	0.7
Mitral regurgitation (moderate/severe)	19 (37)	19 (50)	0.2
Histogram bandwidth (°)	126 ± 67	157 ± 86	0.1
Phase SD (°)	38 ± 20	45 ± 21	0.1
Perfusion defect LV pacing region	7 (13)	10 (26)	0.2
Extent perfusion defect (%)	23 ± 14	29 ± 18	0.1
CRT response after 6 mo.	41 (79)	10 (26)	**<0.01**

Data are represented as mean ± standard deviation or as number (%)

NYHA = New York Heart Association; LVEDV = left ventricular end-diastolic volume; LVESV = left ventricular end-systolic volume; LVEF = left ventricular ejection fraction; SD = standard deviation; CRT = cardiac resynchronization therapy

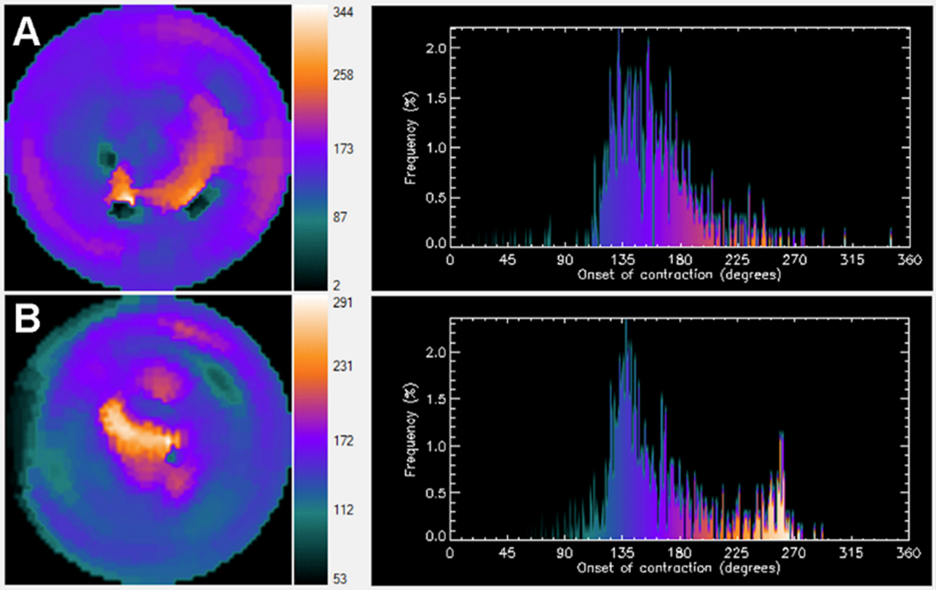

Figure 2. Area of latest mechanical activation as assessed with phase analysis on gated myocardial perfusion single photon emission computed tomography (SPECT) (GMPS).
A. Example of a patient with the left ventricular (LV) lead positioned at the area of latest activation (concordant LV lead position). The area of latest activation was located in the lateral segment. The patient showed a significant improvement in LV end-systolic volume (LVESV) (139 ml vs. 86 ml) and LV ejection fraction (LVEF) (32% vs. 44%) after 6 months of cardiac resynchronization therapy (CRT).
B. Example of a patient with the LV lead positioned outside the area of latest activation (discordant LV lead position). The area of latest activation was located in the anterior segment, whereas the LV lead was positioned in the posterior segment. The patient showed no improvement in LVESV (124 ml vs. 153 ml) and LVEF (27% vs. 22%) after 6 months of CRT.

Baseline and 6-months follow-up

The total patient population showed a significant improvement in NYHA functional class from 3.0±0.4 to 2.5±0.7 ($p<0.05$). In addition, patients showed a significant improvement in echocardiographic variables, including LVESV (160±57 ml vs. 137±55 ml, $p<0.05$), LVEDV (214±64 ml vs. 197±64 ml, $p<0.05$) and LVEF (26±8% vs. 32±11%, $p<0.05$). After 6 months of CRT, patients with a concordant LV lead position showed significant improvement in LVESV (159±57 ml vs. 125±54 ml, $p<0.05$), LVEDV (214±67 ml vs. 188±62 ml, $p<0.05$) and LVEF (27±8% vs. 35±12%, $p<0.05$), as illustrated in Figure 3. Additionally, an improvement in NYHA functional class was observed in patients with a concordant LV lead position (3.0±0.4 vs. 2.3±0.7, $p<0.05$). However, patients with the LV lead positioned outside the region of latest mechanical activation (discordant LV lead position) showed no improvement in NYHA functional class (3.0±0.4 vs. 2.7±0.7, p = NS). In addition, LVESV (161±57 ml vs. 153±53 ml, p = NS), LVEDV (213±62 ml vs. 210±65 ml, p = NS) and LVEF (26±8% vs. 28±9%, p = NS) showed no significant improvement after 6 months of CRT in patients with a discordant LV lead position, as depicted in Figure 3.

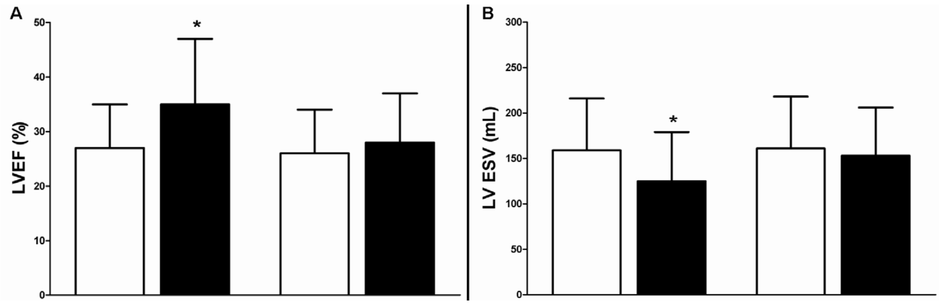

Figure 3. Response to cardiac resynchronization therapy (CRT) in patients with concordant (n = 52) and discordant (n = 38) left ventricular (LV) lead positions. Baseline (white bars) and 6 months follow-up (black bars) echocardiographic measurements are depicted below.
A. Patients with concordant LV lead position showed significant improvement in LV ejection fraction (LVEF) (27±8% vs. 35±12%, $p<0.05$), whereas patients with discordant LV lead position showed no significant improvement in LVEF (26±8% vs. 28±9%, p = NS).
B. Patients with concordant LV lead position showed significant improvement in LV end-systolic volume (LVESV) (159±57 ml vs. 125±54 ml, $p<0.05$), whereas patients with discordant LV lead position showed no significant improvement in LVESV (161±57 ml vs. 153±53 ml, p = NS).

DISCUSSION

The main findings of the current study can be summarized as follows: patients with concordant LV lead position showed significant LV reverse remodeling and improvement in LV systolic function, whereas patients with discordant LV lead position showed no significant improvements. Accordingly, GMPS with phase analysis represents a feasible technique to identify the preferred LV lead position in patients referred for CRT.

Resynchronization therapy is based on the rationale to improve the intrinsic electrical ventricular conductance by pacing the ventricles in a synchronized manner.[1, 2] To optimize synchronicity of the LV contraction, the LV pacing lead should be targeted at the region of latest mechanical activation.[9-13] In this perspective, it is important to note that the region of latest mechanical activation may vary significantly in heart failure patients, with the posterolateral region as the most common site of latest activation.[10,14-16] The study by Becker et al.[16], who sought to determine the effect of LV lead position on reverse remodeling and LV function as assessed with echocardiography, showed that the site of latest mechanical activation differed significantly among 47 heart failure patients. The site of latest mechanical activation was predominantly located in the posterolateral region of the ventricle (60% of patients). Likewise, the current study showed that the posterolateral cardiac segments represented the most common site of latest mechanical activation (66% of patients).

Additionally, the relation between LV lead position, the site of mechanical delay and CRT outcome has been evaluated in several studies.[9-16] An important study was performed by Becker et al.[16] who evaluated the efficacy of CRT in patients with optimal (n = 28) or suboptimal (n = 19) LV lead position. The position of the LV lead was considered optimal if the LV lead was concordant with (≤1 segment between the LV pacing region and the segment with latest mechanical activation) the cardiac segment showing the latest mechanical contraction. Circumferential strain analysis on echocardiography was used to assess the site of delayed mechanical activation. After 10 months follow-up, patients with an optimal LV lead position showed a significantly greater decrease in LVESV and LVEDV as well as a significant improvement in LVEF, as compared to patients with suboptimal LV lead position (all, $p<0.01$).

Recently, Ypenburg et al.[14] evaluated 6-month echocardiographic response to CRT as well as long-term outcome in patients with concordant (n=153) and discordant LV lead (n = 91) position. Speckle-tracking radial strain analysis on 2D echocardiography was used to determine the region of latest mechanical delay. After 6 months of CRT, patients with concordant LV lead position showed a significant decrease in LV volumes as well as a significant improvement in LVEF as compared to patients with discordant LV lead position (all, $p<0.01$). Importantly, a concordant LV lead position was an independent predictor of combined endpoint of hospitalization and all-cause mortality. Similarly, the current study demonstrated that patients with concordant LV lead position showed superior improvement in LVEF after 6 months of CRT (27±8% vs. 35±12%, $p<0.05$) when compared to patients with discordant LV lead position (26±8% vs. 28±9%, p = NS). Additionally, considerable reverse remodeling, as reflected by a significant decrease in LVESV and LVEDV, was observed in patients with the LV lead positioned at the site of latest activation as derived from GMPS with phase analysis. The findings demonstrate that CRT response is related to LV lead position and the region of latest mechanical contraction. More specifically, these observations support the hypothesis that resynchronization of the LV, induced by pacing at the region of latest mechanical activation, exerts positive effects on ventricular geometry and function.

Of interest, a small number of patients with the LV lead placed outside the region of latest activation responded positively to CRT. In these patients, the distance between the region of latest activation and the LV lead position (as reflected by the number of cardiac segments in between) was minimal (≤2 cardiac segments). As a consequence, the contraction pattern may have become less dyssynchronous in these patients. Additionally, 11 (21%) patients did not show CRT response despite the fact that the LV lead was positioned at the latest activated area. This observation may be explained by the fact that extensive perfusion defects were located at or near the site of latest mechanical activation in this subset of patients. It has been demonstrated that the extent and location of scarred myocardium play an important role in CRT response. Bleeker et al.[26] has performed an important study evaluating the effect of posterolateral scar tissue on CRT response in 40 consecutive advanced heart failure patients. The study has shown that patients with posterolateral scar tissue on magnetic resonance imaging showed a significant lower response rate as compared to patients without posterolateral scar tissue (14% vs. 81%, $p<0.05$). Similarly, the current study demonstrated that severe perfusion defects at or adjacent to the region of latest mechanical activation were associated with non-response to CRT. Patients with a concordant LV lead position but with severe perfusion defects at the region of LV pacing showed no response to CRT. Furthermore, the study showed that the extent of myocardial perfusion defects was significantly smaller in patients with response to CRT as compared to patients without CRT response. Accordingly, location and extent of scarred myocardium play an important role in the likelihood of response to CRT.

At present, non-response to CRT has been associated with the absence of pre-existent mechanical dyssynchrony, location and extent of scarred myocardium (particularly at LV pacing region) and suboptimal LV lead position.[7, 8, 26-28] For this reason, phase analysis on GMPS has gained increasingly interest for the evaluation of CRT patients as it allows an integrated evaluation of mechanical dyssynchrony, regional activation pattern and myocardial infarction.[17, 18] More specifically, the presence of infarcted myocardium at or adjacent to the region of maximal mechanical delay can be evaluated using the SPECT data sets. Accordingly, phase analysis on GMPS represents a feasible technique to identify the preferred LV lead position.

At present, different non-invasive imaging techniques are available for the evaluation of patients referred for CRT, including echocardiography, magnetic resonance imaging as well as nuclear imaging. A comprehensive evaluation of CRT patients can be performed by each of these imaging techniques as they provide information on pre-existent LV mechanical dyssynchrony, presence and location of myocardial infarction as well as the site of latest mechanical activation. As they all provide useful information, the choice for one of these techniques is eventually determined by the local expertise and availability.

Some study limitations need to be acknowledged. First of all, the study findings are based on a relatively small number of patients who were referred for CRT. The current study however, represents only a feasibility study evaluating the role of phase analysis on GMPS for assessment of optimal LV lead position in advanced heart failure patients. The novelty of the present study relates to the evaluation of CRT response in patients with concordant and discordant LV lead position as assessed with phase analysis on GMPS. A second limitation is the fact that long-term effects of resynchronization therapy on mortality and/or morbidity rates were not reported in the current study as the patient population was too small for long-term outcome analysis.

Conclusion

Patients with concordant LV lead position showed significant improvement in LV volumes and LV systolic function, whereas patients with discordant LV lead position showed no significant improvement in LV volumes and LV systolic function. Accordingly, phase analysis on GMPS represents a feasible technique that can be used to identify the preferred LV lead position in patients indicated for CRT.

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