Left ventricular pacing in patients with heart failure: evaluation study with Fourier analysis of radionuclide ventriculography

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Biventricular pacing; Congestive heart failure; Fourier analysis.

Background. **In order to correct the activation, contraction, and relaxation asynchronism, multisite biventricular stimulation has been proposed as a non-pharmacological alternative for the treatment of patients with congestive heart failure (CHF) NYHA class II-III-IV, resistant to maximal drug therapy and with a QRS duration > 120 ms. Fourier analysis appears a feasible technique for the quantitative and non-invasive evaluation of the inter- and intraventricular conduction delays. The aim of our study was to evaluate the usefulness of Fourier analysis when estimating the electromechanical resynchronization in CHF biventricular paced patients and to follow up these patients.**

Methods. **Forty-five male patients (mean age 64 ± 5 years) with severe drug-refractory CHF, were submitted to radionuclide ventriculography 14 ± 7 days, 24 and 36 months after the implantation of a biventricular pacemaker, in order to assess left ventricular ejection fraction using Fourier analysis of the right and left ventricular phase images. Each patient was examined during spontaneous sinus rhythm, P-synchronous right ventricle and P-synchronous biventricular pacing.**

Results. **Fourteen days after biventricular pacemaker implantation, QRS duration decreased from 170 ± 25 to 147 ± 25 ms ($p < 0.01$), left ventricular ejection fraction increased from 24 ± 6 to 31 ± 9% ($p < 0.005$), while standard deviation of the left ventricular phase decreased from 53 ± 6 to 35 ± 9° ($p < 0.0005$). Similar results were obtained at 24 and 36 months.**

Conclusions. **Biventricular pacing appears to be associated with shortening of QRS duration and an improvement in NYHA class and left ventricular ejection fraction in CHF patients with inter- and intraventricular conduction delays as assessed at Fourier analysis radionuclide ventriculography.**

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Introduction

Dilated cardiomyopathy (DCM) is characterized by structural abnormalities of the ventricular myocardium, affecting both ventricular activation and mechanical contraction[1]. The delayed electrical activation of the ventricular segments may be consequent to pathological involvement of the ventricular conduction system or to inhomogeneous spread of the excitation wave front across scarred tissue. In patients with left bundle branch block (LBBB) a decreased left ventricular ejection fraction (LVEF) has been observed along with marked interventricular dyssynchrony. An acute hemodynamic improvement has been demonstrated during atrial synchronized biventricular pacing (BIV) in patients with DCM[2-4]. These effects may be achieved through enhanced synchrony of the ventricular contraction[5-7].

The aim of this study was to provide a quantitative and qualitative analysis of ventricular contractile synchrony during BIV[8-10] and follow up patients with DCM and LBBB, analyzed by means of phase imaging techniques at multigated equilibrium blood pool scintigraphy.

Methods

Forty-five male patients (mean age 64 ± 5 years) with pacemaker or implantable cardioverter-defibrillator (ICD) BIV, were enrolled between March 2001 and June 2003.

All patients were implanted with a permanent pacemaker or ICD BIV in the electrophysiology laboratory. BIV was performed using right ventricular endocardial and coronary sinus branch vein left ventricular pacing. Only 3 patients had angio-

graphically proven coronary artery disease. In the remaining patients, coronary angiography was not indicated and, hence, not performed: however, they had no signs or symptoms suggesting any associated cardiac diseases.

The enrollment criteria included: LVEF < 35%, sinus rhythm, QRS duration > 120 ms, LBBB and drug-resistant heart failure (NYHA functional class II-III-IV).

Pacing protocol. Biventricular stimulation was performed for each patient after 14 ± 7 days, 24 and 36 months since the implantation, using BIV with right atrial and right ventricular endocardial leads and an endocardial coronary sinus left ventricular lead.

An atrioventricular delay of 120 ms was chosen to ensure complete biventricular capture and was identified within the optimal range for BIV in patients with DCM and LBBB[11-13]. All patients underwent radionuclide ventriculography and data were acquired in normal sinus rhythm. The pacemakers were programmed to the atrial-sensed right ventricle-paced (RV-VDD) mode and then to the atrial-sensed biventricular paced (BIV-VDD) mode.

Radionuclide techniques. Erythrocyte labeling was performed using technetium-99m pertechnetate[14], 14 ± 7 days, 24 and 36 months following pacemaker implantation.

Multigated equilibrium blood pool scintigrams were acquired at rest in the "best-septal" left anterior oblique projection to provide optimal right ventricular/left ventricular blood pool discrimination.

Scintigraphy was performed at equilibrium for 5 min and for at least 6 million total counts, using 24 frames per cardiac cycle. Scintigrams were acquired for each patient in normal sinus rhythm, RV-VDD and BIV-VDD. Scintigrams were smoothed off-line, and the right ventricular/left ventricular regions of interest were acquired at end-diastole and end-systole for the respective ventricle.

We analyzed the relationship between ventricular contractile synchrony and LVEF by means of phase images, in sinus rhythm, right ventricular and BIV pacing.

Nuclear phase imaging. Phase images were generated from the scintigraphic data using a computer program. The identical scintigraphic data used to generate the right ventricle and LVEF were digitally processed to display the "phase" for each pixel overlying the equilibrium blood pool and gated to the ECG R wave. The phase program assigns a phase angle (σ) to each pixel of the phase image, derived from the first Fourier harmonic of the time vs radioactivity curve (a parallel of the ventricular volume curve) fitted to the cardiac cycle[9]. The phase angle (σ) corresponds to the relative sequence and pattern of ventricular contraction during the cardiac cycle.

Color encoded phase images with the corresponding histograms were generated for each patient in normal sinus rhythm, RV-VDD and BIV-VDD. Scintigrams were intensity-coded for amplitude, a parameter related to stroke volume, setting the background pixel to black (zero amplitude) and providing a clear edge to ventricular regions of interest. Pixels overlying cardiac regions below the amplitude threshold, corresponding with low stroke volume, were also set to black. Phase images were generated for cardiac regions above the amplitude threshold using a continuous rainbow color wheel, corresponding to phase angles ranging from 0 to 360°. To avoid discontinuities of the phase angle display, the entire scale was shifted by 180°, placing the ventricular ejection at the center of the histogram display.

Mean phase angles were computed for the right ventricular and left ventricular blood pools as the arithmetic mean phase angle (σ) for all the pixels in the ventricular region of interest[8,9,15]. Interventricular contractile synchrony was measured as the absolute difference in right ventricular and left ventricular mean phase angles.

Intraventricular contractile synchrony was measured as the SD of the mean phase angle for the right ventricular and left ventricular blood pools and was computed for each patient in normal sinus rhythm, RV-VDD and BIV-VDD.

Patients were paced or not paced (normal sinus rhythm) for a minimum of 3-5 min before image acquisition. The loading conditions were kept constant. Complete biventricular capture was documented on the 12-lead ECG at threshold testing and continuously during scintigraphic image acquisition.

Lead placement. Lead placement was documented fluoroscopically in all patients at the time of image acquisition. The right ventricular lead position was apical in all patients. The left ventricular lead position was placed midway between the base and apex at the lateral left ventricular wall.

Electrocardiography. Surface 12-lead ECGs were acquired in normal sinus rhythm, RV-VDD and BIV-VDD. The QRS duration was measured from the first intrinsic deflection of the QRS complex to the terminal isoelectric component of the complex in normal sinus rhythm and from the first evoked QRS intrinsic deflection to the terminal isoelectric component during RV-VDD and BIV-VDD.

Statistical analysis. All continuous variables were expressed as mean ± SD. Statistical analysis was performed using the Bonferroni modified Student's t-test for paired/unpaired data, as appropriate. Linear regression analysis was performed using the Pearson correlation coefficient. A p value < 0.05 was considered as statistically significant. All data were analyzed using the SPSS 12.0 software (SPSS Inc., Chicago, IL, USA).

Results

None of the patients presented with complications related to lead placement, BIV or radionuclide image acquisition.

Interventricular contractile synchrony was significantly impaired in all patients with manifest bundle branch block during sinus rhythm and it did not change during RV-VDD. During BIV, an improved synchrony was observed in each of the 45 patients with overt bundle branch block. Similarly the QRS duration decreased from 170 ± 25 ms in normal sinus rhythm to 147 ± 25 ms during BIV ($p < 0.01$). A significant positive correlation was observed ($p < 0.01$) between the degree of interventricular dyssynchrony in sinus rhythm or RV-VDD and the degree of improvement in interventricular synchrony during BIV.

The intraventricular contractile synchrony, measured as the SD of the mean phase angle (σ), varied significantly from patient to patient during sinus rhythm. The mean phase angle (σ) varied from 53 ± 6 during normal sinus rhythm to 35 ± 9 during BIV ($p < 0.0005$).

Phase image analysis showed the abnormal (right/left) ventricular contraction and ventricular conduction delay in sinus rhythm (Fig. 1). During RV-VDD there was a more remarkable degree of right ventricular/left ventricular dyssynchrony characterized by an inhomogeneous phase (Fig. 2). On the other hand,

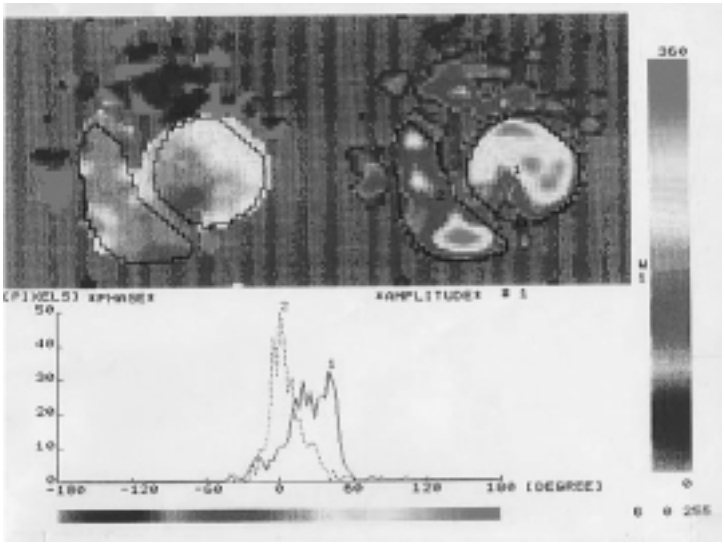

Figure 1. *Spontaneous rhythm and left bundle branch block: the phase histograms, obtained by means of phase analysis of both ventricles, show an abnormal contraction and ventricular conduction delay in sinus rhythm, showing an evident difference between the right ventricular and left ventricular mean phase angles.*

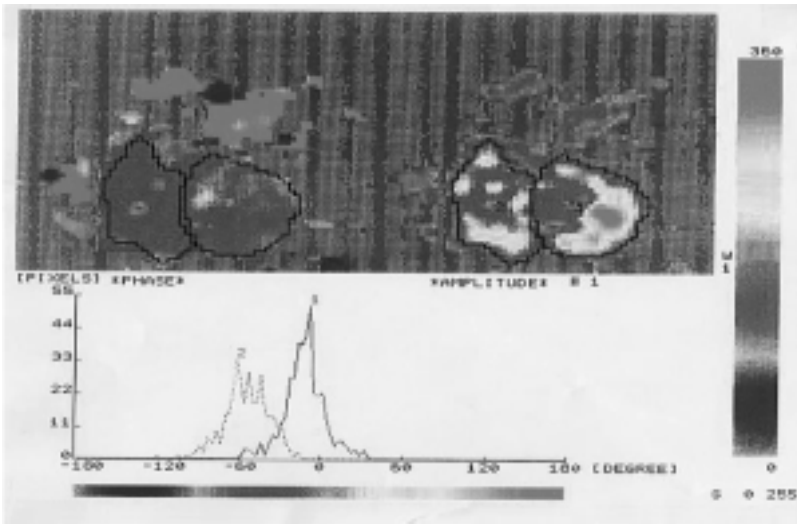

Figure 2. *Right ventricular VDD pacing: the phase histograms obtained by means of phase analysis of both ventricles show an improved asynchrony of the right ventricle/left ventricle, characterized by an inhomogeneous phase, during right ventricular VDD pacing.*

during BIV-VDD, patients achieved a greater improvement in the interventricular synchrony, illustrated as a decrease in the difference between the right ventricular and left ventricular mean phase angles (Fig. 3).

An acute improvement in LVEF was observed in each of the 45 patients during BIV. Overall, LVEF improved from 24 ± 6 to 31 ± 9% ($p < 0.005$), corresponding to a mean relative improvement of 31%.

A significant negative correlation was observed between LVEF and interventricular dyssynchrony ($p < 0.01$), with more dyssynchrony observed in patients with a lower LVEF (Fig. 4). A significant positive correlation was observed ($p < 0.001$) between the degree of improvement in interventricular synchrony and the percent improvement in LVEF during BIV (Fig. 5). A significant negative correlation was observed between LVEF and intraventricular dyssynchrony ($p < 0.01$), with greater dyssynchrony observed in patients with a lower LVEF (Fig. 6).

At 36 months of follow-up, LVEF was found to have decreased slightly (31 ± 9 to 29 ± 9%) whereas the QRS duration and mean phase angle (σ) did not vary significantly (Table I).

Discussion

Our study results confirm the hypothesis that DCM with ventricular conduction delay is associated with significant ventricular contraction abnormalities during sinus rhythm and that right ventricular pacing alone is not to improve or correct this condition. Analysis of nuclear phase images and histograms confirms these observations and suggests that these contraction abnor-

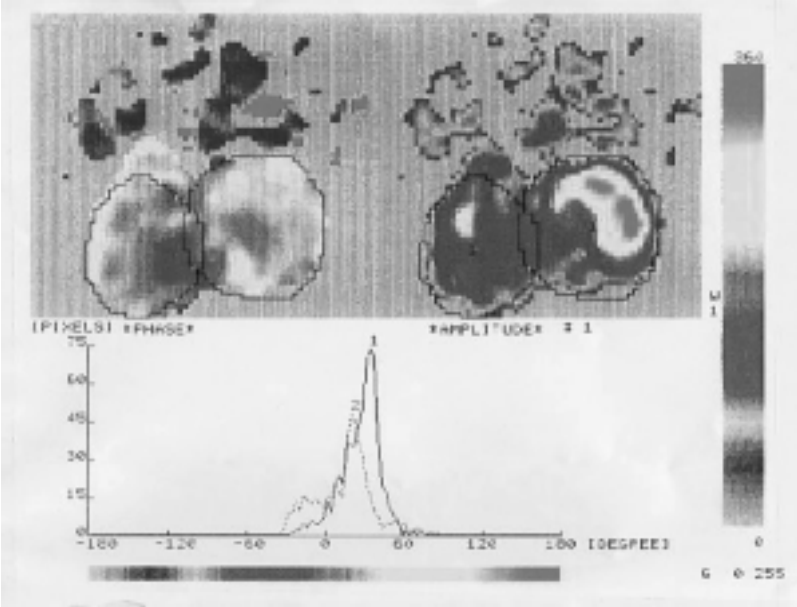

Figure 3. *Biventricular VDD pacing: the phase histograms obtained by means of phase analysis of both ventricles show an improved interventricular synchrony, characterized by a decrease in the difference between the right ventricular and left ventricular mean phase angles, during biventricular VDD pacing.*

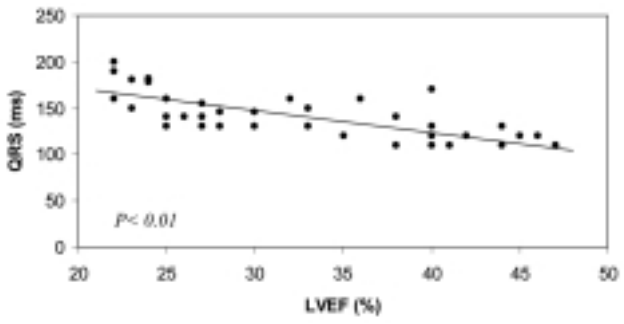

Figure 4. *Negative correlation between interventricular dyssynchrony and left ventricular ejection fraction (LVEF).*

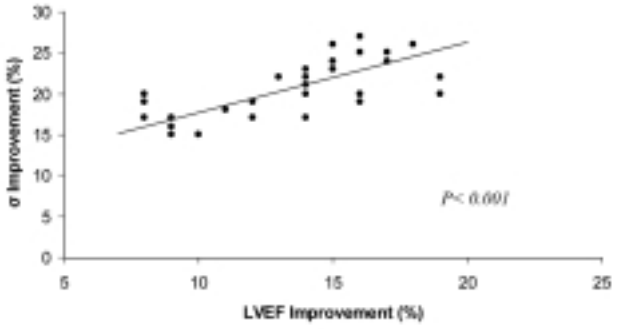

Figure 5. *Positive correlation between the improvement in interventricular synchrony and left ventricular ejection fraction (LVEF) during biventricular pacing.*

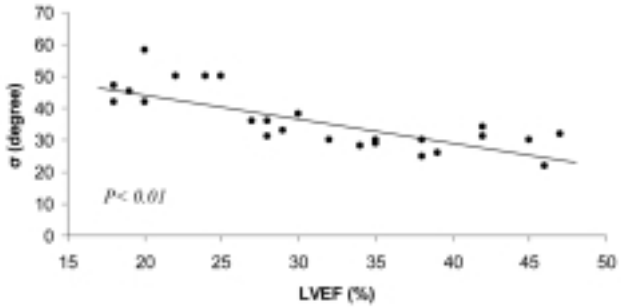

Figure 6. *Negative correlation between intraventricular dyssynchrony (σ) and left ventricular ejection fraction (LVEF).*

Table I. Data collected during the various follow-up visits after biventricular pacemaker implantation.

	QRS (ms)	σ (degree)	LVEF (%)
14 ± 7 days	147 ± 25	35 ± 9	31 ± 9
24 months	145 ± 24	33 ± 8	30 ± 9
36 months	142 ± 24	30 ± 8	29 ± 9

malities exist as multiple levels of dyssynchrony. Intraventricular dyssynchrony is the first level, represented on phase images as an inhomogeneous phase or as a discontinuous progression of the phase angles between adjacent ventricular segments. Interventricular dyssynchrony is the second level represented on phase images as an asymmetric right ventricular/left ventricular phase pattern. The dyssynchrony at this level is related to the site of bundle branch block and is most significant for QRS durations > 120 ms. Our results suggest that the cardiomyopathy itself may contribute to interventricular dyssynchrony, showing that this was most marked in patients with the lowest LVEF.

Our study demonstrated that BIV corrects interventricular dyssynchrony. The degree of improvement in interventricular synchrony during BIV correlates significantly with the improvement in LVEF. These data suggest that left ventricular dysfunction due to interventricular dyssynchrony is a correctable parameter. Patients with less marked interventricular dyssynchrony (QRS < 120 ms) were found to have an improved LVEF during BIV, suggesting that additional mechanisms related to BIV may contribute to the improvement in LVEF[16,17]. Even though several studies have already highlighted the improvement in LVEF following BIV, our data show an earlier (14 days), greater (+31%) and more common (all patients) improvement than previous studies.

Phase image analysis has provided a further means for analyzing the mechanisms by which BIV may modify myocardial performance. In patients with LBBB, the "preexcitation" of a critical bulk of late contracting ventricular myocardium may shorten the delay in right ventricular and left ventricular emptying. The simultaneous activation of the left and right ventricles may contribute to an improved ventricular septal coordination, a parameter associated with a depressed LVEF in patients with LBBB or during right ventricular pacing[18-22]. These, and other hemodynamic alterations, may influence the proportionality between the left ventricular end-diastolic and stroke volumes, despite the persistent heterogeneity of the left ventricular contraction pattern. Moreover, we must point out the usefulness of phase image analysis, in case of difficulty in obtaining a clear echocardiographic window, to quantify asynchrony indexes such as the systolic asynchrony index[23] and the septal-to-posterior wall motion delay[24]. Hence, analysis of the mean phase angle may provide us with a useful index (σ), to better quantify the synchrony and to better evaluate the treatment in patients with heart failure and a biventricular pacemaker.

Study limitations. Hemodynamic indexes that may modify LVEF, such as the intracardiac pressure and volume, were not measured in this study, even though the loading conditions were kept constant (but an arterial line was not in place to measure the beat to beat changes in blood pressure). The effect of BIV on atrioventricular valve regurgitation was not measured and may have contributed to the improvement in LVEF. However, none of the patients included in the present study had more than mild to moderate mitral regurgitation. An atrioventricular delay of 120 ms was programmed to achieve complete biventricular capture and may have contributed to the observed improvement in LVEF. Recent studies of pacing in heart failure have demonstrated a greater relative contribution of the ventricular pacing site to the improvement in left ventricular performance than that achieved by optimizing the atrioventricular delay[11,12].

In conclusion, despite advances in the medical management of congestive heart failure, a significant number of patients with left ventricular systolic dysfunction progress to severe and medically refractory symptoms[20]. Preliminary studies have suggested a possible role for chronic BIV in the management of patients with advanced heart failure and LBBB[25-29]. Our data suggest that BIV, by correcting interventricular contractile dyssynchrony, may in part contribute to improve the ventricular function.

Acknowledgments

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