Quantification of Ventricular Resynchronization Reserve by Radionuclide Phase Analysis in Heart Failure Patients
A Prospective Long-Term Study

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Background—Phase analysis, developed to assess dyssynchrony from ECG-gated radionuclide ventriculography, has shown promising results. We hypothesized that quantifying the cardiac resynchronization reserve, that is, the extent of response to cardiac resynchronization therapy (CRT), by radionuclide imaging could potentially identify patients who are best suited for CRT.

Methods and Results—Seventy-four patients ages 64.8±10.1 years were prospectively studied from July 2004 to July 2006, of whom 62.2% and 37.8%, respectively, were in New York Heart Association class 3 and 4. Mean QRS width was 173±25 ms. ECG-gated radionuclide ventriculography to quantify interventricular and intraventricular dyssynchrony was performed at baseline with and without CRT and at the 3-month follow-up visit. Amino-terminal-pro-brain natriuretic peptide (NT-pro-BNP) levels were also determined at baseline and at 3 months. During a mean follow-up of 10.1±7.6 months, there were 37 (50%) clinical events that defined the nonresponder group, including cardiac death or readmission for worsening heart failure. In multivariate Cox model analysis, higher NT-pro-BNP blood levels were associated with a significant increase in the risk for event (hazard ratio = 1.085 for a 100 pg/L increase in NT-pro-BNP; 95% confidence interval, 1.014 to 1.161). Each 10° elevation in intraventricular dyssynchrony was associated with a decrease in the risk of events (hazard ratio = 0.456, 95% confidence interval, 0.304 to 0.683). Receiver operating characteristic curve analysis demonstrated that an interventricular dyssynchrony cutoff value of 25.5° for intraventricular synchrony yielded 91.4% sensitivity and 84.4% specificity for predicting a good response to CRT.

Conclusions—The quantification of interventricular dyssynchrony with radionuclide phase analysis suggests that early postimplantation interventricular dyssynchrony may provide identification of CRT responders. (Circ Cardiovasc Imaging. 2011;4:114-121.)

Key Words: heart failure ■ cardiac resynchronization therapy

The criteria for selecting heart failure patients for cardiac resynchronization therapy (CRT), namely ejection fraction, New York Heart Association (NYHA) class, and QRS width, have been validated in large-scale, randomized studies. However, the identification of the precise determinants of the resynchronization reserve, that is, the extent and the origin of the response to biventricular pacing, is lacking. Despite a thorough investigation of the electric and mechanical dyssynchrony, identification of good candidates for biventricular (BiV) therapy is still unsatisfactory. Echocardiography, which has the advantages of availability and good time resolution, was somewhat discredited by 2 negative studies. In addition, the confusion caused by the multiple Doppler measurement technique is increased by the use of different end points for defining the response to CRT. Invasive and noninvasive electroanatomic investigations (mapping) are very informative in patients with intramyocardiac conductive problems. Phase scintigraphy provides a precise and reproducible investigation of the propagation of myocardiac electric activation. Studies using asynchronism with phase scintigraphy, an inclusive method that is not very operator dependent, are rare and concern a restricted number of patients. In addition to right ventricular ejection fraction (RVEF) and left (LVEF) ventricular ejection frac-

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tion, this technique makes it possible to quantify interventricular and intraventricular contraction asynchronisms. Recently, Morishama et al\textsuperscript{11} demonstrated a significant decrease in intraventricular dyssynchrony in response to CRT in a patient with narrow QRS and dilated cardiomyopathy.

Clinical Perspective on p 121

In a study of 75 patients with heart failure and wide QRS complex, Chen et al\textsuperscript{13} demonstrated that gated myocardial perfusion single-photon emission-computed tomography (SPECT) provided a good assessment of LV dyssynchrony and suggested that histogram bandwidth and phase standard deviation could be used in outcome studies to validate the use of SPECT in the identification of biventricular responders.

The aim of this prospective study, using planar radionuclide ventriculography with phase analysis, was to identify the scintigraphic markers of improved cardiac function after triple-chamber stimulation. Another goal was to improve the understanding of the electromechanical mechanisms underlying the effect of BiV pacing. At the same time, to fully document response to BiV resynchronization therapy, neurohumoral activation was also evaluated during the follow-up of these patients.

Methods

Study Design

From July 2004 to February 2006, 86 patients undergoing BiV stimulator implantation were prospectively and consecutively included after providing informed consent. The inclusion criteria were (1) chronic LV systolic dysfunction defined as a LVEF $<35\%$, (2) NYHA class III or IV, (3) QRS duration $>130$ ms with an aspect of left branch block, and (4) optimal cardiac failure medical treatment. The implantation technique has already been described. \textsuperscript{14}

Because of procedural difficulties, only 74 of the 86 included patients could benefit from the implantation of a left ventricular lead. The patients in whom we failed to implant a left ventricular lead (ie, in whom resynchronization therapy could not be achieved) were not followed up.

In the remaining 74 patients, ECG and clinical examinations, a stress test with measurement of gas exchanges (peak VO$_2$), and a radionuclide ventriculography were performed. Blood tests were drawn on the eve of implantation and at 2 days and 3 months afterward. Patients were seen again after 3 months and then every 6 months. The composite criteria for distinguishing the responders (group 1) from the nonresponders (group 2) were based on (1) heart failure exacerbation, (2) hospitalization for new cardiac failure decompensation, (3) heart transplantation, and (4) death linked to a cardiac cause. Patients who had 1 or several of these clinical events during the follow-up were considered as nonresponders.

Blood samples were taken after 1 hour in the decubitus position using a previously installed device. Amino-terminal-pro-brain natriuretic peptide (NT-pro-BNP) was evaluated with proBNP essay on Elecsys 20.10 (Roche Diagnostics, Meylan, France).

Scintigraphic Analysis

The initial examination was performed in 2 stages the day after CRT device placement; first in the passive stimulation mode (CRT-OFF) and then in the active stimulation mode (CRT-ON) 10 minutes later. A second examination was performed in the active mode after 3 months of CRT.

Peripheral intravenous administration of technetium-99m, with an activity of 700 to 800 MBq, was preceded by an injection of stannous pyrophosphate to allow in vivo labeling of the patient’s red blood cells. A General Electric DSTi gamma camera (GE Healthcare, Princeton, NJ), equipped with a high-resolution collimation with parallel holes, was used for image acquisition. A General Electric “Vision” postprocessing station was used for image quantification and phase analysis. Planar images were acquired in the “optimal” (best LV-RV separation) left anterior oblique view. The pictures were synchronized by the ECG and each heart cycle was divided into 16 segments. A total of 3200 K-counts (with an average of 200 K-counts per frame) were recorded for a time period that varied from 5 to 12 minutes, depending on the injected activity and the patient’s morphology.

The radionuclide ventriculography analysis software (ECCAP, General Electric) allowed the functional variables of the right and left ventricles to be evaluated.\textsuperscript{11,13} The data were first filtered by a Butterworth (smoothing) filter, with a cutoff frequency of 0.5 cycles/pixel and order of 5. Count-based ejection fractions for both ventricles (LVEF and RVEF) were then computed using semiautomatic regions of interest (automatic drawing with possible manual correction), 2 separate regions (end-diastolic and end-systolic) for LVEF, and 1 single end-diastolic region for RVEF. Phase images are computed using the first harmonic Fourier transform to display the mechanical contraction time for all the ventricular pixels of the image during 1 composite cardiac cycle. A color scale allowed each pixel to correspond to a color value that reflected its phase. Quantitative analysis was performed for each ventricle in the form of phase histograms computed separately for the LV and RV end-diastolic regions of interest. From these histograms representing the distribution of the pixels for each ventricle according to their phases, the mean phase and its standard deviation were calculated (an example is provided in Figure 1). Phases are expressed in degrees on a 0° to 360° scale covering the R-R interval duration of the composite cardiac cycle. On this scale, the beginning of the cardiac cycle is 0°, the location of the end-systole is around 150° (variable with heart rate and the relative durations of systole and diastole), and the end of the cycle is 360°. Compared with phase values expressed in ms (time from R to end-systole), which are highly dependent on heart rate, phases in degrees are less dependent on heart rate.

The scintigraphic data were used in the analysis of 5 quantitative variables from each of the 3 radionuclide acquisitions: LVEF, RVEF, standard deviation of the LV phases (LVSD) (representing intraventricular LV dyssynchrony), standard deviation of the RV phases (RVSD), and the difference of the mean phases of the left and right ventricles as a measure of interventricular dyssynchrony (IVD). The baseline data are CRT-OFF data and were collected again after a short duration of CRT.

Statistical Analysis

All continuous data are reported as mean±SD. Statistical calculations were performed after log-transformation of the variables. The Student $t$ test for paired and unpaired continuous variables was used for intergroup comparisons of the data with and without stimulation from each of the follow-up visits. $\chi^2$, Pearson, and nonparametric Kruskal-Wallis tests were also used when appropriate.

Univariate and multivariate linear regression and logistic regression analyses were performed to study the relationship between variables and response to CRT. Event-free survival was analyzed with Kaplan-Meier method and a log-rank test. SPSS for Windows, version 12.0, SPSS Inc, Chicago, IL) was used. The Cox proportional hazards model with a stepwise procedure was used to determine the predictive factors of good response. The best predictive threshold of cardiovascular events was sought by means of receiver operating characteristic (ROC) curves. Significance was defined as $P<0.05$.

Results

The characteristics of the patient population are presented in Table 1. QRS width decreased from 173.5±27.1 ms to 145.9±24.8 ms after stimulation ($P<0.0001$). The various biological parameters that were studied did not significantly vary with the use of a $\beta$-blocker or spironolactone ($\chi^2$ at 3 ddl <7.81, $P>0.05$).
Ventricular contraction heterogeneity decreased from baseline to after the 3-month follow-up in the entire population (16.8±5.3% versus 11.7±6.2%, P<0.0001). The decrease in heterogeneity was also statistically significant for the group 1 (17.3±5.4% before versus 10.8±5.2% at 3 months, P<0.0001). An example is provided in Figure 1.

**Survival Analysis: Predictive Factors for Cardiovascular Events**

During a mean follow-up of 10.1±7.6 months, 37 of 74 (50%) patients had at least 1 clinical event: 21 of 74 (28.4%) had hospitalization for cardiac failure, 2 of 74 (2.7%) had transplantation, and 14 of 74 (18.9%) died. Among the deaths, 11 (78.6%) were caused by terminal cardiac failure and 3 (21.4%) because of sudden death of rhythmic origin. The multivariate Cox-Model analysis identified 2 statistically significant parameters: NT-pro-BNP and IVD. Any elevation in NT-pro-BNP of 100 pg/L was accompanied by an adverse event increase of 8.5% (hazard ratio [HR]=1.085; 95% confidence interval, 1.014 to 1.161; P=0.018) and each elevation of 10° of IVD was associated with a decrease of 54.4% in the risk for adverse outcome (HR=0.456; 95% confidence interval, 0.304 to 0.683; P<0.0001) (Figure 2). In a subsequent ROC curve analysis, we found that an IVD value of 25.5° was associated with a sensitivity of 91.4% and a specificity of 84.4% and with positive and negative predictive values of 90% and 86.6%, respectively (Figure 3 and Figure 4).

**Association Between NT-Pro-BNP Blood Levels and IVD**

Before implantation, NT-pro-BNP was significantly correlated with IVD variation at 3 months (r=−0.279, P=0.037); NT-pro-BNP variation at 3 months was correlated with IVD before implantation and with its variation at 3 months (r=−0.352, P=0.008 and r=+0.312, P=0.019, respectively).

**Discussion**

In the present prospective outcome study, we found that all radionuclide cardiac dys synchrony and contraction parameters improved after implantation in responder patients. NT-pro-BNP decreased as early as the second day after implantation in responder patients, which was in contrast to nonresponder patients. Interventricular dys synchrony was identified as an independent predictive factor of good clinical response with a practical cutoff value of 25.5°, a sensitivity of 91.4%, and a specificity of 84.4%.

**Scintigraphic Dysynchrony Parameters**

Asynchronism studies using scintigraphic imaging are relatively rare and only concern a limited number of patients. Fauchier et al15 studied phase analysis from gated blood pool scintigraphy in patients with dilated myocardopathy and left branch block. These authors showed that intraventricular rather than interventricular dys synchrony was an independent predictive indicator of the occurrence of cardiac events. The absence of indications for the role of interventricular dys synchrony was expected because the patients in the study were not all candidates for multisite stimulation (mean QRS duration, 113±32 ms).

Toussaint et al16 used phase analysis to quantify the short- and long-term impact of ventricular resynchroniza-
tion in 34 patients with dilated cardiomyopathy and wide QRS (179 ± 18 ms). Radionuclide angiography was performed before implantation, 8 days after implantation, and during follow-up (20 ± 8 months). The authors observed that an interventricular asynchronism threshold of 60 ms associated with an LVEF baseline of >15% predicted an improvement in LVEF of >5%, with a positive predictive value of 83%.

### Table 1. Patient Baseline Characteristics

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Total (n=74)</th>
<th>Group 1 (n=37)</th>
<th>Group 2 (n=37)</th>
<th>1 Versus 2 P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, y</td>
<td>64.8±10.1</td>
<td>64±10</td>
<td>65.5±10.4</td>
<td>0.54</td>
</tr>
<tr>
<td>Sex, male (%)</td>
<td>89.2%</td>
<td>86.5%</td>
<td>91.9%</td>
<td>0.454</td>
</tr>
<tr>
<td>NYHA functional class</td>
<td></td>
<td></td>
<td></td>
<td>0.632</td>
</tr>
<tr>
<td>Class III</td>
<td>62.2%</td>
<td>59.5%</td>
<td>64.9%</td>
<td></td>
</tr>
<tr>
<td>Class IV</td>
<td>37.8%</td>
<td>40.5%</td>
<td>35.1%</td>
<td></td>
</tr>
<tr>
<td>Blood pressure, mm Hg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>109.8±14.7</td>
<td>110.5±12.7</td>
<td>109.1±16.6</td>
<td>0.067</td>
</tr>
<tr>
<td>Diastolic</td>
<td>72.7±9</td>
<td>72.2±8.8</td>
<td>73.2±9.4</td>
<td>0.638</td>
</tr>
<tr>
<td>Intrinsic QRS width, ms</td>
<td>173.2±24.8</td>
<td>176.5±25.4</td>
<td>170±24.2</td>
<td>0.264</td>
</tr>
<tr>
<td>PR interval, ms</td>
<td>201.4±33</td>
<td>207.4±37</td>
<td>194.3±26.6</td>
<td>0.182</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>74.8±11.7</td>
<td>73.8±12.8</td>
<td>75.9±10.5</td>
<td>0.441</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>37.8%</td>
<td>32.4%</td>
<td>43.2%</td>
<td>0.338</td>
</tr>
<tr>
<td>Etiology, %</td>
<td></td>
<td></td>
<td></td>
<td>0.809</td>
</tr>
<tr>
<td>Ischemic</td>
<td>36.5%</td>
<td>35.1%</td>
<td>37.8%</td>
<td></td>
</tr>
<tr>
<td>Nonischemic</td>
<td>63.5%</td>
<td>64.9%</td>
<td>62.2%</td>
<td></td>
</tr>
<tr>
<td>Diabetic</td>
<td>27.0%</td>
<td>24.3%</td>
<td>29.7%</td>
<td>0.601</td>
</tr>
<tr>
<td>Tabagism</td>
<td>48.6%</td>
<td>54.1%</td>
<td>43.2%</td>
<td>0.352</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>37.8%</td>
<td>32.4%</td>
<td>43.2%</td>
<td>0.338</td>
</tr>
<tr>
<td>Hypertension</td>
<td>28.4%</td>
<td>29.7%</td>
<td>27.0%</td>
<td>0.797</td>
</tr>
<tr>
<td>Natremia, mmol/L</td>
<td>135.8±4.6</td>
<td>135.2±4.2</td>
<td>136.6±4.8</td>
<td>0.186</td>
</tr>
<tr>
<td>Creatininemia, μmol/L</td>
<td>130.4±39.8</td>
<td>126.5±34.7</td>
<td>134.3±44.2</td>
<td>0.401</td>
</tr>
<tr>
<td>Treatment, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diuretics</td>
<td>100.0%</td>
<td>/</td>
<td>/</td>
<td></td>
</tr>
<tr>
<td>ACE inhibitors and/or ARB</td>
<td>95.9%</td>
<td>97.3%</td>
<td>94.6%</td>
<td>0.556</td>
</tr>
<tr>
<td>Aldactone</td>
<td>68.9%</td>
<td>83.8%</td>
<td>54.1%</td>
<td>0.006</td>
</tr>
<tr>
<td>β-blockers</td>
<td>51.4%</td>
<td>54.1%</td>
<td>48.6%</td>
<td>0.642</td>
</tr>
<tr>
<td>Cordarone</td>
<td>33.8%</td>
<td>35.1%</td>
<td>32.4%</td>
<td>0.806</td>
</tr>
<tr>
<td>Digoxin</td>
<td>50.0%</td>
<td>59.5%</td>
<td>40.5%</td>
<td>0.104</td>
</tr>
</tbody>
</table>

ACE indicates angiotensin-converting enzyme; ARB, angiotensin II receptor blocker.

### Table 2. Comparison of Biological and Scintigraphic Parameters Between Groups 1 and 2 During Passive Stimulation (CRT-OFF) and Active Stimulation (CRT-ON) Mode on the Eve of Implantation

<table>
<thead>
<tr>
<th>Setup</th>
<th>Total</th>
<th>Group 1</th>
<th>Group 2</th>
<th>1 Versus 2 P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>NYHA functional class</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRT-OFF</td>
<td>3.4±0.5 (n = 74)</td>
<td>3±0.5† (n = 72)</td>
<td>3.4±0.5 (n = 37)</td>
<td>2.8±0.6† (n = 37)</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>23±10</td>
<td>24.8±10†</td>
<td>23.2±9</td>
<td>25.7±8.8†</td>
</tr>
<tr>
<td>RVEF, %</td>
<td>16.2±6</td>
<td>17.2±6</td>
<td>16.5±9</td>
<td>17.2±6.6†</td>
</tr>
<tr>
<td>IVD, degrees</td>
<td>26.2±12.6</td>
<td>14.5±8.5†</td>
<td>35.1±8.6‡</td>
<td>14.9±9.2‡</td>
</tr>
<tr>
<td>LVSD, degrees</td>
<td>68.5±12</td>
<td>50.4±13.3†</td>
<td>70.7±10.3</td>
<td>48.9±12.9‡</td>
</tr>
<tr>
<td>RVSD, degrees</td>
<td>49±18.4</td>
<td>42.4±18.5†</td>
<td>49.7±16.6</td>
<td>38.4±14.3†</td>
</tr>
</tbody>
</table>

*Values are expressed as median [minimum to maximum]; statistical counting was performed after log-transformation of variables.
†P significant, CRT-OFF versus CRT-ON.
‡P significant, group 1 versus group 2.
Le Rest et al.17 studied the effect of LV stimulation in 7 patients with dilated or ischemic cardiomyopathy with NYHA classes III or IV. Scintigraphic studies were performed before and 2 months after implantation. Clinical improvement was observed in patients with a standard deviation of the left ventricular phase superior to 50°. The authors concluded that a decrease in the interventricular phase shift was the most important predictor of functional recovery for paced patients with heart failure.

The study by Kerwin et al.18 also showed, thanks to scintigraphy, an improvement in interventricular contraction with multisite pacing. In their study of 13 patients, the degree of baseline interventricular dysynchrony was positively correlated with the degree of improvement in the left ventricular ejection fraction.

Recently, Chen et al.13,19 suggested that LV dyssynchrony evaluated by gated perfusion SPECT was equal to the results obtained with tissue Doppler imaging. In this methodology, the RV is scarcely seen on images, and only the intraventricular dyssynchrony of the LV can be measured. These authors did not provide any information about interventricular dyssynchrony.

In accordance with most of the above studies, our findings confirmed the utility of studying interventricular dyssynchrony in addition to intraventricular dyssynchrony. We therefore propose that a cutoff value of 25.5° of IVD could be as a good marker for selecting patients eligible for CRT.

From a pathophysiologic point of view, radionuclide imaging could help to explain an absence of CRT response when dyssynchrony is less than the above mentioned cutoff and therefore probably not a major determinant of heart failure.

Previously, Bleeker et al.20 demonstrated that the existence of left intraventricular dyssynchrony was obligatory for a positive response from multisite pacing, but, similar to our findings, this variable was not found to be valuable for selecting BiV patients by Soliman et al.21,22 In a follow-up study that included 60 CRT patients, these authors investigated the use of spectral pulsed-wave myocardial tissue Doppler imaging to predict cardiovascular events. Their results suggested that in the population studied, left intraventricular dyssynchrony failed to predict the outcome.

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**Table 3. Comparison of Biological and Scintigraphic Parameters Between Groups 1 and 2 in the Passive Stimulation (CRT-OFF) and in the Active Mode at 3 Months**

<table>
<thead>
<tr>
<th>Setup</th>
<th>Total</th>
<th>Group 1</th>
<th>Group 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>NYHA functional class</td>
<td>CRT-OFF 3 Months</td>
<td>CRT-OFF 3 Months</td>
<td>CRT-OFF 3 Months</td>
</tr>
<tr>
<td></td>
<td>3 ± 0.5 (n = 74)</td>
<td>2.3 ± 0.9* (n = 63)</td>
<td>3.4 ± 0.5 (n = 37)</td>
</tr>
<tr>
<td></td>
<td>4.2 ± 4.1</td>
<td>13.4 ± 4.1</td>
<td>16.5 ± 4.3*</td>
</tr>
<tr>
<td></td>
<td>15.8 ± 3.9*</td>
<td>16.5 ± 3.9</td>
<td>16.5 ± 3.9*</td>
</tr>
<tr>
<td></td>
<td>26.2 ± 12.6</td>
<td>26.2 ± 12.6</td>
<td>26.2 ± 12.6</td>
</tr>
<tr>
<td></td>
<td>11.8 ± 7.9*</td>
<td>35.1 ± 8.6</td>
<td>10.7 ± 7.2*</td>
</tr>
<tr>
<td></td>
<td>68.5 ± 12 (n = 67)</td>
<td>70.7 ± 10.3 (n = 35)</td>
<td>66.2 ± 13.3 (n = 32)</td>
</tr>
<tr>
<td></td>
<td>46.5 ± 14.2* (n = 56)</td>
<td>42.1 ± 12.7* (n = 35)</td>
<td>53.9 ± 13.7* (n = 21)</td>
</tr>
<tr>
<td></td>
<td>49 ± 18.4</td>
<td>49.7 ± 16.6</td>
<td>48.2 ± 20.5</td>
</tr>
<tr>
<td></td>
<td>40.2 ± 14.9*</td>
<td>36.9 ± 12.3*</td>
<td>45.8 ± 17.3</td>
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*P significant, CRT-OFF versus 3 months; †P significant, group 1 versus group 2.

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**Figure 2.** Multivariate logistic regression analysis (Cox) showing odds ratios and 95% confidence intervals. NA indicates noradrenaline.

**Figure 3.** ROC curve showing that an IVD value of 25.5° with a sensitivity of 91.4% and a specificity of 84.4% had positive and negative predictive values of 90% and 96.6%, respectively.
In a study involving 85 patients with end-stage heart failure, Bax et al.\textsuperscript{22} reported that intra-LV dyssynchrony did not improve in nonresponders and that the extent of change was significantly higher in responders versus nonresponders. Interestingly, in our patients, LV dyssynchrony measured by LVSD (in the basal state, CRT-OFF, LVSD was 70.7° in responders versus 66.2° in nonresponders; \(P_{\text{NS}}^{}\)) became significantly improved in the responder group versus the nonresponder group at the 3-month postimplantation follow-up visit only (42.0° in responders versus 53.9° in nonresponders, \(P_{0.05}^{}\)). This demonstrates that LV intra-ventricular dyssynchrony was initially comparable in both groups and improved in nonresponders as well as in responders, but to a lesser extent (mean decrease in LVSD of 21.8° in responders versus 13.9° in nonresponders). This indicates that pacing may mechanically reduce intraventricular dyssynchrony in any patient, responder (from the clinical point of view) or not, but that when there is little improvement, the severity of heart failure and the prognosis of patients does not improve.

On the other hand, RVSD did not improve in the nonresponder group but was not found as an independent variable for prediction of response to CRT. RVSD improved early and at 3 months in the responder group, indicating that RV remodeling may be a manner in which patients can benefit from sequential pacing.

Taken together, the above findings suggest that high-grade interventricular dyssynchrony in the basal state, before implantation, may predict for a response to CRT and that subsequently, patients who respond best are those with marked dyssynchrony of the LV. This can be interpreted in the following way: The more interventricular dyssynchrony plays a role in the origin or evolution of heart failure, the more the patients will benefit from resynchronization. The initial presence of intraventricular dyssynchrony is not, in our experience, a predictive variable of success because it is present in all patients referred for CRT, but it may be a postresynchronization sign of effective response when it is notably improved by pacing.

Our results, therefore, favor phase analysis quantification of the resynchronization reserve, that is, the extent of interventricular and interventricular dyssynchrony for presynchronization identification of CRT responders. These results emphasize the need for global and complete evaluation of not only LV but also RV mechanical activation to assess the possible benefits of multisite pacing.

**Neurohumoral Activation and CRT**

Data on the effects of CRT on natriuretic peptides are scarce. In a series of 30 patients, Molboek et al.\textsuperscript{23} reported a decrease of BNP and atrial natriuretic peptide at 7 months, but only in patients whose NYHA class was improving. Sinha et al.\textsuperscript{24} reported a negative correlation between the variation in BNP and improvement in the ability to exercise in 20 patients. Other results are conflicting. In an ancillary study, MIRACLE\textsuperscript{25} reported no significant difference between the BNP rate in the treated (\(n^{}_{228}\)) and control (\(n^{}_{225}\)) groups at 6 months. A study performed in 17 patients who received BiV stimulation for more than 6 months showed that only patients with a BNP rate less than the median during stimulation had inverse remodeling compared with the values before implantation.\textsuperscript{26}

In the present study, neurohormonal activation was diminished in the group with no clinical events. We observed that when LVEF improved, hypokinetic or even dyskinetic segments recovered normal contractility. This improvement continued after 3 months, in agreement with the beneficial anatomic remodeling induced by CRT. In addition, the limited number of cardiac deaths in this study suggests that lack of baseline dyssynchrony (and resultant poor response to CRT) may itself predict cardiac death. This hypothesis warrants further study.

**Limitations**

The present study included patients with ischemic cardiomyopathy and idiopathic dilated cardiomyopathy. Since the
existence of scar tissue may be relevant in patients with ischemic disease, a scintigraphic study including only patients with this pathology is required. In patients with manifest dyskinesia (LV aneurysm), our most recent method of analysis is based on dual LV phase analysis; one measurement for the whole LV including the dyskinetic part and a second analysis excludes the dyskinetic area from the LV region of interest on which the phase histogram is constructed. This newer approach may allow a more precise measurement of interventricular dys synchrony by taking into account only the contractile regions of the LV that can respond to stimulation. Another possibility for identifying scar tissue would be combining the blood pool scintigraphy with resting (thallium-201) perfusion SPECT. Gated radio nuclide ventriculography imaging accuracy is limited by time resolution, but we used the highest framing rate reported in the literature. Using more sensitive detectors may be adequate for higher time resolution (eg, 64 frames/cycle instead of 16). In addition, because we did not adjust the V-V interval in our patients, the optimal benefit of CRT may not have been achieved. This issue remains to be evaluated. Finally, both the 25.5° cutoff value and the BNP cutoff value should be tested prospectively.

Only 74 of the 86 patients included in the study were followed-up. Indeed, LV lead implantation could not be achieved in 12 patients. Because the goal of our study was to determine the parameters associated with response to CRT, the lack of information in patients in whom CRT could not be implanted do not impair the validity of our results. In addition, there may be bias introduced by exclusion of patients with unsuccessful lead placement, particularly if these patients had more myocardial scar preventing capture. Finally, the use of CRT-OFF as opposed to pre-CRT phase measurements for the baseline is a limitation of the study.

Conclusion
The present study suggests that phase analysis can predict response to CRT. Radio nuclide ventriculographic phase may offer advantages compared with echocardiographic variables and the SPECT myocardial perfusion phase in selecting patients for CRT. IVD probably is an important predictor of response to CRT. The threshold for IVD determined by ROC analysis in the present study requires prospective evaluation before generalized use in a heart failure population.

Disclosures
None.

References
18. Kerwin WF, Botvinick EH, O’Connell JW, Merrick SH, DeMarco T, Chatterjee K, Scheibl K, Saxon LA. Ventricular contraction abnormalities in dilated cardiomyopathy: effect of biventricular pacing to...


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**CLINICAL PERSPECTIVE**

The criteria for selecting heart failure patients for cardiac resynchronization therapy (CRT), namely ejection fraction, New York Heart Association class, and QRS width, have been validated in large-scale randomized studies. However, the identification of the precise determinants of the resynchronization reserve, ie, the extent and the origin of the response to biventricular pacing, is lacking. Phase analysis, developed to assess dysynchrony from electrocardiography-gated radionuclide ventriculography, has shown promising results. We hypothesized that quantifying the cardiac resynchronization reserve, ie, the extent of response to CRT, by radionuclide imaging could potentially identify patients who are best suited for CRT. ECG-gated radionuclide ventriculography was performed in 86 patients at baseline with and without CRT and again after 3 months of follow-up. Receiver operative characteristic curve analysis demonstrated that an optimal cutoff value of 25.5° for interventricular dysynchrony (IVD) yielded 91.4% sensitivity and 84.4% specificity in predicting a good response to CRT. It was also found that neurohormonal activation was diminished in the group with no clinical events and that, when the left ventricular ejection fraction improved, hypokinetic or even dyskinetic segments recovered normal contractility. This improvement continued after 3 months, in agreement with the beneficial anatomic remodeling induced by CRT. Radionuclide ventriculographic phase may offer advantages compared with echocardiographic variables and single-photon emission-computed tomography-based phase measurements in selecting patients for CRT. IVD is likely an important predictor of response to CRT. The threshold for IVD determined by receiver operating characteristic analysis in the present study requires prospective evaluation before generalized use in a heart failure population.
Quantification of Ventricular Resynchronization Reserve by Radionuclide Phase Analysis in Heart Failure Patients: A Prospective Long-Term Study
Raphael Dauphin, Emilie Nonin, Laurence Bontemps, Madeleine Vincent, Alain Pinel, Serge Bonijoly, Denis Barborier, Arnaud Ribier, Christine Mestre Fernandes, Patrick Bert-Marcaz, Roland Itti and Philippe Chevalier

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