Cardiac Resynchronization Therapy

Ventricular Asynchrony Predicts a Better Outcome in Patients With Chronic Heart Failure Receiving Cardiac Resynchronization Therapy

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OBJECTIVES
The aim of this study was to evaluate whether the clinical benefit of cardiac resynchronization therapy (CRT) can be prospectively predicted by means of the baseline evaluation of left ventricular asynchrony.

BACKGROUND
The reverse remodeling associated with CRT is more evident in patients with severe heart failure (HF) and left bundle branch block (LBBB) who have left ventricular asynchrony.

METHODS
Baseline left ventricular asynchrony was assessed in 60 patients with severe HF and LBBB by calculating the electrocardiographic duration of QRS and the echocardiographic septal-to-posterior wall motion delay (SPWMD). Left ventricular size and left ventricular ejection fraction (LVEF), mitral valve regurgitation, and functional capacity were also evaluated. The progression toward HF (defined as a worsening clinical condition leading to a sustained increase in conventional therapies, hospitalization, cardiac transplantation, and death) was assessed during follow-up, as were the changes in LVEF after six months.

RESULTS
During the median follow-up of 14 months, 16 patients experienced HF progression. Univariate analysis showed that ischemic cardiomyopathy, changes in the QRS duration after implantation, and SPWMD significantly correlated with events. At multivariate analysis, a long SPWMD remained significantly associated with a reduced risk of HF progression (hazard ratio: 0.91; 95% confidence interval: 0.83 to 0.99; p < 0.05). An improvement in LVEF was observed in 79% of the patients with a baseline SPWMD of >130 ms and in 9% of those with an SPWMD of <130 ms (p < 0.0001).

CONCLUSIONS
Baseline SPWMD is a strong predictor of long-term clinical improvement after CRT in patients with severe HF and LBBB. (J Am Coll Cardiol 2005;45:65–9) © 2005 by the American College of Cardiology Foundation

There is increasing evidence supporting the routine use of cardiac resynchronization therapy (CRT) in treating patients with electrocardiographic ventricular asynchrony (i.e., left bundle branch block [LBBB] and severe heart failure [HF]) despite optimal medical treatment (1–4). Not all patients have subjective and/or objective responses to CRT (5,6), and so there is a need for parameters other than LBBB that could prospectively identify the patients who would benefit most (5–12).

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We have previously demonstrated that the presence of a delay in posterior wall contraction in comparison with the septum is a useful marker for selecting the patients who benefit most in terms of post-CRT reverse remodeling (6,11), but the possibility of being able to identify patients in whom the implantation of the device not only improves ventricular remodeling but also outcome would be a great clinical advantage.

We evaluated whether our proposed echocardiographic measurement of left ventricular asynchrony can identify the patients receiving CRT who have a better outcome (i.e., a reduction in the progression of HF).

METHODS

Study population. Between June 2000 and September 2003, we consecutively screened all of the patients referred to our HF unit. Seventy-two patients had New York Heart Association functional class III chronic HF of any origin, LBBB (QRS duration >130 ms) (4), and a left ventricular ejection fraction (LVEF) of ≤35%. We excluded patients if their conditions were not stable, if they had spontaneous or provoked angina or the need for revascularization procedures (6), or if they had not been receiving optimal drug therapy for at least three months. The study was approved by the local ethics committee, and the procedures followed were in accordance with institutional guidelines. All of the patients gave their written consent.

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### Baseline evaluations.
Between seven and three days before implantation, the patients underwent a clinical examination, 12-lead electrocardiography, mono- and two-dimensional echocardiographic and Doppler evaluations, and a cardio-pulmonary test.

Echocardiography recordings were made using a phased-array echo-Doppler system (Sonos 5500, Philips, Andover, Massachusetts) equipped with a 3-MHz transducer. After resting for 10 min, the patients were examined in the left lateral recumbent position using standard parasternal, short- and long-axis, and apical views. Intraventricular asynchrony was evaluated by calculating the delay between the motion of the septum and left posterior wall (septal-to-posterior wall motion delay [SPWMD]; in ms) (6). In two patients with myocardial infarction involving the septum wall, akinesia was observed, and no delayed contraction was registered. Therefore, we considered the SPWMD equal to zero. As previously described, the intraobserver as well as the interobserver reproducibility of this parameter were very high (6). Baseline left ventricular end-diastolic diameter, LVEF, mitral (MR) and tricuspid (TR) regurgitation (quantified by arbitrary units) were also calculated.

The patients also underwent symptom-limited cycloergometer exercise testing (10 W per min) with the assessment of oxygen consumption (VO$_2$) by means of mass spectrometry (Sensormedics System 2900, Anaheim, California); VO$_2$ at peak exercise was defined as the highest oxygen consumption (VO$_2$) by means of mass spectrometry (6). Baseline left ventricular end-diastolic diameter, LVEF, mitral (MR) and tricuspid (TR) regurgitation (quantified by arbitrary units) were also calculated.

### Pacemaker implantation.
A total of 42 patients received a biventricular pacemaker (Contak TR CHFD, Guidant, St. Paul, Minnesota; or InSync III, Medtronic, Minneapolis, Minnesota), and 30 patients received a biventricular cardioverter-defibrillator (Contak CD CHFD or Contak Renewal, Guidant; or InSync ICD or InSync Marquis, Medtronic; or Epic HF V-339, St. Jude Medical, St. Paul, Minnesota). Left ventricular pacing was obtained transvenously using a unipolar lead with an over-the-wire system (Easytrak, Guidant; or Attain OTW, Medtronic; or Aescula, St. Jude Medical) positioned into the lateral or posterolateral cardiac vein as previously described (6). The pacing mode was programmed in DDD with the lower rate set at 50 beats/min. The atrioventricular interval was optimized using Doppler echocardiography (6). An electrocardiogram was recorded within the first 2 h of CRT activation.

### Follow-up.
Patients were followed up as outpatients in our HF clinic for at least six months. The clinical end point considered was HF progression defined as death or hospitalization due to increased HF or symptoms of progression supported by a change in medication for the treatment of HF, as indicated by any of the following: 50% increase in the dose of oral medication, addition of new class of medication, addition of intravenous medication, or introduction of medication for HF, if not present at the time of the event (13,14). The events were evaluated by a physician who was unaware of baseline intraventricular dyssynchrony.

Clinical examination and LVEF were evaluated after six months; LVEF was considered improved if it had increased by >5% (15).

### Statistical analysis.
Data are shown as mean values ± SD. The continuous variables were compared using Student t-test for dependent (intragroup comparisons) and independent (intergroup comparisons) variables, and frequencies by means of the Fisher’s exact test. Survival was analyzed using the Cox proportional hazards model, and expressed as hazard ratios (HR) and 95% confidence intervals (CI). The variables significantly associated with the events at univariate analysis were included in a multivariate Cox regression model. The event-free curves were based on Kaplan-Meier analyses. The receiver-operating characteristic (ROC) curves for sensitivity and specificity were constructed in order to evaluate the predictive values of the studied variables, and the areas under the curves (AUC) were statistically compared in order to estimate the accuracy of the variables. A p value of <0.05 was considered statistically significant.

### RESULTS
Sixty-five of 72 screened patients met the enrollment criteria; SPWMD was not available in three patients because of poor image quality, and the implantation failed in two cases. The patients’ baseline characteristics are shown in Table 1.

During the median follow-up of 14 months, four patients died of congestive HF, and 12 were hospitalized. The patients with deteriorating HF more frequently had an ischemic etiology, a smaller reduction in QRS after CRT (ΔQRS), a shorter baseline SPWMD, and more severe TR (Table 1). In 14 patients the significant functional and hemodynamic improvement led to diuretic therapy reduction.

At univariate analysis, only SPWMD, ΔQRS, ischemic cardiomyopathy, and TR significantly correlated with HF progression (Table 2). Multivariate analysis showed that only SPWMD remained significantly associated with HF progression (HR: 0.91; 95% CI: 0.83 to 0.99; p < 0.05). The Kaplan-Meier curves for the patients with an SPWMD.
above or below the median value (130 ms) are shown in Figure 1.

After six months, LVEF was available in 51 patients (Fig. 2). Improvement was evident in 22 of 28 patients (79%) with baseline SPWMD ≥130 ms and in 9 of 23 patients (39%) with SPWMD <130 ms (p < 0.0001). There was a significant linear correlation between SPWMD and LVEF improvement (r: 0.69; p = 0.001). Patients' New York Heart Association functional class improved by at least one class in 22 of 28 patients (79%) with baseline SPWMD ≥130 ms and in 9 of 23 patients (39%) with SPWMD <130 ms (p < 0.01).

The ROC curves showed that the AUC of SPWMD was a significant linear correlation between SPWMD and LVEF improvement (r: 0.69; p = 0.001). Patients' New York Heart Association functional class improved by at least one class in 22 of 28 patients (79%) with baseline SPWMD ≥130 ms and in 9 of 23 patients (39%) with SPWMD <130 ms (p < 0.01).

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The abovementioned parameters are somehow related to the presence of a ventricular dyssynchrony in the left ventricle. The degree of left ventricular dyssynchrony measured by a variety of techniques (8–12) has been shown to be able to successfully predict responders to resynchronization therapy. We have recently suggested that a long delay between the displacements of the septum and the posterior wall distinguishes the patients who will experience early post-CRT (6) and long-term reverse remodeling (11) from those who will not. In this study, we found that the presence of echocardiographic left ventricular asynchrony predicts an improvement in LVEF of $>5\%$ with a sensitivity of 92% and a specificity of 78%.

Moreover, our results show that the benefit goes beyond hemodynamic improvement. When CRT is given to patients with an SPWMD of $\geq 130$ ms, it reduces HF-worsening events to a significantly greater extent than that observed in patients with less or no intraventricular asynchrony. This finding should have a considerable impact on clinical practice, as the benefit can be prospectively predicted in each individual patient before the decision to implant the device has been taken.

When baseline evaluation reveals a prolonged SPWMD, CRT is associated with an improved clinical outcome, but some patients with a short delay may also benefit from the device, which indicates the possible value of other echocardiographic methods of identifying asynchrony (8,9) or other pacing methods (16).

We found a high percentage of non-responders among ischemic patients. The lack of functional improvement was not due to the presence of ischemia, as provocative testing did not induce ischemia before implantation. Therefore, it is possible that, in ischemic patients, LBBB may be associated with the presence of asynchrony in areas other than those explored by our parameter, and, if this is the case, CRT aimed at pre-exciting the lateral or posterolateral left ventricular wall is not an adequate therapeutic strategy (17).

In line with the results of a previous study (7), a post-CRT reduction in QRS is also associated with a better outcome. However, if we consider patients with the same reduction, SPWMD provides further information concerning who will not experience events during follow-up. Furthermore, the echocardiographic evaluation of SPWMD (but obviously not the reduction in QRS) can be used for patient selection.

In conclusion, baseline SPWMD is a strong predictor of a long-term improvement in post-CRT clinical outcome in patients with severe HF and LBBB and can be proposed as a method of screening candidate patients.

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REFERENCES


