Echocardiographic measures of acute haemodynamic response after cardiac resynchronization therapy predict long-term clinical outcome

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Aims Although acute haemodynamic improvement in response to cardiac resynchronization therapy (CRT) is reflective of a favourable cardiac contractile response, there is limited information regarding not only its ability to predict long-term clinical outcome but also cardiac-substrate-specific differences in the prognostic value of this measure.

Methods and results Fifty-three heart failure patients (69 ± 11 years) with low left ventricle ejection fraction (LVEF) (22 ± 6%), wide QRS (169 ± 31 ms), and indications for CRT were included. There were no significant differences in age, New York Heart Association (NYHA) class, medications, QRS width, or LVEF between ischaemic (n = 37) and non-ischaemic (n = 16) groups. Echocardiograms were performed within 24 h of implantation with device OFF and ON. Acute haemodynamic response was measured as LV dP/dt derived from the CW Doppler of mitral regurgitation. Percentage change in dP/dt was used to classify patients: high- (HR: ΔdP/dt > 25%) or poor-responders (PR: ΔdP/dt ≤ 25%). Clinical response to CRT was defined by a combined endpoint of hospitalizations and all-cause mortality at 12 months. HR group had a significantly better outcome compared to the PR group (P-value = 0.004) irrespective of the aetiology of the cardiomyopathy.

Conclusion Echocardiographic assessment of the acute haemodynamic response to CRT predicts long-term clinical outcome in both ischaemic and non-ischaemic cardiomyopathy.

Introduction

Cardiac resynchronization therapy (CRT) improves ventricular dyssynchrony, and in turn is associated with an improvement in symptoms, quality of life, and prognosis in patients with severe heart failure. Despite CRT being a useful strategy to treat patients with drug-refractory heart failure, a substantial proportion of patients has little or no improvement. It is well understood that patients with high degrees of cardiac dyssynchrony show an acute haemodynamic benefit from restoration of mechanical synchrony with pacing late-activated portions of the heart. Previous reports have suggested that baseline mechanical ventricular dyssynchrony may predict the haemodynamic response to CRT. Also, recent work has indicated that acute beneficial haemodynamic changes are sustained at a 6-month follow-up. However, there is limited information regarding whether an acute haemodynamic response to CRT (assessed as percent change of the baseline dP/dt) is associated with a favourable clinical course, and whether there are cardiac substrate specific differences in its ability to predict long-term outcome. The objective of our study was to determine if the extent of acute haemodynamic response to CRT predicts long-term outcome in ischaemic and non-ischaemic cardiomyopathy.

Methods

Subjects

Only patients eligible for CRT (chronic systolic heart failure of New York Heart Association Class ≥ 3 despite optimal medical therapy and QRS duration ≥ 120 ms) were screened for this study. Patients with acute heart failure decompensation, recent myocardial infarction (<3 months), coronary artery bypass graft surgery within the previous 3 months, or severe aortic stenosis were excluded. Before device implantation, all patients underwent coronary angiography to define the aetiology of their cardiomyopathy and a Doppler Echocardiography for assessment of prior mitral regurgitation (MR). If there was not sufficient MR to appropriately measure dP/dt as described below, the patient was excluded. The study was approved by the local ethics committee.

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CRT devices

CRT devices were implanted transvenously, with the left ventricular lead placed in a suitable anatomical position in a branch of the coronary venous tree at a site which produced an acceptable pacing threshold without diaphragmatic pacing. At the time of this study, the right ventricular leads were generally positioned in the right ventricle apex or apico-septal region. The devices were manufactured by Medtronic (Insync models) and Guidant (Contak Renewal models). All patients received simultaneous left and right ventricles pacing.

Echocardiographic protocol

Non-invasive haemodynamic assessment of the acute effects of CRT by trans-thoracic echocardiography was performed within 24 h of device placement. Doppler echocardiography was performed using a General Electric Vivid 7 cardiac ultrasound machine (General Electric, Milwaukie, USA). A 3.5 MHz phased array probe was used to obtain standard 2D- and colour-Doppler images. The colour-coded tissue Doppler imaging frame rate was optimized with an average of 160 frames/s, and a minimum of five cardiac cycles were digitally acquired in each view. Data were analysed offline using commercially available computer software (Echopac System, General Electric). A fixed atrio-ventricular delay of 110–130 ms was used in diastole. CRT device turned OFF and then re-measured with CRT device turned ON, with 10 min allowed for haemodynamic stabilization in each mode before measurements were made. Left ventricle dP/dt (mmHg/s) was defined as the slope traced between 1 and 3 ms on the MR jet recorded at a sweep speed of 100 mm/s.10 The haemodynamic response to CRT was defined as the percentage increase in dP/dt (ΔdP/dt) with CRT device turned ON (ON-dP/dt) compared to the baseline dP/dt (OFF-dP/dt). Acute haemodynamic high responders (HR) to CRT were defined as those with ΔdP/dt > 25%.11,12 Poor-responders (PR) were divided into two subgroups: low-responders (LR) with ΔdP/dt between 0 and 25% and non-responders (NR) with a ΔdP/dt < 0. The severity of MR was estimated using the proximal isovelocity surface area (PISA) method.13 Additionally, left ventricular end-diastolic diameter (LVEDD), left ventricular ejection fraction (LVEF), and LV asynchrony were assessed. For the colour- and Tissue Doppler Imaging recordings, the velocities of longitudinal wall motion were assessed in the apical 4- and 2-chamber views, with a sample volume of 6 mm positioned at the basal segments of septal, lateral, inferior, and anterior walls. The time from the beginning of the QRS to the peak of systolic velocity was measured. LV dysynchrony was defined as the maximum delay (MTD) between peak systolic velocities among the four walls within the LV as well as the standard deviation of the mean of these times.14 Intra- and inter-observer variabilities were tested on 10 randomly selected cases. Intra-class correlation coefficients for dP/dt and Tissue Doppler values were between 0.91 and 0.95, respectively.

Follow-up

Patients were followed up in the Arrhythmia service ICD and pacemaker clinic at 1 month post-implant and then 3-monthly. Additional follow-up information was also obtained by reviewing hospital and outpatient records. The clinical endpoints evaluated included: all-cause mortality and hospitalization for worsening heart failure. These events were determined by a physician blinded to the echocardiographic results.

Statistical analysis

Sample size was determined to find a 30% difference in event-free rates between responders and non-responders at 1 year with 80% power and an alpha error of 0.05 (28 patients per arm). Comparisons between CRT device turned OFF and CRT device turned ON were performed using two-tailed paired Student’s t-test. Event-free survival curves and log-rank tests (combined end-point of death and hospitalization for heart failure) were also used to compare groups. Finally, predictors of events over time were analysed by creating a Cox proportional hazard multivariable model. The normal distribution of the continuous variables was confirmed by evaluating the skewness and kurtosis of the distribution, and by Shapiro-Wilk test. The variable of interest, change in dP/dt from CRT (expressed as a percentage), was treated as a continuous variable and forced into the model. Other significant variables on univariable analysis were considered for inclusion into the model. Variables were added sequentially in order of statistical significance by assessing model strength. Collinear variables were excluded. The final model included the following variables: percent change in LVEF after CRT, percent change in ESV after CRT, LV internal diameter in diastole, ischaemic aetiology of LV dysfunction, hematocrit (HCT), and creatinine level, as well as the variable of interest. A two-sided P-value < 0.05 was considered as statistically significant. For event-free survival analysis, Bonferroni adjustment was applied for paired comparisons and a P-value of 0.017 was considered as significant. Data are presented as mean ± standard deviation for continuous data and as mean and inter-quartile ranges for follow-up data. Analyses were performed using SAS 9.1.3 (SAS Institute).

Results

Subjects

Of the 97 patients evaluated, 53 heart failure patients had significant MR allowing dP/dt measurement and were included in this study (ischaemic=37 and non-ischaemic=16). Most patients were in New York Heart Association Class III (89%), in sinus rhythm (75%), and had severe left ventricle dysfunction (LVEF 22–40%). Baseline characteristics are reported in Table 1. All patients were considered to be on optimal medical therapy. The patients were followed up for 11 [6, 12] months. At the end of the study, there were four deaths (7.5%), all in the ischaemic group, while three of the 16 (18.7%) non-ischaemic heart failure patients were admitted to the hospital for worsening heart failure symptoms, compared with eight of 37 (21.6%) in the ischaemic group.

dP/dt

After CRT, asynchrony, and dP/dt were significantly improved (P = 0.004 and P < 0.0001 respectively) in this group of patients overall, with no difference between the ischaemic and non-ischaemic groups (Table 2). However, a significant relationship existed between the percent increase in dP/dt and the baseline severity of dysynchrony (r = 0.580, P < 0.0001). In addition, there was a correlation between changes in dP/dt and changes in asynchrony measurements using MTD criteria (r = –0.574, P < 0.0001) as well as the standard deviation (r = –0.546, P < 0.0001) as shown in Figure 1.

Outcome

Overall there were 28 HR, 17 LR, and 8 NR patients. Figure 2 shows the proportion of these three groups in ischaemic and

Follow-up

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non-ischaemic patients and a comparable number of NR patients are seen in each group. Baseline characteristics were similar in HR and PR (Table 3).

There was a significant difference in the combined endpoint among the NR, LR, and HR groups at follow-up. As shown in Figure 3, 89.2% of HR patients were event-free after 1 year compared to 58.9% in the LR group (P < 0.001). The HR group also had a better outcome compared to a 52.0% event free survival in the combined PR group (P = 0.004). No significant difference was observed between the ischaemic and non-ischaemic groups with respect to the combined endpoint of death and hospitalization for worsening heart failure. There was a trend towards a lower event rate in non-ischaemic patients, but this was not significant because of the low overall event-rate (Figure 4).

In the Cox proportional hazard model, change in dp/dt was the only significant predictor of event-free survival after adjustment (HR = 0.95 per unit dp/dt change, P = 0.0176). Other clinical variables kept in the model (HCT, creatinine, aetiology of the cardiomyopathy, percent change in EF acutely after CRT, and percent change in ESV acutely after CRT), were not significant predictors after adjustment.

**Mitral regurgitation**

In our population, we did not observe a significant change in MR in the overall population between CRT turned OFF and CRT turned ON; effective orifice regurgitant area 17 ± 12 mm². There was a significant difference in the combined endpoint of death and hospitalization for worsening heart failure. There was a trend towards a lower event rate in non-ischaemic patients, but this was not significant because of the low overall event-rate (Figure 4).

In the Cox proportional hazard model, change in dp/dt was the only significant predictor of event-free survival after adjustment (HR = 0.95 per unit dp/dt change, P = 0.0176). Other clinical variables kept in the model (HCT, creatinine, aetiology of the cardiomyopathy, percent change in EF acutely after CRT, and percent change in ESV acutely after CRT), were not significant predictors after adjustment.

**Discussion**

Our study shows for the first time that echocardiographic assessment of the acute haemodynamic response to CRT (in the immediate post-implant period) is a useful predictor of long-term clinical outcome in ischaemic and non-

### Table 1 Study group, baseline characteristics

<table>
<thead>
<tr>
<th>Study group</th>
<th>Non-ischaemic group</th>
<th>Ischaemic group</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n = 53</td>
<td>n = 16</td>
<td>n = 37</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>68.8 ± 10.7</td>
<td>66.4 ± 13.2</td>
<td>69.7 ± 9.7</td>
</tr>
<tr>
<td>Sex (%)</td>
<td>31.0/69.0</td>
<td>60.0/40.0</td>
<td>18.9/81.1</td>
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<tr>
<td>NYHA III (%)</td>
<td>88.7</td>
<td>87.2</td>
<td>89.2</td>
</tr>
<tr>
<td>NYHA IV (%)</td>
<td>11.3</td>
<td>12.8</td>
<td>10.8</td>
</tr>
<tr>
<td>Atrial fibrillation (%)</td>
<td>24.5</td>
<td>25.6</td>
<td>27.0</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>36.5</td>
<td>31.2</td>
<td>37.8</td>
</tr>
<tr>
<td>HBP (%)</td>
<td>34.0</td>
<td>25.0</td>
<td>37.8</td>
</tr>
<tr>
<td>Diuretics (%)</td>
<td>88.7</td>
<td>87.2</td>
<td>86.5</td>
</tr>
<tr>
<td>Aldactone (%)</td>
<td>37.7</td>
<td>35.9</td>
<td>32.4</td>
</tr>
<tr>
<td>Digoxin (%)</td>
<td>54.7</td>
<td>51.3</td>
<td>54.0</td>
</tr>
<tr>
<td>Beta-blockers (%)</td>
<td>75.5</td>
<td>79.5</td>
<td>78.4</td>
</tr>
<tr>
<td>ACE or ARB’s (%)</td>
<td>49.0</td>
<td>87.5</td>
<td>62.2</td>
</tr>
<tr>
<td>QRS (ms)</td>
<td>169.5 ± 30.7</td>
<td>173.7 ± 32.2</td>
<td>167.8 ± 30.5</td>
</tr>
<tr>
<td>Sodium (mM)</td>
<td>137.5 ± 3.2</td>
<td>138.5 ± 2.8</td>
<td>137.4 ± 3.3</td>
</tr>
<tr>
<td>BUN (mg/dL)</td>
<td>33.2 ± 18.2</td>
<td>27.8 ± 16.0</td>
<td>35.4 ± 18.9</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>1.9 ± 1.5</td>
<td>1.7 ± 1.5</td>
<td>1.9 ± 1.5</td>
</tr>
<tr>
<td>HCT (%)</td>
<td>35.4 ± 4.9</td>
<td>36.4 ± 5.5</td>
<td>35.1 ± 4.7</td>
</tr>
<tr>
<td>LV EF (%)</td>
<td>47.9 ± 2</td>
<td>43.8 ± 2</td>
<td>46.0 ± 2</td>
</tr>
<tr>
<td>LV EDV (mm)</td>
<td>65.8 ± 10.0</td>
<td>69.8 ± 11.4</td>
<td>64.2 ± 9.2</td>
</tr>
</tbody>
</table>

ACE, Angiotensin Converse Enzym; ARB’s, angiotensine receptor blockers; BUN, blood urea nitrogen; HBP, high blood pressure.

**Table 2 Left ventricle dp/dt and asynchrony before and after CRT**

<table>
<thead>
<tr>
<th>Follow-up (months)</th>
<th>Study group n = 53</th>
<th>Non ischaemic group n = 16</th>
<th>Ischaemic group n = 37</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>DP/dt CRT OFF (mmHg/s)</td>
<td>9.3 ± 3.6</td>
<td>9.9 ± 3.4</td>
<td>13.3 ± 3.6</td>
<td>0.58</td>
</tr>
<tr>
<td>DP/dt CRT ON (mmHg/s)</td>
<td>592.3 ± 186.9</td>
<td>560.4 ± 209.5</td>
<td>606.1 ± 177.5</td>
<td>0.42</td>
</tr>
<tr>
<td>Change in dp/dt (mM/s)</td>
<td>772.7 ± 246.9</td>
<td>702.7 ± 178.8</td>
<td>802.9 ± 267.6</td>
<td>0.18</td>
</tr>
<tr>
<td>Asynchrony CRT OFF (ms)</td>
<td>180.4 ± 32.5</td>
<td>142.2 ± 105.7</td>
<td>196.8 ± 274.3</td>
<td>0.45</td>
</tr>
<tr>
<td>Asynchrony CRT ON (ms)</td>
<td>82.7 ± 46.0</td>
<td>75.2 ± 39.9</td>
<td>85.2 ± 48.6</td>
<td>0.50</td>
</tr>
<tr>
<td>Change in asynchrony (ms)</td>
<td>52.9 ± 36.1</td>
<td>50.9 ± 20.4</td>
<td>53.8 ± 41.2</td>
<td>0.80</td>
</tr>
</tbody>
</table>

LV asynchrony reported as the standard deviation of the mean of the times to systolic velocity peak, P-value comparing Non-ischaemic and Ischaemic groups.

ACE, Angiotensin Converse Enzym; ARB’s, angiotensine receptor blockers; BUN, blood urea nitrogen; HBP, high blood pressure.

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ACOE and the only significant predictor of event-free survival after adjustment (HR = 0.95 per unit dp/dt change, P = 0.0176). Other clinical variables kept in the model (HCT, creatinine, aetiology of the cardiomyopathy, percent change in EF acutely after CRT, and percent change in ESV acutely after CRT), were not significant predictors after adjustment.

**Discussion**

Our study shows for the first time that echocardiographic assessment of the acute haemodynamic response to CRT (in the immediate post-implant period) is a useful predictor of long-term clinical outcome in ischaemic and non-ischaemic patients.
ischaemic cardiomyopathy. This is consistent with previous work from Olguz et al., showing that LV \(\frac{dP}{dt}\)-rise was the single variable significantly different between responders and non-responders (defined by the change in NYHA-class). Several studies have attempted to identify predictors of response using either patient selection criteria such as QRS width, measures of baseline asynchrony, or pacing site selection. Most of these studies have been limited by the fact that there is usually more than one predictive factor in determining response within the individual patient; these include extent of impaired left ventricular contractility, degree of mechanical ventricular dyssynchrony, and optimal placement of the left ventricle and possibly right ventricle pacing leads.

Previous work has indicated that ventricular contractility as measured by \(\frac{dP}{dt}\) is a predictor of outcome in patients with heart failure. The percent change in LV \(\frac{dP}{dt}\) with CRT, a measure of the acute impact of resynchronization on global systolic function, serves as a more integrated measure of the impact of CRT on overall cardiac performance. In our patient group, LV \(\frac{dP}{dt}\) was measured with CRT on and off in close temporal proximity, providing a more accurate measure of the extent of acute haemodynamic improvement due to CRT, with minimal chance for time-dependent changes in factors such as pre-load to confound the analysis.

Although previous studies have indicated that CRT benefits patients with both ischaemic and non-ischaemic cardiomyopathy, a greater benefit from CRT in non-ischaemias has been suggested. Our results demonstrate that CRT can improve haemodynamics in both ischaemic and non-ischaemic cardiomyopathy, and that this is predictive of clinical outcome in both subgroups. Consistent with prior reports, patients in our study with non-ischaemic cardiomyopathy had a trend towards reduced clinical events after CRT placement compared to ischaemic patients. This response is potentially explained by data from another study demonstrating more favourable long-term left ventricular remodelling in the subjects with non-ischaemic vs.
but also unchanged or increased in some). These variations of MR (reduced by CRT in a large proportion of the patients, individual variability in the extent of change in the severity population. We also observed that there was considerable did not observe any significant reduction in MR in the overall fraction of the patients (30%) had non-ischaemic disease, we measurement35 as non-circular shape of the mitral regurgi-outcome. However, classical technical issues in PISA shorter inter-lead (between RV and LV lead), may have a shown that more anteriorly positioned leads, because of a haemodynamic response. Previous work from our group has this impact, since patients did not undergo an MRI for scar localization.

CRT has a favourable impact on MR32 and previous publications31,34 suggest that the increase in dp/dt is the cause rather than the effect of a decrease in MR. Prior work has shown that the impact of CRT on MR is mainly present in non-ischaemic cardiomyopathy; since in our study, only a small fraction of the patients (30%) had non-ischaemic disease, we did not observe any significant reduction in MR in the overall population. We also observed that there was considerable individual variability in the extent of change in the severity of MR (reduced by CRT in a large proportion of the patients, but also unchanged or increased in some). These variations did not affect the predictive value of dp/dt for long-term outcome. However, classical technical issues in PISA measurement35 as non-circular shape of the mitral regurgitant area or variability of the heart rate especially in patients with atrial fibrillation could have affected the results. Several studies have shown that left ventricular lead position can affect clinical outcome.36,37 It is possible that this impact maybe reflective of an altered acute haemodynamic response. Previous work from our group has shown that more anteriorly positioned leads, because of a shorter inter-lead (between RV and LV lead), may have a worse acute haemodynamic response.27,38 The present study takes this work further showing that the acute haemodynamic response in fact predicts long-term outcome.

Clinical implication

Although the measure of acute haemodynamic response used in this study was made in the immediate post-implant period (and thus can not be used as a pre-procedural predictor of CRT response), one could speculate that such a measure made intra-procedurally could facilitate selecting an optimal site for left or right ventricular pacing. Additionally, measure of dp/dt may also prove useful in post-procedural device optimization as recently shown.39

Study limitations

Our analysis of acute response to CRT was confined to patients with sufficient MR to accurately measure dp/dt. It is quite possible that patients without significant MR, especially after resynchronization, may have a different acute haemodynamic response to CRT compared to the group in this study. Also, unlike the true peak left ventricle dp/dt measured by pressure-tip catheters, dp/dt assessed by echocardiography is reflective of an ‘average peak’. Therefore, the results of this study may differ from those which use pressure-tip micromanometre catheters. As indicated earlier, dp/dt measured in this study was a post-implant measure, hence has a predictive role only after the implant. In this patient cohort, dp/dt was measured with the device turned ‘OFF’ and ‘ON’ during the same period of measurement, thereby reducing the impact of time, remodelling, or any other confounding variable on cardiac performance. Atrio-ventricular optimizations were performed only in patients who did not respond clinically during their follow-up. It is possible that pro-active post-procedural atrio-ventricular optimizations could have impacted the results of this study. Moreover the small sample size could have impacted our results, when the patients were sub stratified into ischaemic and non-ischaemic aetiologies. Unlike previous work from Yu et al.40 where changes in LV end systolic volume were most predictive of long-term outcomes, our study did not examine the impact of reverse remodelling on clinical outcome. Our results emphasize that amongst the acute echocardiographic changes (e.g. CRT-induced acute changes in MR, EF or LV end systolic volume), only dp/dt was predictive of long-term clinical outcome.

Conclusion

In patients receiving CRT, echocardiographic assessment of the acute haemodynamic response to CRT is a useful predictor of long-term clinical outcome in ischaemic and non-ischaemic cardiomyopathy.

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Conflict of interest. F.B.T. received research grants from Guidant France, Medtronic France, St Jude Medical France. K.H. received consulting and speaker fees from Guidant, Medtronic Biotronik. J.P.S. was a consultant to Medtronic Inc. J.R.S. received Research grant, consulting and speaker fees from Guidant, Medtronic Biotronik and St Jude Medical.

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