Sympathetic control after cardiac resynchronization therapy: responders versus nonresponders

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Methods

Subjects. The responder status to CRT was determined before the experimental recording session. All had undergone a careful determination of their NYHA functional class by their cardiologist before inclusion in the study.

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RESULTS

Sympathetic activation is a key component of the pathophysiology of chronic congestive heart failure (CHF) (12, 14, 25). This sympathetic overactivity is directly related to the severity of heart failure and is implicated in the poor prognosis of the disease (9). One of the major aims of the therapeutic approach in heart failure is to reduce sympathetic overactivity while improving cardiac hemodynamics and functional capacity (15, 19, 32).

Cardiac resynchronization therapy (CRT) by atrio-biventricular pacing (BIV) improves symptoms, quality of life, exercise tolerance, and prognosis of patients with drug-refractory CHF and left bundle branch block (1, 5, 7, 8).

Biventricular pacing reduces muscle sympathetic nerve activity (MSNA) compared with atrio-right ventricular pacing (ARV) (24) and right atrial pacing (22) in the acute setting. These beneficial effects persist up to 6 mo after resynchronization therapy (21, 28).

However, it is not yet known whether the clinical response to CRT is related to the MSNA inhibitory effects of this therapy. This is of importance because a significant proportion of patients who appear to be ideal candidates for CRT do not show the expected clinical benefits (4). Factors responsible for this relatively high prevalence of nonresponders are not clear (3).

Unknown, also, is whether the favorable MSNA effects of CRT persist during even longer follow-up periods.

We tested the hypothesis that long-term sympathoinhibition induced by CRT is acutely reversible when the pacemaker is switched to a nonsynchronous condition (NSC) [i.e., to a conventional ARV mode and pacing cessation (OFF mode)] and that this occurs only in those who respond to CRT by an improved New York Heart Association (NYHA) functional class. This would indicate that persistent MSNA inhibition after CRT is a marker of the clinical response to this therapy.

In CHF patients treated by CRT, we determined MSNA, clinical variables, and noninvasive cardiac hemodynamics during BIV pacing, ARV pacing, and, if the patient was not pacemaker dependent, in the OFF mode.

METHODS

The study was approved by the Ethical Committee of the Erasme Hospital, Brussels. Each subject signed an informed consent before inclusion in the study.

Subjects. The responder status to CRT was determined before the experimental recording session. All had undergone a careful determination of their NYHA functional class by their cardiologist before CRT. NYHA functional class before CRT was retrospectively determined in the medical record of the patient by the referring cardiologist. NYHA functional class at the time of the study was determined by the same referring cardiologist (P. Unger, N. Preumont, A. Friart, L. De Roy, and J.-L. Vandenbossche). Thus assessments of NYHA classes were fully independent of the investigators (B. Najem, A.
Houssière, A. Pathak, O. Xhaet, L. Gabriel, and P. van de Borne) and blinded to the recordings of the study. A nonresponder patient to CRT was defined prospectively as a patient who had not decreased his or her NYHA functional class at the time of the study (31). A patient who presented a symptomatic improvement by one or more NYHA functional classes at the time of the study was defined as a responder.

Sixteen patients responded to CRT (4 women). In seven patients (1 woman), NYHA functional class did not change (n = 5) or worsened (n = 2) 12 ± 4 mo after CRT.

In all patients, indication for CRT was drug-refractory CHF (NYHA functional class >II) in the presence of a left bundle branch block with a QRS duration >120 ms, a left ventricular ejection fraction assessed by echocardiography <35%, a left ventricular end-diastolic diameter >55 mm, interventricular asynchrony (difference between aortic and pulmonary prejection time delay >40 ms, interventricular mechanical delay). In six patients, the left bundle branch block was induced by a conventional atrio-right ventricular pacemaker that was upgraded to a biventricular pacemaker. In these pacemaker-dependent patients, the OFF mode was not performed.

Measurements. Multiunit recordings of postganglionic MSNA were obtained in all patients with a unipolar tungsten electrode inserted selectively into a nerve fascicle of the right or left peroneal nerve, posterior to the fibular head (28). After obtaining 10 min of an acceptable recording of MSNA during BIV pacing, we performed, in random order, recordings during 10 min of ARV pacing, 10 min in OFF mode, and 10 min of BIV pacing. The OFF mode was recorded only in 17 patients who were not pacemaker dependent (11 responders and 6 nonresponders). MSNA recordings were acquired and analyzed on a MacLab 8/s data acquisition system (ADInstruments, Castle Hill, NSW, Australia).

During the study protocol, we also recorded heart rate (Siemens Medical, ECG Monitoring, Erlangen, Germany), oscillometric blood pressure measurements every 2 min with a Physiocontrol Colin BP-880 sphygmomanometer (Colin Press Mate, Colin, Komaki City, Japan) and continuous oxygen saturation determinations (Nellcor N-100 C pulse oxymeter, Pleasanton, CA).

Blood samples for plasma norepinephrine were obtained in 10 patients in each mode during the MSNA recording in carefully standardized supine resting conditions. Samples were collected in prechilled heparinized tubes (10 ml), immediately placed on ice, and then centrifuged at 4°C. Norepinephrine levels were assayed by high-performance liquid chromatography (17).

A blood sample was also taken in all patients to determine brain natriuretic peptide (BNP) plasma concentrations by the triage BNP levels point-of-care test (Biosite Diagnostics, San Diego, CA).

An electrocardiogram (Hewlett-Packard XLS electrocardiograph, Palo Alto, CA) was recorded in the three modes to determine the QRS axis and duration. Standard echocardiography, including Doppler measurement (Vivid 7, General Electric, Horten, Norway), was performed in patients according to the American Society of Echocardiography recommendations (16). Measurements were performed in the three modes in the same order as in the MSNA recordings. The echocardiographer was blinded according to the pacemaker stimulation mode. Three consecutive beats were measured and averaged. Left ventricular end-diastolic and end-systolic volumes were measured by the biplane Simpson method and were used for left ventricular ejection fraction determinations. Aortic and pulmonary prejection times were derived from continuous-wave Doppler measurements, allowing calculation of interventricular mechanical delay. Doppler echocardiography allowed measurements of cardiac output at the level of the left ventricular outflow tract. The rate of pressure rise in systole (dP/dt) was estimated from the continuous-wave Doppler mitral regurgitation (16).

All patients underwent a functional evaluation by a 6-min walking test conducted according to Bittner (6). All completed the self-administered Minnesota Living with Heart Failure questionnaire for scoring quality of life on a scale from 0 (best) to 105 (worst).

Sympathetic nerve traffic analysis. Sympathetic bursts were identified by careful inspection of the voltage neurogram by a trained observer (B. Najem) blinded to the pacemaker stimulation mode and clinical status of patients. Sympathetic activity was expressed as burst frequency per minute and bursts per 100 heartbeats. The amplitude of each burst was determined. Integrated sympathetic activity was calculated as burst frequency multiplied by mean burst amplitude and expressed as the percentage from BIV value. Burst frequency permits comparison of sympathetic nerve activity between patients, whereas both burst frequency and percentage of change in integrated sympathetic activity were used to assess the effects of a change in pacemaker stimulation mode.

Statistical analysis. Analysis of all recordings was fully blinded to the pacemaker stimulation mode and clinical status of patients. Results are expressed as means ± SE. Comparisons of patient characteristics, hemodynamics, and sympathetic activity between responders and nonresponders were made with unpaired two-tailed Student t-tests, whereas comparisons of nominal data were made with a χ²-test. The link between norepinephrine concentration and MSNA was assessed by a correlation analysis. Significance was assumed at P < 0.05. Comparisons of changes from BIV pacing to NSC (i.e., conventional ARV mode and OFF mode) between responders and nonresponders were made with an ANOVA, with pacing mode and responder status as factors. Bonferroni contrasts were made posteriori (4 contrasts, significance assumed at P < 0.0125).

RESULTS

Patient characteristics. Responders and nonresponders did not differ in age, sex, body mass index, postimplantation delay, and medical treatment (Table 1). In the responders, there were nine patients with ischemic cardiomyopathy, two patients who previously had surgery for valvular heart disease, and five patients with idiopathic cardiomyopathy. In the nonresponders, three patients had ischemic heart disease and four patients had idiopathic cardiomyopathy (P = 0.40).

Comparisons between responders and nonresponders before changes in the pacing modes. Responders had a better clinical status than that of nonresponders, with a longer 6-min walking distance, a better quality of life, and lower levels of BNP (Table 2). In the responders, two patients were in NYHA class I, 13 were in class II, and one was in class III (this patient was in class IV before CRT). In the nonresponders, all patients were in NYHA class III (P < 0.001). Blood pressure, heart rate, left ventricular ejection fraction, and cardiac index did not differ between both groups.

Table 1. Patient characteristics

<table>
<thead>
<tr>
<th></th>
<th>Responders</th>
<th>Nonresponders</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>16</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>64±3</td>
<td>72±2</td>
<td>NS</td>
</tr>
<tr>
<td>Sex</td>
<td>4 women and 12 men</td>
<td>1 woman and 6 men</td>
<td>NS</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>27±1</td>
<td>27±2</td>
<td>NS</td>
</tr>
<tr>
<td>Beta blockers</td>
<td>12</td>
<td>5</td>
<td>NS</td>
</tr>
<tr>
<td>ACE inhibitor/AIIR blocker</td>
<td>15</td>
<td>7</td>
<td>NS</td>
</tr>
<tr>
<td>Aldactone</td>
<td>8</td>
<td>4</td>
<td>NS</td>
</tr>
<tr>
<td>Diuretics</td>
<td>10</td>
<td>6</td>
<td>NS</td>
</tr>
<tr>
<td>Vasodilators</td>
<td>6</td>
<td>4</td>
<td>NS</td>
</tr>
<tr>
<td>Postimplantation delay</td>
<td>15±5</td>
<td>12±4</td>
<td>NS</td>
</tr>
</tbody>
</table>

Values are means ± SE. ACE, angiotensin-converting enzyme; AIIR, angiotensin II receptors; NS, not significant.
MSNA (normalized for heart rate) tended to be lower in the responders than in the nonresponders ($P = 0.06$), and plasma norepinephrine levels did not differ.

Our observation of a longer 6-min walking distance, a better quality of life, and lower levels of BNP is consistent with the improved NYHA functional class in the responders.

**Effects of switching biventricular pacing into a NSC (ARV and OFF) on sympathetic and hemodynamic parameters.**

MSNA amplitude increased only in the responders when biventricular pacing was switched to a NSC ($+25 \pm 7\%$ vs. $-5 \pm 4\%$, respectively, in the responders and nonresponders) (Table 3 and Figure 1; $P < 0.01$). A similar, albeit not significant, trend was observed for MSNA burst frequency/100 heartbeats. Blood pressure did not change in responders when switching to a NSC, whereas it decreased in the nonresponders ($P < 0.01$). Cardiac output decreased by $0.7 \pm 0.2$ l/min when shifting from the BIV to a NSC in the responders ($P < 0.01$) but did not change in the nonresponders. The decrease in $dP/dt$ and diastole duration and the increase in interventricular delay after switching to NSC were comparable in responders and nonresponders.

**Correlation between MSNA and norepinephrine levels in each mode.** The MSNA in each mode was related to norepinephrine levels in the same mode and taken during the MSNA recording (Figure 2; $n = 10$ patients, $r = +0.7$, $P < 0.0001$).

**DISCUSSION**

The main new findings of our study were that 1) sympathoinhibition induced by chronic CRT is acutely reversible when patients are shifted from a synchronous to a NSC; 2) this is observed only in patients who are clinically improved by CRT, even more than a year after initiation of the therapy; and 3) MSNA is positively correlated to norepinephrine levels and reflects overall sympathetic activity in CRT patients.

We are not aware of previous studies on the effects of the responder status to CRT on MSNA. This is also, to the best of our knowledge, the first study to assess effects of different programming modes on sympathetic activity more than a year after CRT.

Our study provides direct evidence that reversible sympathoinhibition is a marker of the clinical response to CRT. Biventricular pacing interruption induced an acute and marked increase in MSNA only in those who improved their NYHA functional class with CRT. This was not due to a pacemaker rate dependency in the responders, because the pacing was stopped only in those who were not pacemaker dependent. Differences in sympathetic reactivity on changes in the pacing mode did not translate, however, into clear-cut reductions in sympathetic burst frequency during BIV pacing in the responders ($P = 0.06$). There are several possible reasons for the apparent discrepancy between more marked acute increases in MSNA on loss of synchrony and lack of marked MSNA inhibition during chronic synchronous pacing in the responders. First, sympathetic activation involves both increases in burst amplitude and frequency in multiunit recordings (13, 22, 24, 33, 34, 36). Burst frequency, which is used for comparisons of multiunit recordings between subjects (22, 24, 33, 34, 36, 37). Second, it may be that responders to CRT preserve the ability to show acute changes in MSNA, whereas a somewhat more saturated MSNA may have less reserve to further increase sympathetic nerve traffic in the nonresponders (26). Third, baroreceptors are important regulators of acute changes in MSNA but may be less involved in the tonic regulation in baseline MSNA (27). Thus preservation of the acute ability to modify MSNA may not necessarily translate into sustained reductions in mean baseline sympathetic drive.

More functional baroreceptors, which sense changes in cardiac and arterial pressures, could have contributed to differences in MSNA reactivity in our patients (20). In the nonresponders, switching to the NSC induced an acute decrease in blood pressure without any significant effect on MSNA, sug-

### Table 2. Comparison of hemodynamic and sympathetic parameters between responders and nonresponders during BIV pacing before changing the pacing modes

<table>
<thead>
<tr>
<th></th>
<th>Responders</th>
<th>Nonresponders</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$n$</td>
<td>16</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Systolic BP, mmHg</td>
<td>120±4</td>
<td>125±8</td>
<td>NS</td>
</tr>
<tr>
<td>Diastolic BP, mmHg</td>
<td>66±3</td>
<td>69±6</td>
<td>NS</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>61±2</td>
<td>68±2</td>
<td>NS</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>35±3</td>
<td>39±6</td>
<td></td>
</tr>
<tr>
<td>Cardiac index, 1min^{-1}·m^{-2}</td>
<td>2.8±0.2</td>
<td>3.2±0.4</td>
<td>NS</td>
</tr>
<tr>
<td>Quality of life score</td>
<td>18±3</td>
<td>40±4</td>
<td>0.001</td>
</tr>
<tr>
<td>6-Min walking distance, m</td>
<td>456±26</td>
<td>320±70</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>BNP, pg/ml</td>
<td>199±57</td>
<td>541±170</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>MSNA/100 heartbeats</td>
<td>69±4</td>
<td>83±4</td>
<td>0.06</td>
</tr>
<tr>
<td>Norepinephrine, ng/ml</td>
<td>0.38±0.04</td>
<td>0.43±0.19</td>
<td>NS</td>
</tr>
</tbody>
</table>

Values are means ± SE. BIV, atrio-biventricular pacing mode; BNP, brain natriuretic peptide; BP, blood pressure; LVEF, left ventricular ejection fraction; MSNA, muscle sympathetic nerve activity.

### Table 3. Effect of switching to a nonsynchronous mode (BIV and ARV) on hemodynamic and sympathetic parameters

<table>
<thead>
<tr>
<th></th>
<th>Responders</th>
<th>Nonresponders</th>
<th>ANOVA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BIV</td>
<td>NSC</td>
<td>BIV</td>
</tr>
<tr>
<td>$n$</td>
<td>16</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Systolic BP, mmHg</td>
<td>118±4</td>
<td>119±4</td>
<td>127±6</td>
</tr>
<tr>
<td>Diastolic BP, mmHg</td>
<td>64±2</td>
<td>64±2</td>
<td>69±5</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>64±2</td>
<td>64±2</td>
<td>68±1</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>36±3</td>
<td>33±3</td>
<td>39±4</td>
</tr>
<tr>
<td>Cardiac output, l/min</td>
<td>5.5±0.4*</td>
<td>4.8±0.3</td>
<td>6.3±0.9</td>
</tr>
<tr>
<td>Mitral regurgitation volume, ml</td>
<td>13±3</td>
<td>15±2</td>
<td>16±4</td>
</tr>
<tr>
<td>dP/dt, mmHg/ms</td>
<td>695±53</td>
<td>477±49</td>
<td>914±103</td>
</tr>
<tr>
<td>Interventricular delay, ms</td>
<td>32±5</td>
<td>63±6</td>
<td>15±2</td>
</tr>
<tr>
<td>Diastole duration, % cycle</td>
<td>51±2</td>
<td>46±3</td>
<td>51±3</td>
</tr>
<tr>
<td>MSNA, bursts/min</td>
<td>46±2</td>
<td>48±2</td>
<td>53±2</td>
</tr>
<tr>
<td>MSNA, bursts/100 heartbeats</td>
<td>72±4</td>
<td>76±3</td>
<td>78±3</td>
</tr>
<tr>
<td>MSNA, amplitude</td>
<td>100±0*</td>
<td>125±7</td>
<td>100±20</td>
</tr>
</tbody>
</table>

Values are means ± SE. ARV, atrio-right ventricular pacing mode; dP/dt, rate of pressure rise in systole; NSC, nonsynchronous condition. Statistical significance of ANOVA is presented for the pacing mode vs. responder status interaction. *$P < 0.0125$ BIV vs. NSC in responders; †$P < 0.0125$ BIV vs. NSC in nonresponders.
gesting that arterial baroreceptors were impaired in those patients.

Preservation of MSNA reactivity in responders may have clinical implications. The magnitude of sympathoexcitation is an important determinant of the hemodynamic outcome of ventricular tachycardia (23). The late recovery of blood pressure during ventricular tachycardia is related to the magnitude of early sympathetic responses (23). The larger sympathetic response when BIV pacing is stopped may explain why blood pressure remained unchanged in the responders but decreased in the nonresponders. Preservation of sympathetic homeostatic mechanisms in CRT patients may thus also prove beneficial during acute conditions such as cardiac arrhythmias (23).

Plasma norepinephrine did not differ between the responders and the nonresponders in our study. This has also been reported after 10 wk of successful cardiac resynchronization as well as in a study where patients were randomized to 3 mo of CRT-on or CRT-off therapy (2, 21). Similar findings have been observed in several conditions where lower MSNA did not translate into reduced plasma norepinephrine concentrations (21, 35). This could be explained by the limited reproducibility of plasma norepinephrine measurement (18) as well as by modifications in norepinephrine clearance in CHF patients (10). MSNA recordings provided more relevant insights into sympathetic regulation during sudden modifications in CRT pacing than plasma norepinephrine in our study. Norepinephrine is, however, an important prognostic factor inversely correlated with survival in CHF (9). The positive correlation between MSNA and norepinephrine underscores the clinical and prognostic relevance of our sympathetic nerve traffic recordings after CRT.

Limitations of the study. Our study has several limitations. First, the study was cross-sectional and included no pre-CRT baseline measurements. Second, previous studies on MSNA and CRT therapy included between 11 and 15 patients. Although a larger number of patients participated in our study, only a small group of seven patients were nonresponders. Third, although severe heart failure was likely the main mechanism for altered autonomic control in our study, we cannot exclude a limited contribution of aging on our findings in the nonresponders. Fourth, we cannot exclude the possibility that the positive correlation between MSNA and norepinephrine is due to a selection bias. Responders and nonresponders did not differ in several parameters known to affect MSNA, such as body mass index (29), sex (30), and medical therapy (11). Moreover, only patients who were not pacemaker dependent were switched to an OFF mode. This allowed us to rule out a contribution of pacemaker dependency on our findings when patients were in the OFF mode. Finally, the sequence of the pacing modes was randomized and recordings were analyzed in a blinded fashion.

In conclusion, our study provides direct evidence that reversible sympathoinhibition is a marker of the clinical response to CRT.
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