Biventricular pacing in chronic heart failure acutely facilitates the arterial baroreflex

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Submitted 18 February 2008; accepted in final form 6 June 2008

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CHRONIC HEART FAILURE (CHF) is characterized by permanent neurohumoral activation, i.e., elevated sympathetic tone, depressed parasympathetic tone, and activation of the renin-angiotensin-aldosteron system. This neurohumoral activation is accompanied by an increased peripheral chemoreflex and a decreased arterial baroreflex. Baroreflex sensitivity (BRS) has independent prognostic value in CHF (20).

Several mechanisms play a role in the blunting of the arterial baroreflex in CHF, e.g., an increased sympathetic outflow, an increase in circulating and central angiotensin II, an increased chemoreflex, and an increased cardiac sympathetic afferent reflex (CSAR) (13, 19). CSAR, a reflex that is not excited in the normal heart at rest, is activated by mechanical stretch and by metabolites like potassium, hydrogen ion, adenosine, bradykinin, and prostaglandins, which are elevated during myocardial ischemia and with cardiac stretch (25, 34). In CHF, CSAR is not only enhanced because of an increase in discharge intensity at the receptor level, but also because of an increase in central reflex gain (18, 38).

Cardiac resynchronization therapy (CRT), a relatively new therapy in CHF, is known to acutely decrease left ventricular (LV) dyssynchrony, to lower LV filling pressure, and to increase myocardial efficiency (32, 37). Besides these acute effects on cardiac functioning, CRT also induces acute effects in autonomic functioning. Najem et al. (21) showed that muscle sympathetic nerve activity (MSNA) acutely increased in responders of CRT when biventricular pacing was switched off. A plausible and clinically relevant explanation for this observation would be that CRT reduces metabolic and mechanical stress in affected ventricular muscle, thus reversing CSAR activation and sympathetic outflow. However, direct proof of this CRT working mechanism is difficult to obtain, as CSAR afferent activity cannot be measured in humans. Since CSAR afferent firing is known to decrease arterial BRS (13, 38), CRT-induced CSAR deactivation should be accompanied by a BRS increase. Therefore, we hypothesized that biventricular pacing acutely facilitates the arterial baroreflex.

Although a CRT-induced BRS increase is not sufficient to prove that CRT deactivates CSAR, it is a necessary condition. Hence, in addition to a possible improved prognosis, the significance of finding a CRT-induced BRS increase is that it comparts suggestive evidence for CSAR deactivation as one possible working mechanism of CRT, underlining the need for further experimental verification.

METHODS

Patients. The protocol was approved by the local Medical Ethics Committee. Thirty-two consecutive CHF patients eligible for CRT implantation were included in this study. Patients with atrial fibrillation, atrioventricular conduction defects, or frequent supraventricular or ventricular ectopy were not included, as noninvasive BRS measurement requires sinus rhythm.

Protocol. Baseline echocardiography was performed on the day of implantation preceding the implantation procedure. One day after implantation of a CRT device, echocardiography was repeated, and a BRS and HRV evaluation was performed. BRS and HRV were measured in each patient in two conditions: CRT device switched on and switched off (on/off order randomized). After the first BRS and HRV evaluation, CRT modality was changed conform the randomization protocol. After this change in CRT modality, 10 min of rest followed before the second BRS and HRV evaluation.

Instrumentation. During baroreflex and HRV evaluation the patients, were in the supine position. To prevent respiratory discomfort,

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the upper part of the bed was inclined in accordance with the individual’s sleeping habits. The finger cuff of a continuous noninvasive arterial blood pressure measurement device (Finometer; Finapres Medical Systems, Amsterdam, The Netherlands) was attached around the second phalanx of the left middle finger. The arm cuff of an automatic sphygmomanometer (Accutorr 3, Datascpe, Montvale, NJ) was attached around the right upper arm. A standard 12-lead ECG was derived. Two electrodes were applied to the lateral sides of the lower part of the thorax to monitor respiration (impedance method). Blood pressure, respiration, and ECG were recorded with an ST Surveyor monitoring system [Mortara Rangoni Europe, Casalecchio di Reno (BO), Italy] with a 500-Hz sampling rate.

**Measures.** First, blood pressure and heart rate (Accutorr, average of 5 subsequent readings) were measured after a 15-min resting period. These measurements were used to establish a reliable systolic blood pressure (SBP) measurement with the noninvasive arterial blood pressure measurement device. Then, after the patient had been lying for 30 min, the ECG, the noninvasive continuous arterial blood pressure signal, and the respiration signal were recorded for 10 min for later BRS and HRV calculation. During this period, patients performed 0.25-Hz metronome respiration [preventing the direct mechanical component of respiration and the respiratory gating effect to enter the low-frequency band (0.04–0.15 Hz), in which we compute BRS; Ref. 12]. After switching the CRT device on or off and an additional 10 min of rest, this measurement was repeated.

**BRS and HRV calculation.** To characterize arterial baroreflex function, we computed BRS, the reflex-induced increase/decrease of the interval between heart beats, in milliseconds per unit rise/fall of SBP. First, the arrhythmia-free and stationary periods longer than 60 s in the metronome respiration episode were selected (stationary sinus rhythm and blood pressure are prerequisites for a reliable BRS value). Compliance to the metronome respiration protocol was visually verified in the respiration signal. Then, BRS was computed in each of the selected episodes. The BRS algorithm computes the magnitude of the transfer function between the SBP variability (baroreflex input) and the interbeat interval (IBI) variability (output), averaged over the 0.04–0.15-Hz band. Additionally, it calculates 95% two-sided BRS confidence intervals (33). Finally, the overall BRS was composed from all data segments by the best linear unbiased estimator (BLUE) method (36). Mean SBP and mean IBI were computed from all data segments by the best linear unbiased estimator (BLUE).

**LV dyssynchrony.** LV dyssynchrony was assessed by tissue Doppler imaging on the apical 2- and 4-chamber view and calculated as the maximum time delay between the peak systolic velocities of 4 opposing basal walls (3).

The sample volume was placed between the tips of the mitral leaflets to assess Doppler pulsed-wave mitral inflow. The mitral inflow peak early velocity (E) to mitral annular peak early velocity (E') (E/E' ratio) was assessed by dividing E by E' at the basal septal segment (22).

**Statistics.** Results are presented as means ± SD. A paired Student’s t-test was used to evaluate the changes in BRS, HRV, LV dyssynchrony, LVEF, LVEDV, LVESV, E/E' ratio, SBP, and IBI between the different CRT modes. Linear regression analyses was performed to evaluate the relationship between CRT-associated LVEF change and BRS change.

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**RESULTS**

**Study group.** Baseline characteristics of the study group are listed in Table 1. A total of 32 patients were included. All CRT devices were successfully implanted [Contak Renewal (n = 16), Guidant; InSync Sentry (n = 14), Medtronic; Concerto (n = 1), Medtronic; Lumax (n = 1), Biotronik]. The atrioventricular delay (AV-delay) was optimized by two-dimensional echocardiography so that it provided the longest filling time for completion of the end-diastolic filling flow before LV contraction; AV-delay was set at 120 ± 10 ms. No adjustments were made to the interventricular pacing delay (V-V interval, set at 0 ms).

**BRS, HRV, SBP, and IBI.** BRS was significantly larger with biventricular pacing than without: 3.79 ± 4.04 ms/mmHg and 2.96 ± 3.19 ms/mmHg, respectively (average individual change 35%; P < 0.05). SDNN was also larger with biventricular pacing than without: 24.0 ± 14.3 ms and 18.5 ± 9.5 ms, respectively (average individual change 32%; P < 0.05). SBP and IBI did not change significantly (Table 2).

**Correlations between changes in BRS and in LVEF.** The relative change in BRS correlated with the relative change in LVEF (r = 0.44; P < 0.01; Fig. 1).

**Ischemic vs. nonischemic etiology.** There were 15 patients with nonischemic etiology and 17 patients with ischemic etiology. In both groups, BRS tended to be larger with biventricular pacing than without: in the nonischemic group, BRS increased by 37% from 3.15 ± 4.5 ms/mmHg to 4.10 ± 5.5 ms/mmHg (P = 0.08), and, in the ischemic group, BRS increased by 33% from 2.79 ± 1.4 ms/mmHg to 3.51 ± 2.37.1 ms/mmHg (P = 0.10). No significant difference in increase in BRS was found between the two groups (P = 0.85).

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**Table 1.** Patient characteristics before pacemaker implantation

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<table>
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<tr>
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<tbody>
<tr>
<td><strong>Sex</strong></td>
<td>26 males, 6 females</td>
<td></td>
</tr>
<tr>
<td><strong>Age (yr)</strong></td>
<td>66±9</td>
<td></td>
</tr>
<tr>
<td><strong>NYHA class I/II/III/IV</strong></td>
<td>2/13/15/2</td>
<td></td>
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<tr>
<td><strong>Etiology</strong></td>
<td></td>
<td></td>
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<tr>
<td>Ischemic</td>
<td>17 (47%)</td>
<td></td>
</tr>
<tr>
<td>Nonischemic</td>
<td>15 (53%)</td>
<td></td>
</tr>
<tr>
<td><strong>QRS duration (ms)</strong></td>
<td>154±30</td>
<td></td>
</tr>
<tr>
<td><strong>LVEF (%)</strong></td>
<td>27±6</td>
<td></td>
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<tr>
<td><strong>LVEDV (ml)</strong></td>
<td>227±79</td>
<td></td>
</tr>
<tr>
<td><strong>LVESV (ml)</strong></td>
<td>168±63</td>
<td></td>
</tr>
<tr>
<td><strong>LV dyssynchrony (ms)</strong></td>
<td>62±43</td>
<td></td>
</tr>
<tr>
<td><strong>Medication</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACE inhibitor/All blocker</td>
<td>30 (94%)</td>
<td></td>
</tr>
<tr>
<td>Diuretic</td>
<td>22 (69%)</td>
<td></td>
</tr>
<tr>
<td>Spironolactone</td>
<td>17 (53%)</td>
<td></td>
</tr>
<tr>
<td>β-Blocker</td>
<td>27 (84%)</td>
<td></td>
</tr>
<tr>
<td>Amiodarone</td>
<td>6 (19%)</td>
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</tbody>
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NYHA, New York Heart Association; LVEF, left ventricular (LV) ejection fraction; LVEDV, LV end-diastolic volume; LVESV, LV end-systolic volume; ACE, angiotensin-converting enzyme; All, angiotensin II.
receives projections of cardiac vagal afferents (5). In heart failure, decreased sympathetic outflow, which was found to decrease BRS (10). However, Eckberg (10) showed that variations of dP/dt max within 550–3,300 mmHg/s did not influence BRS. As CHF patients have dP/dt max values within this range (31), it is unlikely that the CRT-induced increase in dP/dt max will have influenced BRS.

Changes in SBP might also explain BRS improvement due to biventricular pacing since a change in SBP influences the logistic curve of the BRS (15). Blanc et al. (6) showed with an invasive arterial blood pressure measurement at the level of the heart that CRT may acutely increase blood pressure. We, however, did not find such an increase in SBP with CRT. This discrepancy might be caused by the different SBP measurement methods, since we did not measure SBP invasively but rather using a noninvasive device that measures arterial blood pressure more distally (at the finger). Whatever the cause of the difference in the observations by Blanc et al. (6) or the current study, our data do not support a possible influence of SBP on the logistic function curve of the BRS (15). This leaves us with the plausible explanation of the observed CRT-induced BRS increase, i.e., facilitation of the baroreflex due to CRT-induced

caused by continuous stretching of the receptors due to a sustained increase in left ventricular end-diastolic pressure (LVEDP) (7). Like others (37), we found that CRT acutely decreased LVEDP (expressed as E/E’ ratio; see Table 2). Hence, in addition to reducing CSAR afferent firing, CRT may positively influence vagal afferent mechanoreceptor functioning by decreasing LVEDP. It is known that, at the NTS, cardiac vagal afferents interact occlusively with cardiac sympathetic afferents (34). Hence, a weakened input at the NTS due to the CRT-mediated decrease in sympathetic afferent firing may have been further weakened by simultaneously occurring increased vagal afferent firing. It is difficult to draw conclusions about the likeliness of such an extra contribution to a BRS increase by CRT-induced changes in vagal afferent activity. Paradoxically, in healthy animals, stimulation of cardiac vagal mechanoreceptors results in an attenuated BRS (40), and no research has been conducted to establish the effect of CSAR afferent stimulation on BRS in CHF.

CRT also acutely increases the maximal rate of LV pressure change (dP/dt max) (2). An increase in dP/dt max may cause more intense firing of the arterial baroreceptors, which could increase BRS (10). However, Eckberg (10) showed that variations of dP/dt max within 550–3,300 mmHg/s did not influence BRS. As CHF patients have dP/dt max values within this range (31), it is unlikely that the CRT-induced increase in dP/dt max will have influenced BRS.

Our data demonstrate that CRT acutely increases BRS and HRV irrespective of etiology: the relative change in BRS correlates with the change in LVEF.

LV dyssynchrony is associated with a decline in systolic performance, an increase in end-systolic volume and wall stress, a delayed relaxation, and a decline in myocardial efficiency (14, 26). LV dyssynchrony is probably one of the factors causing CSAR activation, as CSAR is activated under influence of metabolic and mechanical stress in the failing heart (38). Optimization of the mechanical activation pattern of the left ventricle is the primary working mechanism of CRT (17). CRT induces early excitation of the region, which is otherwise late activated due to delayed intrinsic conduction. In concordance with other studies (8), we found that CRT acutely decreased LV dyssynchrony as well LV filling pressures, expressed as E/E’ ratio (Table 2). Previous studies have also shown that CRT acutely lowers LV filling pressures (37) and enhances myocardial efficiency (32). Moreover, Nelson et al. (23) found that CRT enhanced systolic function with modestly diminished energy cost, which is probably explained by lowering of lateral wall stress. Hence, resynchronization might well reduce CSAR activation.

A schematic representation of the CSAR pathway is outlined in Fig. 2. CSAR afferents project on the rostroventral lateral medulla (RVLM) and on the nucleus tractus solitarii (NTS). CSAR afferents activate sympathetic afferents at the level of the RVLM. At the level of the NTS, CSAR afferents activate interneurons (28, 39). These interneurons release the neuromodulator GABA that inhibits the barosensitive NTS neurons (39). Thus a decrease in CSAR afferent firing will lead to a stronger baroreflex. Several studies in normal animals and in animals with heart failure have shown that electrical or mechanical stimulation of CSAR decreases BRS (13, 38). We found that BRS was larger with the CRT device switched on. Logically, the CRT-induced increase in BRS as well as less excitation of the sympathetic efferents in the RVLM will contribute to a decreased sympathetic outflow, which was found by Najem et al. (21), who showed that stopping of CRT instantly increased MSNA.

Other factors than a decrease in CSAR afferent firing might also explain the improvement of BRS with biventricular pacing. In addition to cardiac sympathetic afferents, the NTS also receives projections of cardiac vagal afferents (5). In heart failure, vagal mechanoreceptors are desensitized, possibly

Table 2. Outcome variables with and without biventricular pacing

<table>
<thead>
<tr>
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<th>CRT Device Off</th>
<th>CRT Device On</th>
<th>P</th>
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<tr>
<td>BRS (ms/mmHg)</td>
<td>2.96 ± 3.19</td>
<td>3.79 ± 4.04</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td>SDNN (ms)</td>
<td>18.5 ± 9.5</td>
<td>24.0 ± 14.3</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>109.6 ± 19.2</td>
<td>110.5 ± 19.1</td>
<td>0.54</td>
</tr>
<tr>
<td>IBI (ms)</td>
<td>857 ± 165</td>
<td>864 ± 164</td>
<td>0.11</td>
</tr>
<tr>
<td>LV dyssynchrony (ms)</td>
<td>62 ± 43</td>
<td>35 ± 38</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>27 ± 6</td>
<td>32 ± 7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LVEDV (ml)</td>
<td>227 ± 79</td>
<td>216 ± 77</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LVESV (ml)</td>
<td>168 ± 63</td>
<td>150 ± 63</td>
<td>&lt;0.001</td>
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CRT, cardiac resynchronization therapy; BRS, baroreflex sensitivity; SDNN, SD of the intervals between normal heart beats; SBP, systolic blood pressure; IBI, interbeat interval.

DISCUSSION

Our data demonstrate that CRT acutely increases BRS and HRV irrespective of etiology: the relative change in BRS correlates with the change in LVEF.

Fig. 1. Correlation between % change in baroreflex sensitivity (BRS) and left ventricular ejection fraction (LVEF) [cardiac resynchronization therapy (CRT) switched off vs. CRT switched on].
CSAR deactivation. However, as recording of CSAR afferent activity is currently not possible in humans in vivo, new animal studies are needed to determine whether the CRT-induced BRS increase is indeed caused by CSAR deactivation.

Seminal to our study was the publication by Sarzi et al. (29), who described in a case report that BRS normalized after 3 mo of CRT. This finding is of high importance, and therefore we tested this hypothesis on group level. Obviously, this case report could also not separate between the direct and indirect effect of CRT, i.e., the direct effect of CRT in terms of a pacing-related reduction in CSAR afferent nerve traffic, as described above, or the indirect effect of a BRS increase that might be due to on the long term remodeling and associated increase in $\Delta p/\Delta t_{\text{max}}$ (31) and to the training effect of enhanced physical activity (27) that is to be expected in a patient in whom cardiac function is improved. In our current study, we noted that CRT acutely increased BRS; this proves the existence of a direct effect of CRT 1 day after implantation. It is, however, not known whether this acute increase in BRS will be followed by a further gradual increase over time and what could be the possible mechanism underlying such a further gradual increase. These issues demand clarification as lowered BRS in CHF parallels deterioration of clinical and hemodynamic status and is significantly associated with poor survival (20).

Also, HRV has a strong prognostic value in CHF (24). We used SDNN as a measure of HRV because SDNN is one of the most commonly computed HRV parameters. Furthermore, SDNN has the advantage that it is not sensitive to algorithmic variants as seen in spectral HRV analysis (33a), and it can also be determined in short recordings like the standard diagnostic 12-lead ECG (9). Several studies have already shown that CRT increases HRV (1, 11), but, to our knowledge, this is the first study to show that HRV increases acutely after initiation of biventricular pacing. The average individual increase in HRV (35%) was in line with the increase in BRS (32%). This is according to expectation: an increase in BRS will result in an increase in HRV because a greater part of HRV is caused by baroreflex-mediated vagal and sympathetic transmission of blood pressure variability to the sinus node (35).

When placed in a wider time perspective, the on-off experiments in our study could have been done earlier (immediately after CRT implantation) or later (e.g., 3 or 6 mo after CRT implantation). The earlier these measurements, the purer the on-off BRS difference reflects the acute effect of CRT institution. When measured later, the on-off BRS difference gives an impression of the acute effect of CRT withdrawal rather than of CRT institution, as therapeutic effects like inverse remodeling might have occurred. Therefore, we have chosen the earliest evaluation moment possible; earlier than 1 day after implantation would have confounded the measurements with the implantation procedure-related effects of stress and anesthetics on BRS.

Our protocol was designed to study differences in BRS and thereby to probe the mechanism by which CRT might exert its beneficial influence. We interpret an acute BRS increase with CRT as suggestive evidence for inactivation of CSAR by CRT. Basically, the magnitude of the BRS response is less important here as long as the BRS increase with CRT remains demonstrable. Theoretically, we could have measured a larger contrast between the CRT-on and CRT-off BRS if we had chosen longer periods during which CRT was on or off. In the current

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**Fig. 2.** Neural pathways involved in sympathoexcitation and baroreflex inhibition by cardiac sympathetic afferents. A: thoracic spinal and caudal and rostral medullar sections. B: nucleus tractus solitarii (NTS) details (based on Ref. 28). ALS, anterolateral (spinohalamic) system; CVLM, caudal ventrolateral medulla; Glu, excitatory neurotransmitter L-glutamate; NA, nucleus ambiguus; NG, nodose ganglion; NRM, nucleus raphe magnus; PAG, periaqueductal gray; PG, petrosal ganglion; RVLM, rostral ventrolateral medulla; SP, excitatory neuromodulator substance P; IX, 9th cranial (glossopharyngeal) nerve; X, 10th cranial (vagus) nerve. Dark gray spots: involved areas. Inhibiting neurons at the level of the brainstem: gray, dashed; sympathetic efferents: gray, continuous; parasympathetic efferents: gray, dotted.
protocol, this period was 10 min. By inclusion of a BRS measurement before implantation of the CRT device, we could have verified whether BRS, after switching of the pacemaker, returned to preimplantation values. This and related questions address another interesting research topic, namely what influence CRT has on BRS in terms of a prognostic factor (16) and whether the acute effect, as we measured it, has predictive value for the long-term effect. This issue was not addressed by our protocol, however.

BRS changes correlated significantly, but weakly ($r = 0.44$), with the changes in LVEF, which we used as a measure of acute mechanical response to CRT. As the acute change in BRS correlated with acute mechanical response to CRT, we would also expect a correlation between acute BRS and late mechanical response. Long-term follow-up studies are needed to verify whether acute BRS increase facilitated by CRT predicts clinical outcome.

CRT acutely facilitates the baroreflex. Further studies should verify whether this positive effect is caused by CRT-induced CSAR deactivation. Also, the predictive value of an acute CRT-induced BRS increase for a further BRS increase with time (29) and for a positive clinical response to CRT should be investigated.

ACKNOWLEDGMENTS

We thank Mortara Rangoni Europe for providing us with the ST Surveyor monitoring system used for recording of ECG, blood pressure, and respiration.

GRANTS

Financial support by the Netherlands Heart Foundation (Grant 2003B094) is gratefully acknowledged.

DISCLOSURES

M. J. Schalij and J. J. Bax receive research grants from Boston Scientific, Medtronic, St. Jude, GE Healthcare and BMS medical imaging. There exist no conflicts of interest for the other authors.

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