Sustained Sympathoinhibitory Effects of Cardiac Resynchronization Therapy in Severe Heart Failure

Guido Grassi, Antonio Vincenti, Roberta Brambilla, Fosca Quarti Trevano, Raffaella Dell’Oro, Antonio Cirò, Giuseppe Trocino, Antonella Vincenzi, Giuseppe Mancia

Abstract—Evidence is available that in heart failure, cardiac resynchronization therapy by biventricular pacing improves myocardial function and exercise capacity. Whether this is accompanied by a sustained inhibition of heart failure–dependent sympathoexcitation is uncertain. In 11 heart failure patients (mean±SEM age, 68.4±1.5 years) in New York Heart Association (NYHA) class III and IV under medical treatment with an intraventricular conduction delay (QRS duration ≥130 ms), with a markedly depressed left ventricular ejection fraction, and undergoing implantation of a biventricular pacemaker, we measured beat-to-beat blood pressure and muscle sympathetic nerve traffic. Measurements, which also included echocardiographic and clinical variables, were performed before and ∼10 weeks after successful resynchronization therapy. Ten age- and NYHA class–matched heart failure patients who were under medical treatment for the same time period served as controls. Long-term resynchronization therapy improved cardiac function and caused a significant increase in systolic blood pressure coupled with an improvement in maximal oxygen consumption and exercise capacity. These effects were coupled with a significant and marked reduction in sympathetic nerve traffic when expressed both as burst frequency over time (44.1±3.6 vs 30.7±3.0 bs/min, −30.5%, P<0.02) and as burst frequency corrected for heart rate (68.3±5.9 vs 47.3±4.3 bs/100 beats, −32.1%, P<0.02). No significant change in the aforementioned parameters was seen in the control group. These data provide the first direct evidence that in severe heart failure, resynchronization therapy exerts a marked and sustained sympathoinhibition. Because in heart failure sympathetic overactivity adversely affects prognosis, this may have important clinical implications. (Hypertension. 2004;44:727-731.)

Key Words: electrical stimulation ▪ heart failure ▪ sympathetic nervous system ▪ autonomic nervous system

Cardiac resynchronization therapy (CRT) by biventricular pacing exerts favorable effects in patients with congestive heart failure (CHF) and intraventricular conduction delay in whom it improves symptoms, functional class, and quality of life with an increase in exercise tolerance.1–3 Whether the favorable effects include a reduction in the enhanced sympathetic cardiovascular drive characterizing CHF4–6 is uncertain, however, because the studies that have addressed this issue so far had either methodological or design limitations. That is, they assessed adrenergic function only indirectly by plasma norepinephrine assay3,7 or used direct measurement of muscle sympathetic nerve activity (MSNA) that was confined, however, to the acute phase of biventricular pacing.8,9

The present study was designed to determine the long-term sympathetic effects of CRT in CHF patients with an intraventricular conduction delay by using a design similar to the 1 used in the MIRACLE trial, which had shown CRT to be accompanied by a sustained improvement in patient clinical status.3 Sympathetic activity was quantified both indirectly by measurement of plasma norepinephrine levels and directly by microneurographic recording of MSNA. We thought this information to be of clinical relevance because the prognosis in CHF is linked to the level of activation of the sympathetic nervous system.6,10,11

Methods

Population

The study population consisted of 21 male patients with stable CHF in New York Heart Association (NYHA) class III or IV because of ischemic or idiopathic cardiomyopathy. Eleven patients (mean±SEM age, 68.4±1.5 years; range, 58 to 74 years) had an intraventricular conduction delay (QRS complex duration ≥130 ms; range, 150 to 220 ms) and underwent an electrophysiological study and implantation of a device for biventricular pacing without (Medtronic InSync model 8040 [n=2], Medtronic InSync III Model 8042 [n=3], InSync ICD 7272 [n=2], InSync III Marquis 7279 [n=3], InSync III Marquis 7277 [n=1])...
defibrillator capabilities. The remaining 10 patients (mean±SEM age, 68.2±1.7 years; range, 56 to 75 years) had no significant intraventricular conduction delays (QRS complex duration <130 ms) and thus did not undergo implantation of the biventricular pacemaker; these patients served as controls. All patients were in sinus rhythm and under optimized pharmacological treatment with diuretics, angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers and β-blockers, according to current therapeutic guidelines. The drug treatment schedule and daily dosage were left unchanged throughout the study period. All subjects gave their written consent to the study after being informed of its nature and purpose. The study protocol was approved by the Ethics Committee of our institution.

Measurements
Measurements consisted of an ECG, the NYHA functional classification, Minnesota Living Heart Failure questionnaire, the distance expressed in meters walked by the patients during a 6-minute corridor test, peak maximal oxygen consumption during a cardiopulmonary exercise test, and left ventricular end-diastolic diameter, end-systolic diameter, and calculated ejection fraction by M-mode and B-mode echocardiography. Echocardiographic data were collected by a single operator. The within-operator coefficients of variation (ie, the assessment of within-operator reproducibility of the measurements) of left ventricular diameter data were 5.9%. Blood pressure (BP) was measured by (1) a mercury sphygmomanometer, taking the first and fifth Korotkoff sounds to identify systolic and diastolic values, respectively, and (2) a finger photoplethysmographic device (Finapres 2300, Ohmeda) capable of providing accurate and reproducible beat-to-beat systolic and diastolic values.Heart rate (HR) was monitored continuously by a cardiometer triggered by the R wave of an ECG lead. Respiration rate was monitored by a strain-gauge pneumograph positioned at mid-chest level. Multiunit recording of efferent postganglionic MSNA was obtained from a microelectrode inserted in the right or left peroneal nerve posterior to the fibular head, as previously described. Blood pressure was amplified (70/2000), fed through a bandpass filter (700 to 2000 Hz), and integrated with a custom nerve traffic analysis system (Bioengineering Department, University of Iowa, Iowa City). Integrated nerve activity was monitored by a loudspeaker, displayed on a storage oscilloscope (model 511A, Tektronix), and recorded with BP, HR, and respiratory movements on an ink polygraph. The muscle nature of MSNA was assessed according to published criteria, and the recording was accepted only if the signal-to-noise ratio was >3. MSNA was quantified as bursts per minute and bursts per 100 heart beats. Plasma norepinephrine was measured by high-performance liquid chromatography on blood withdrawn from an antecubital vein of the arm opposite the one used for BP measurements.

Protocol and Data Analysis
Patients underwent a 3-day screening period during which the ECG, the 6-minute corridor walking test, cardiopulmonary exercise test, and echocardiogram were obtained. The patients were then taken to the laboratory in the morning after an overnight fast, placed supine, and fitted with the intraventricular cannula, the microelectrodes for MSNA recording, and the other measuring devices. A venous blood sample for assessment of plasma norepinephrine was withdrawn, and BP was measured 3 times with a mercury sphygmomanometer. After a 30-minute interval, BP, HR, respiration rate, and MSNA were continuously measured over a 30-minute period. Patients were thereafter discharged from the laboratory and assigned, according to the presence or absence of the intraventricular conduction delay (see above), to either CRT or observation without intervention. The CRT implantation was done after 2.3±0.2 days (range, 1 to 3) from the end of the previously mentioned examinations. All measurements were repeated according to the same sequence after an interval of 10.2±0.3 weeks (range, 7.2 to 12.5). The CRT device was programmed in the biventricular atrial-triggered pacing mode, with a lower and an upper tracking rate amounting, respectively, to 50 and 130 bpm. The atrial-ventricular interval value was chosen on the basis of the best mitral Doppler spectrum in terms of timing and amplitude of the E and A wave. In the CRT group, the second experimental session was performed in the spontaneous atrial-sensed sinus rhythm with the device left in the biventricular atrial-triggered pacing mode. No exercise training program was performed in the 2 groups of patients during the 2-month period of the study or in the 2 months preceding it.

Data were collected and analyzed by investigators unaware of the experimental design. Values from individual subjects were averaged for each group and each experimental session and expressed as mean±SEM. The significance of differences between the 2 sessions was assessed by 2-way ANOVA. Spearman analysis was used to determine the correlation between different variables. A value of P<0.05 was considered statistically significant.

Results
As shown in the Table and in the Figure, the 2 groups of patients showed a similar average NYHA functional class as well as a similar marked abnormality in the maximal oxygen consumption during the cardiopulmonary exercise test, the score of the Minnesota questionnaire, the walking test, and left ventricular end-diastolic diameter and ejection fraction. BP, HR, and respiration rate were similar in the 2 groups, which also showed similar elevations in plasma norepinephrine and number of sympathetic neural bursts. In the group maintained on pharmacological therapy, no value showed a significant change. In contrast, in the group that had undergone CRT, there was, together with the expected reduction in the QRS duration, a significant increase in systolic but not in diastolic BP and a marked and significant improvement in left ventricular ejection fraction, NYHA functional class, and score of the Minnesota questionnaire. This was accompanied by no significant change in plasma norepinephrine but by a reduction in MSNA, which was significant and marked when expressed both as the number of bursts over time (−30.5%, P<0.02) and as burst number corrected for heart rate (−32.1%, P<0.02). There was no relation between (1) the initial QRS width and MSNA (r=0.29, P=NS), (2) the initial QRS width and the MSNA changes induced by CRT (r=0.41, P=NS), and (3) the changes in QRS width and MSNA induced by CRT (r=0.03, P=NS). No relation was also found between the change in MSNA and the change in left ventricular ejection fraction and systolic or diastolic BP induced by CRT (r=0.32, r=0.27, and r=0.18, respectively; P=NS for all).

Discussion
In our patients with severe CHF, maintenance of a drug treatment (diuretic, an angiotensin-converting enzyme inhibitor [or an angiotensin II receptor blocker], and a β-blocker) for 2 months did not affect MSNA values. This was not the case, however, in severe CHF patients in whom maintenance of the aforementioned treatment for 2 months was complemented by CRT with biventricular pacing. In this group, MSNA showed a reduction in most patients (9 of 11) and a significant and marked fall in the group as a whole. This expands previous data obtained by assessing the acute sympathetic effect of biventricular pacing on 2
Clinical, Hemodynamic, ECG, and Echocardiographic Variables in the Groups of Patients Undergoing and Not Undergoing CRT

<table>
<thead>
<tr>
<th>Variable</th>
<th>CRT (n=11)</th>
<th>No CRT (n=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variable</td>
<td>Control 2 Months</td>
<td>Control 2 Months</td>
</tr>
<tr>
<td>Sphygmo SBP/DBP, mm Hg</td>
<td>123.4±5.8/75.1±3.9</td>
<td>126.6±5.0/72.0±4.1</td>
</tr>
<tr>
<td>Finger SBP/DBP, mm Hg</td>
<td>120.8±5.3/71.6±3.3</td>
<td>123.3±4.4/68.8±2.9</td>
</tr>
<tr>
<td>HR, beats/min</td>
<td>66.5±4.1</td>
<td>68.4±3.1</td>
</tr>
<tr>
<td>Respiration rate, breaths/min</td>
<td>16.9±0.9</td>
<td>16.5±0.8</td>
</tr>
<tr>
<td>NYHA class</td>
<td>3.0±0.09</td>
<td>3.0±0.01</td>
</tr>
<tr>
<td>VO2 max, mL/kg per min</td>
<td>12.4±0.6</td>
<td>12.5±0.8</td>
</tr>
<tr>
<td>Minnesota test, AU</td>
<td>37.9±4.0</td>
<td>39.0±4.1</td>
</tr>
<tr>
<td>Six-minute walking test distance, m</td>
<td>392.1±26.0</td>
<td>414.2±30.0</td>
</tr>
<tr>
<td>QRS width, ms</td>
<td>174.5±7.5</td>
<td>105.2±3.2</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>22.5±1.6</td>
<td>26.8±1.2</td>
</tr>
<tr>
<td>LVEDD, mm</td>
<td>70.9±2.1</td>
<td>68.9±2.2</td>
</tr>
</tbody>
</table>

Data are shown as mean±SEM. Sphygmo indicates sphygmomanometer; SBP, systolic blood pressure; DBP, diastolic blood pressure; VO2 max, maximal oxygen consumption; LVEF, left ventricular ejection fraction; and LVEDD, left ventricular end diastolic diameter. All other abbreviations are as defined in text. Six-minute walking test refers to the distance (expressed in meters) walked by the patients during a 6-minute corridor test.

*P<0.05, †P<0.01, refer to the level of statistical significance between data recorded before (baseline) and after 2 months from CRT in each group.

Grassi et al Sympathoinhibition in Heart Failure 729

Finding that 3 months after implantation of a biventricular pacemaker HR variability showed a clear increase suggests that for the heart, this may be the case, although with the caveat that HR variability reflects not only sympathetic but also vagal cardiac drive. Third, our study was not designed to investigate the mechanisms responsible for the sympathoinhibitory effect of CRT. The results, however, allow several hypotheses to be advanced. The sympathoinhibition may, for example, originate from the activation of arterial baroreceptors brought about by systolic BP, which increased during CRT by ≈10 mm Hg. However, the MSNA and the BP changes showed no significant relation, which suggests that, although probably involved, the baroreflex does not play an exclusive role, and its function is markedly depressed in severe CHF. It may also originate from an increased activity of vagally innervated receptors anatomically located in the left ventricle that (1) exert a powerful reflex inhibition on sympathetic drive and (2) respond not only to an increase in left ventricular pressure but also to an increase in left ventricular contractility, which was most likely improved by CRT. This is not incompatible with the observation that in animals, left ventricular receptors cause bradycardia, which was not evident in our patients because (1) the bradycardic effect has been described mostly after massive receptor stimulation and (2) in humans, physiologic (and more modest) alterations in cardiopulmonary receptor drive do not cause substantial HR changes. The sympathoinhibition may also originate from removal of reflex sympathoexcitatory influences originating from receptors located in the cardiac and central vascular structure after improvement of the hemodynamic status by CRT. It cannot be excluded, however that, at least in part, the MSNA reduction seen after prolonged CRT also results from (1) resumption of physical activity (due to the improvement in clinical status), because physical training exerts sympathoinhibitory effects, and/or (2) a CRT-
Effects of CRT by biventricular pacing or observation without intervention (Control) on MSNA, expressed as burst frequency over time (upper panels) and as burst incidence corrected for HR (middle panels) and plasma norepinephrine (NE) values (lower panels). Individual and average data are shown. Asterisks (P<0.02) refer to the level of statistical significance between data obtained before and after CRT. B, Baseline; 2 months, after 2 months. All other abbreviations are as defined in text.

related improvement in central sleep apnea ad thus, in chemoreflex function.24

Perspectives

The results of the current study show that the marked sympathetic overactivity characterizing advanced heart failure states may be favorably affected in the long-term period by CRT. This procedure in our patients was also accompanied by an improvement in left ventricular ejection fraction, a decrease in NYHA functional class, and an increase in exercise tolerance. This is in line with the results of the MIRACLE trial,3 to which our study adds the information on sympathetic nerve function in congestive heart failure. This is in line with the results of the reduction in NYHA functional class, and an increase in sympathetic activation and loss of reflex sympathetic control in mild congestive heart failure. Circulation. 1995;92:1317–1321.


Sustained Sympathoinhibitory Effects of Cardiac Resynchronization Therapy in Severe Heart Failure

Guido Grassi, Antonio Vincenti, Roberta Brambilla, Fosca Quarti Trevano, Raffaella Dell'Oro, Antonio Cirò, Giuseppe Trocino, Antonella Vincenzi and Giuseppe Mancia

Hypertension. 2004;44:727-731; originally published online September 20, 2004; doi: 10.1161/01.HYP.0000144271.59333.a7

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2004 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://hyper.ahajournals.org/content/44/5/727

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Hypertension can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Hypertension is online at:
http://hyper.ahajournals.org/subscriptions/