Cardiac Sympathetic Reserve and Response to Cardiac Resynchronization Therapy

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Background—The objective of the present study was to investigate the effect of cardiac resynchronization therapy (CRT) on cardiac autonomic function.

Methods and Results—This prospective study included 45 consecutive patients with heart failure who received CRT devices with defibrillator and 20 age-matched, healthy control subjects. At baseline and 3 months and 6 months after CRT, we assessed New York Heart Association (NYHA) class, 6-minute walk distance, plasma sympathetic biomarker nerve growth factor, echocardiography, heart rate variability and cardiac presynaptic sympathetic function determined by iodine 123 metaiodobenzylguanidine scintigraphy. After CRT, NYHA class improved by 1 class (p<0.001), and left ventricular ejection fraction increased by 8% (p<0.001). Along with improvement in the standard deviation of all normal-to-normal R-R intervals (85.63±31.66 ms versus 114.79±38.99 ms; p=0.004) and the standard deviation of the averaged normal-to-normal R-R intervals (82.62±23.03 ms versus 100.50±34.87 ms; p=0.004), the delayed heart/mediastinum (H/M) ratio increased (1.82 [0.58] versus 1.97 [0.59]; p=0.03), whereas the mean (SD) H/M washout rate was reduced (48% [19%] versus 37% [22%]; p=0.01). Twenty-two of 45 study patients responded to CRT, with a reduction of left ventricular end-systolic volume index >15%. Compared with nonresponders, responders had a higher delayed H/M ratio (2.11 versus 1.48; p=0.003) and lower H/M washout rate (37% versus 62%; p=0.003) at baseline.

Conclusions—CRT improved sympathetic function. Cardiac sympathetic reserve may be a marker for the reversibility of failing myocardial function. (Circ Heart Fail. 2011;4:339-344.)

Key Words: cardiac resynchronization therapy ■ heart failure ■ nerve growth factor ■ sympathetic nerve ■ metaiodobenzylguanidine iodine 123

Cardiac resynchronization is an effective therapy in improving symptoms, quality of life, and survival in patients with advanced heart failure (HF) by correction of biventricular electric and mechanical dyssynchrony caused by severe dilated cardiomyopathy.1–6 HF is associated with an abnormally activated sympathetic nervous system, attenuated cardiovascular reflexes, and downregulation of adrenergic nerve terminals.7,8 The role of cardiac resynchronization therapy (CRT) in neurohormonal regulation of cardiac chronotropic and inotropic activity has not been well characterized. Nerve growth factor (NGF) is a neurotrophin with a pivotal role in the differentiation, maturation, and survival of sympathetic innervation.9 One study showed a marked reduction of circulating NGF levels and local cardiac NGF production that may be an adaptive response to sympathetic overactivity in HF.10 Recently, several radiolabeled compounds have been used for noninvasive imaging of cardiac neuronal function. The catecholamine analog iodine 123 metaiodobenzylguanidine (123I-MIBG) is the tracer most commonly used to map myocardial presynaptic sympathetic innervation and activity.11–13 In the present study, we aimed to examine the effect of CRT on neurohormonal integrity by studying plasma levels of NGF and cardiac presynaptic sympathetic function, as determined by nuclear cardiac im-

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aging modalities ($^{123}$I-MIBG scintigraphy), in patients with HF who received CRT.

Methods
The study was approved by the Mayo Institutional Review Board. Written informed consent was obtained from each study subject.

Study Patients
From January 1, 2005, through June 30, 2008, 45 consecutive patients with advanced HF at the Mayo Clinic (Rochester, MN) were enrolled in the study. All met clinical criteria for CRT (left ventricular ejection fraction [LVEF] $\leq 35\%$, New York Heart Association [NYHA] functional class III or IV, QRS duration $\geq 120$ ms). Patients also met criteria for an implantable cardioverter-defibrillator for primary or secondary sudden death prevention. All patients received a cardiac resynchronization therapy device with defibrillator (CRT-D). Twenty age-matched healthy volunteers without evidence of structural heart disease served as control subjects.

Clinical Evaluation Before CRT
Before device implantation, each enrolled subject underwent clinical evaluation to determine NYHA functional class and medication use; a 12-lead ECG evaluation was performed. Exercise capacity was assessed by a 6-minute walk. Cardiac structure and function were assessed using transthoracic echocardiography. Peripheral venous blood samples were collected to measure plasma NGF levels. Cardiac autonomic function was assessed using 24-hour ambulatory ECG monitoring. Presynaptic cardiac sympathetic activity was determined by $^{123}$I-MIBG scintigraphy (n=24). Normal control subjects underwent echocardiographic examination to exclude structural heart diseases. Details about echocardiography, 24-hour ambulatory ECG monitoring, plasma NGF level, and $^{123}$I-MIBG scintigraphy are described in the online-only Data Supplement.

CRT-D Implantation and Patient Follow-Up
Clinically available CRT-D devices and leads were used. The right ventricular lead was positioned in the right ventricular apex. The desired position for left ventricular (LV) lead placement was prioritized as follows: lateral/posterolateral, anterior lateral, antero-interventricular, or middle cardiac veins. The standard device settings included ativoventricular delay of 100 ms (sensed) and 130 ms (paced), with DDD or DDDR mode and standard lower and upper pacing rates ($50$ and $120$ to $130$ bpm, respectively).

All patients (and control subjects) returned for follow-up at 3 and 6 months after CRT implantation. Patients underwent NYHA class and 6-minute walk reassessment, repeated blood tests for plasma NGF levels, and underwent 24-hour ambulatory ECG monitoring and an echocardiography study at 3- and 6-month follow-up. The percentages of biventricular pacing, as well as appropriate or inappropriate antitachycardia pacing or defibrillation (or both) within 6 months after receiving the CRT-D. Table 2 shows the effects of CRT at the 3- and 6-month follow-ups. NYHA class, distance of 6-minute walk, and echocardiographic parameters were improved 3 months after CRT and sustained or further improved at 6 months. At the 6-month follow-up, NYHA class improved by approximately 1 class ($<0.001$). The mean improvement in LVEF was 8% ($<0.001$), and the LVESV index was reduced by 15% ($<0.001$). The heart rate variability after CRT, as determined by SDNN ($P=0.004$) and SDANN ($P=0.004$), was improved. The delayed H/M ratio was increased ($P=0.03$), whereas the H/M washout rate was reduced (improved, $P=0.01$) overall. Of 24 patients who had $^{123}$I-MIBG studies, $13$ (54%) showed improvement in delayed H/M ratio and/or H/M washout rate ($\geq 10\%$ change compared with baseline) 6 months after CRT.

Of our cohort, 35 patients had continued clinical follow-up after 6 months at our institution. The improvements in NYHA class (2.0 [2.0, 3.0] versus baseline 3.0 [3.0, 3.0], $P<0.001$) and LVEF (30.7±14.0% versus baseline, 25.8±5.3%, $P<0.001$) were sustained during a mean follow-up duration of 36±16 months.

CRT Response
Overall, 22 of 45 study patients had a reduction in LVESV index of at least 15%. Most patients with nonischemic
cardiomyopathy responded to CRT (65%), but the response rate was lower for patients with ischemic cardiomyopathy (32%; \( P=0.03 \)). Before CRT, responders had longer 6-minute walk distance (387 versus 320 m; \( P=0.003 \)) and greater interventricular conduction delay (47 ms versus 28 ms, \( P=0.005 \)) and intraventricular dyssynchrony (123 ms versus 87 ms; \( P=0.005 \), Figure 1A). Of 24 patients who had 123I-MIBG studies and LVESV index measures, responders had a higher baseline delayed H/M ratio (2.11 versus 1.48; \( P=0.003 \)) and lower H/M washout rate (37% versus 62%; \( P=0.003 \)), compared with nonresponders (Figure 1B). No differences were observed between responder and nonresponder groups for baseline NYHA class, LVEF, LVESV index, NGF level, or SDNN and SDANN values.

Several factors, determined at baseline, were significantly correlated with changes in the LVESV index after CRT; specifically, these included distance of the 6-minute walk \( (r=-0.36; \ P=0.02) \), interventricular conduction delay \( (r=-0.47; \ P=0.002) \), and intraventricular dyssynchrony averaged over 12 LV segments \( (r=-0.63; \ P<0.001) \). Of 24 patients who had 123I-MIBG studies, the changes in the LVESV index after CRT were significantly correlated with delayed H/M ratio \( (r=-0.42; \ P=0.048 \text{; Figure 2A}) \) and H/M washout rate \( (r=0.45; \ P=0.03 \text{; Figure 2B}) \). Decreased 123I-MIBG uptake and higher H/M washout rates at baseline were associated with a nonresponse after CRT. The other baseline variables were not correlated with improvement in LVESV index.
ratio changed from 1.49 to 1.57 \( P = 0.59 \) and H/M washout rate changed from 61\% to 56\% \( P = 0.54 \)).

**Response to CRT and Prognosis**

Two patients died during the 6-month follow-up period. An additional 11 events occurred more than 6 months after CRT, during a mean period of 36 months after CRT-D implantation. These events included 6 deaths, 2 heart transplantations, and 3 LV assist device implantations. Of the total 13 death, transplant, and LV assist device events, affected patients included 3 responders and 10 nonresponders \( P = 0.02 \).

**Discussion**

**Main Findings**

Our study found that CRT reverses cardiac autonomic remodeling by upregulating presynaptic receptor function, as evidenced by increased \(^{123}\text{I}-\text{MIBG} \) H/M ratio and attenuated H/M washout rate, with concomitantly improved heart rate variability. The baseline cardiac sympathetic reserve, assessed by \(^{123}\text{I}-\text{MIBG} \) scintigraphy, may be a potential marker of clinical response to CRT.

**Cardiac Autonomic Remodeling in HF**

HF is associated with abnormally activated sympathetic and altered parasympathetic tone, attenuated cardiovascular reflexes, and maladaptive downregulation of adrenergic nerve terminals.\(^7^,^8\) The attenuated heart rate variability, as observed in this study, conferred a dysregulation of heightened sympathetic tone and weakened parasympathetic outflow.\(^17^-^20\) However, the plasma NGF concentrations did not differ among patients with HF and control subjects. This result differed from findings previously reported by Kaye et al.\(^10\)

**Figure 1.** Differences between responders and nonresponders before CRT. **A**, Graphs show baseline values for LVEF, LVESV index, interventricular conduction delay, and intraventricular conduction delay (mean±SD). **B**, Graphs show baseline values for delayed H/M ratio and metaiodobenzylguanidine iodine 123 H/M washout rate (mean±SD).

**Figure 2.** Correlation between change in LVESV index after CRT and baseline values. **A**, Iodine 123 delayed H/M ratio. **B**, Metaiodobenzylguanidine H/M washout rate.
who described reduced plasma NGF concentration in patients with HF. In their study, patients had severe HF, with a mean LVEF of 17%. Our patients were receiving optimal medical therapy and had a comparatively higher average LVEF. The circulating NGF level may be modulated after HF treatment to mask the degree of sympathetic dysregulation.21

Cardiac adrenergic control is governed by sympathetic transmitter norepinephrine that is synthesized within neurons and released to the synaptic cleft. Most norepinephrine undergoes reuptake into presynaptic nerve terminals through the uptake-1 pathway; 123I-MIBG, the radiolabeled neurotransmitter analogs, have the specificity and affinity for the uptake-1 mechanism.2 In this study, we found a significantly lower baseline delayed H/M ratio and a higher baseline H/M washout rate in patients with HF than in control subjects, consistent with previous studies that showed downregulation of the uptake-1 carrier protein at the synaptic level.22–24

Rebalancing Cardiac Autonomic Function by CRT
Consistent with the CRT outcomes from multicenter randomized trials,1–3,25 our study findings also support the benefits of CRT with regard to improving NYHA functional class, the distance of the 6-minute walk, LV systolic function, and reversal of LV structural remodeling. These significant improvements in HF were revealed at 3 months and sustained at 6 months after CRT. These symptomatic and hemodynamic improvements continued to be seen at a mean follow-up duration of 3 years. We showed that at the sympathetic terminal level, CRT upregulates presynaptic 123I-MIBG uptake and retention, as evidenced by increased H/M ratio and reduced H/M washout rate and confirmed findings of previous reports (of small patient groups).18,26,27 Further, we showed that these effects were mainly observed in patients who responded to CRT by a reduction of LVESV index. In parallel, heart rate variability, as measured by SDNN and SDANN, was improved by CRT, indicating a favorable rebalance of cardiac sympathetic function and vagal cardiac reflex response. Our study results, therefore, uniquely suggest that CRT, as an additional and effective therapy for HF, improves cardiac sympathetic activity beyond that achieved by pharmacological therapy with β-blockers or renin-angiotensin-aldosterone axis inhibition.

Cardiac Sympathetic Reserve and CRT Response
Echocardiographically determined dyssynergic indices inconsistently identify those who would respond to CRT. Single-center studies have shown that traditional echocardiographic techniques, including tissue Doppler imaging, have the ability to distinguish CRT responders from nonresponders.16,28–30 However, the PROSPECT (Predictors of Response to CRT) multicenter trial showed that the ability of echocardiographic parameters to predict clinical composite score response varied widely.31 In our study, we found that CRT responders had longer 6-minute walk distance at baseline, representing their greater exercise tolerance. The physical functional status was related to the improvement in LV function, as observed from this study. The less-impaired presynaptic uptake function was associated with a greater LV reverse remodeling as judged by the 15% reduction in the LVESV index. Cardiac damage is followed by nerve sprouting, and nerve sprouts that successfully connect with viable myocardium will survive, whereas those located in irreversibly damaged areas such as within the future scars regress during the postinfarct period.31 We speculate that 123I-MIBG imaging detects not only sympathetic nerve activity but also indirectly suggest a successful connection of these nerves within viable myocardial tissue.

Limitations
The study sample size was less robust to evaluate the predictive value of measurements. A larger-scale 123I-MIBG imaging study will be beneficial to assess the predictive value of CRT response in clinical applications. Medications used by patients in the study may affect assessment of cardiac autonomic function. However, all patients were maintained on a stable dosage of medications during the study. β-Blocker use may affect interpretation of 123I-MIBG studies. However, withdrawal from β-blocker therapy is not ethical; hence, to minimize the effect of variations in medications, the same type of β-blocker and stable dosage were maintained carefully throughout the study. Using a single criterion of LVESV index change to assess CRT response may have the limitation to evaluate response to CRT; however, at the present time, a consensus on the criteria in assessing CRT response is lacking, based on a recent meta-analysis evaluating response to CRT by Fornwalt et al.25

Conclusion
To our knowledge, this is the first study to comprehensively investigate the impact of CRT on cardiac autonomic function, specifically, neuronal receptor function. Cardiac sympathetic reserve may be considered a characteristic of the candidate who potentially will benefit from CRT. For patients who may have insufficient myocardial adrenergic preservation, consideration of therapeutic options other than CRT may be reasonable. Larger studies are needed to confirm these findings.

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Disclosures
Dr Cha received a Medtronic Research Grant. Dr Hayes served on the Advisory Board for St Jude Medical, Boston Scientific, and Medtronic Inc; as speaker at educational venues: St Jude Medical, Boston Scientific, Sorin Medical, Biotronik, and Medtronic; and on the steering committee at St Jude Medical, Medtronic.

References
Heart failure is associated with disregulated autonomic function with abnormally activated sympathetic and altered parasympathetic tone. The present study reports a novel finding that cardiac resynchronization therapy (CRT) modulates sympathetic function, concomitant with its beneficial clinical outcome in patients with drug-refractory heart failure. Electrically and mechanically resynchronized biventricular contractility by CRT upregulates presynaptic receptor function, concomitant with its beneficial clinical outcome in patients with drug-refractory heart failure.

**CLINICAL PERSPECTIVE**

Heart failure is associated with disregulated autonomic function with abnormally activated sympathetic and altered parasympathetic tone. The present study reports a novel finding that cardiac resynchronization therapy (CRT) modulates sympathetic function, concomitant with its beneficial clinical outcome in patients with drug-refractory heart failure. Electrically and mechanically resynchronized biventricular contractility by CRT upregulates presynaptic receptor function, as evidenced by increased iodine 123 metaiodobenzylguanidine (123I-MIBG) heart/mediastinum ratio and attenuated cardiac nerve growth factor expression in human and experimental heart failure.

Cardiac resynchronization therapy (CRT) modulates sympathetic function, concomitant with its beneficial clinical outcome in patients with drug-refractory heart failure. Electrically and mechanically resynchronized biventricular contractility by CRT upregulates presynaptic receptor function, concomitant with its beneficial clinical outcome in patients with drug-refractory heart failure.
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Supplemental Material

Cardiac Sympathetic Reserve and Response to Cardiac Resynchronization Therapy

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Abbreviations

EDTA, ethylenediaminetetraacetic acid
LV, left ventricle, left ventricular
$^{123}$I-MIBG, iodine 123 metaiodobenzylguanidine
Online Supplement to the Methods

Echocardiography

Echocardiographic studies were performed and interpreted by a cardiologist who was masked to the patients’ clinical status. All echocardiographic parameters were measured in triplicate and averaged. Echocardiographic parameters included left ventricular (LV) ejection fraction (derived from 2-dimensional measurements of diastolic and systolic LV dimension or volumetric analysis using the method of disks), pulmonary artery systolic pressure (estimated from the tricuspid regurgitant velocity and an estimate of right atrial pressure), mitral regurgitation severity grade (0=none/trivial; 1=mild; 2=moderate; 3=severe), and LV end-diastolic volume and LV end-systolic volume (calculated by using the biplane method). Tissue Doppler and strain imaging were used to assess LV dyssynchrony. Intraventricular dyssynchrony was determined by the standard deviation of timing intervals from QRS onset to peak negative strain from 12 basal and mid LV segments. The interventricular mechanical delay was defined as the timing difference between pulmonary valve and aortic valve opening, as measured by pulsed-wave Doppler echocardiography.

24-Hour Ambulatory Electrocardiographic Monitoring

The stored data from 24-hour ambulatory electrocardiographic recordings (Del Mar Avionics, Irvine, California) were analyzed by an independent observer who was masked to the patients’ clinical status. Time domain analysis of heart rate variability included the standard deviation of all normal-to-normal R-R intervals and the standard deviation of the average normal-to-normal R-R intervals in all 5-minute segments.1

Plasma Biomarker Measurements
Plasma nerve growth factor concentrations were detected with sandwich enzyme-linked immunosorbent assay. All assays were performed on F-bottom 96-well plates (Nunc, Wiesbaden, Germany). Tertiary antibodies were conjugated to horseradish peroxidase. Nerve growth factor content was quantified against a standard curve calibrated with known amounts of protein. All samples were assayed in triplicate and expressed as means.²

**Metaiodobenzylguanidine Iodine 123 Scintigraphy**

All metaiodobenzylguanidine iodine 123 (¹²³I-MIBG) imaging studies were performed at rest after an overnight fast. Thyroid uptake was blocked by potassium iodide (200 mg), administered orally 1 hour before intravenous injection of ¹²³I-MIBG (10 mCi). ¹²³I-MIBG scintigraphy was performed with a standard dual-head gamma camera (Hawkeye, GE Medical Systems, Haifa, Israel) with medium-energy collimators. Fifteen minutes (initial) and 240 minutes (delayed) after the injection of the radiopharmaceutical, planar images of the thorax were acquired for 10 minutes in the anterior position. A 20×20-pixel region of interest was placed over the upper mediastinum. The heart/mediastinum ratio was calculated as mean counts per pixel over the left ventricle divided by mean counts per pixel in the upper mediastinum. The decay-corrected myocardial ¹²³I-MIBG washout was calculated according to the following algorithm.³:

\[
\text{Cardiac } ¹²³\text{I-MIBG washout} = \frac{(\text{early heart count density} – \text{late heart count density})}{\text{early heart count density}} \times 100\%
\]

No patients were taking sympathomimetic agents or other medications known to interfere with MIBG uptake at the time of ¹²³I-MIBG imaging. The techniques of imaging were kept the same for individuals at baseline and 6 months.
References