Published in final edited form as:

J Cardiovasc Electrophysiol. 2008 October ; 19(10): 1045–1052. doi:10.1111/j.1540-8167.2008.01190.x.

Cardiac Resynchronization Therapy Upregulates Cardiac Autonomic Control

YONG-MEI CHA, M.D., JAE OH, M.D., CHINAMI MIYAZAKI, M.D., DAVID L. HAYES, M.D., ROBERT F. REA, M.D., WIN-KUANG SHEN, M.D., SAMUEL J. ASIRVATHAM, M.D., BRAD J. KEMP, PH.D., DAVID O. HODGE, M.S., PENG-SHENG CHEN, M.D.^{*}, and PANITHAYA CHAREONTHAITAWEE, M.D.

Division of Cardiovascular Diseases, Department of Medicine, Mayo Clinic College of Medicine, Rochester, Minnesota, USA

^{*}Krannert Institute of Cardiology, Division of Cardiology, Department of Medicine, Indiana University School of Medicine, Indianapolis, Indiana, USA

Abstract

Objective: To determine the effect of cardiac resynchronization therapy (CRT) on sympathetic nervous function in heart failure (HF).

Background: Neurohormonal dysregulation and cardiac autonomic dysfunction are associated with HF and contribute to HF progression and its poor prognosis. We hypothesized that mechanical resynchronization improves cardiac sympathetic function in HF.

Methods: Sixteen consecutive patients receiving CRT for advanced cardiomyopathy and 10 controls were included in this prospective study. NYHA class, 6-minute walk distance, echocardiographic parameters, plasma norepinephrine (NE) were assessed at baseline, 3-month and 6-month follow-up. Cardiac sympathetic function was determined by ¹²³iodine metaiodobenzylguanidine (¹²³I-MIBG) scintigraphy and 24-hour ambulatory electrocardiography.

Results: Along with improvement in NYHA class (3.1 ± 0.3 to 2.1 ± 0.4 , $P < 0.001$) and LVEF ($23 \pm 6\%$ to $33 \pm 12\%$, $P < 0.001$) delayed heart/mediastinum (H/M) ¹²³I-MIBG ratio increased significantly (1.8 ± 0.7 to 2.1 ± 0.6 , $P = 0.04$) while the H/M ¹²³I-MIBG washout rate decreased significantly ($54 \pm 25\%$ to $34 \pm 24\%$, $P = 0.01$) from baseline to 6-month follow-up. The heart rate variability (HRV) measured in SD of normal-to-normal intervals also increased significantly from baseline (82 ± 30 ms) to follow-up (111 ± 32 ms, $P = 0.04$). The improvement in NYHA after CRT was significantly associated with baseline ¹²³I-MIBG H/M washout rate ($r = 0.65$, $P = 0.03$). The improvement in LVESV index was associated with baseline ¹²³I-MIBG delayed H/M ratio ($r = -0.67$, $P = 0.02$) and H/M washout rate ($r = 0.65$, $P = 0.03$).

Conclusion: After CRT, improvements in cardiac symptoms and LV function were accompanied by rebalanced cardiac autonomic control as measured by ¹²³I-MIBG and HRV.

Keywords

cardiac resynchronization therapy; heart failure; cardiomyopathy; ventricular dyssynchrony; sympathetic nerve; ¹²³iodine metaiodobenzylguanidine

Introduction

A primary pathophysiologic mechanism in heart failure (HF) is an abnormally activated sympathetic and altered parasympathetic system associated with increased concentration of circulating norepinephrine (NE), profound peripheral vasoconstriction, attenuated cardiovascular reflexes, and downregulation of adrenergic nerve terminals.^{1,2} The altered sympathetic control over myocardial function and impaired cardiac vagal reflex contributes to the progression of pump failure and susceptibility to ventricular arrhythmic sudden death.³⁻⁵ The success in treating HF by pharmacological neurohumoral antagonists such as beta-receptor blockade and angiotensin II-converting enzyme inhibitor underscores the importance of modulating the neurohumoral axis to improve clinical outcome.^{6,7} An emerging nonpharmacologic approach, cardiac resynchronization therapy (CRT), has shown promise for improving symptoms, quality of life, and survival in patients with New York Heart Association (NYHA) functional class III or IV, left ventricular ejection fraction (LVEF) $\leq 35\%$, and a widened QRS complex.⁸⁻¹¹ The beneficial effects of CRT are accompanied by favorable cardiac structural and functional changes of reverse ventricular remodeling, including significant reductions in LV endsystolic and end-diastolic dimensions, and mitral regurgitation. While the main mechanisms of these structural benefits are attributed to improved mechanical synchrony, we hypothesize that cardiac structural reverse remodeling associated with CRT may also be accompanied by reverse modulation of the cardiac sympathetic system, facilitating attenuation of excessive sympathetic drive associated with HF, thereby rebalancing cardiac autonomic activity and improving outcome in patients with HF.

The principal aim of this study was to determine the effect of CRT on cardiac symptoms, function, and cardiac sympathetic nerve activity in patients with advance HF undergoing clinically indicated CRT. Cardiac sympathetic nerve activity was assessed by both heart rate variability (HRV)¹² and ¹²³I-metaiodobenzylguanidine (¹²³I-MIBG) imaging. The ¹²³I-MIBG is an NE analog that is taken up by sympathetic nerve endings via the uptake-1 system similar to NE. ¹²³I-MIBG imaging therefore provides an assessment of presynaptic sympathetic activity.^{13,14}

Methods

Patient Population

Sixteen consecutive patients with advanced HF who met clinical criteria for a CRT-defibrillator (CRT-D) implantation (LVEF $< 35\%$, NYHA function class III or IV, QRS duration ≥ 120 ms and on optimal medical therapy)⁸⁻¹¹ were enrolled in the study. Patients with recent myocardial infarction, cardiac surgery (< 3 months), unstable medical condition, and chronic atrial fibrillation were excluded. Ten age- and gender-matched healthy subjects with normal cardiac function served as controls. The study was approved by The Mayo Institutional Review Board. Informed consent was obtained in each study subject.

Study Protocol

Clinical evaluation—One week prior to device implantation, each HF subject underwent clinical evaluation for symptom status, NYHA functional class assessment, medication use, and a 12-lead electrocardiogram (ECG). Exercise capacity was assessed by a 6-minute walk. QRS duration was manually measured from the standard 12-lead ECG. Cardiac structure and function were assessed using echocardiography. Cardiac autonomic function was assessed using 24-hour ambulatory ECG monitoring. Presynaptic cardiac sympathetic activity was determined by ¹²³I-MIBG imaging. Normal control subjects were interviewed to ascertain symptoms, illnesses, and medication use. All HF and control subjects had 3 and 6 months

follow-up reassessing NYHA class, 6-minute walk, echocardiography, and cardiac autonomic function. ^{123}I -MIBG imaging was repeated at 6 months.

Twenty-four-hour ambulatory ECG monitoring—The stored data from 24-hour ambulatory ECG recording (Del Mar Avionics, Irvine, CA, USA) were analyzed by an independent observer who was blinded to the clinical status of the patients. Time domain analysis of heart rate variability (HRV) included the standard deviation of all normal to normal intervals (SDNN), and the standard deviation of the average NN intervals in all 5-minute segments (SDANN).¹⁵

^{123}I -MIBG scintigraphy

All ^{123}I -MIBG imaging studies were performed at rest following an overnight fast. Thyroid uptake was blocked by use of oral 200 mg potassium iodide 1 hour before intravenous injection of 10 mCi of ^{123}I -MIBG. ^{123}I -MIBG scintigraphy was performed with a standard dual-head gamma camera (Hawkeye, GE Medical Systems, Haifa, Israel) with medium-energy collimators. At 15 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. Images were then transferred to a workstation for analysis using PMOD (version 2.75, PMOD Technologies, Zurich, Switzerland). An independent observer unaware of the clinical status of patients assessed cardiac ^{123}I -MIBG activity. Regions of interest were manually drawn on the planar anterior images over the myocardium excluding the left ventricular cavity.¹⁶ 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 ^{123}I -MIBG washout was calculated by use of count densities according to the following algorithm: Cardiac ^{123}I -MIBG washout = (early heart count density – late heart count density)/early heart count density $\times 100\%$.¹⁶ No patients were taking sympathomimetic agents or other drugs known to interfere with MIBG uptake at the time of ^{123}I -MIBG imaging.

Echocardiography—Echocardiograms were performed and interpreted by a single echo cardiologist blinded to the patient's clinical status. Echocardiographic parameters recorded from the clinical echocardiogram included EF derived from 2D measurements of diastolic and systolic LV dimension or volumetric analysis using method of disks, LV end diastolic dimension (measured with 2D echocardiography), pulmonary artery systolic pressure (PASP) (estimated from the tricuspid regurgitant velocity and an estimate of right atrial pressures), mitral regurgitation (MR) severity grade (0 = none/trivial; 1 = mild; 2 = moderate; or 3 = severe), LV diastolic dysfunction grade (1 = normal; 2 = mild (impaired relaxation); 3 = moderate (pseudo normal); 4 = severe (restrictive)) (based on mitral inflow, tissue Doppler imaging of mitral annulus motion, pulmonary venous inflow and left atrial volume as previously described).¹⁷ LV end-diastolic volume (LVEDV) and LV end-systolic volume (LVESV) were calculated by using biplane method. Tissue Doppler and strain imaging were obtained to assess LV dyssynchrony. The intraventricular dyssynchrony was determined by standard deviation of differences in timing intervals from QRS onset to peak negative strain of 12 basal and mid LV segments. The interventricular mechanical delay was the timing difference between pulmonary valve and aortic valve opening (RV–LV, normal < 40 ms) measured by pulsed wave Doppler echocardiography.

CRT-D implantation—Commercially available devices (Contak Renewal, Guidant, Minneapolis, MN, USA; and Insync Marquis III or Sentry, Medtronic, Minneapolis, MN, USA) and leads were used. The LV lead placement was prioritized as lateral/posterolateral, anterior lateral, anterior or middle cardiac veins as allowed by ability to cannulate the veins, pacing thresholds, or diaphragmatic stimulation. The standard settings included atrioventricular (AV)

delay of 100 ms (sensed) and 130 ms (paced), with DDD or DDDR mode and standard lower (50 bpm) and upper (120–130 bpm) pacing rates. Device follow-up was performed initially at 1 month then every 3 months postimplant as per standard clinical practice at our institution.

Statistical Analysis

Results are presented as mean $\pm$ SD. Student's *t*-test or Wilcoxon's nonparametric test were used for comparison of continuous factors between groups. Categorical variables were compared using Fisher's exact tests. Pearson's correlation coefficient was used to determine the association between the changes in clinical, echocardiographic parameters after CRT, and the baseline continuous factors. $P < 0.05$ was considered statistically significant.

Results

Baseline Patient Characteristics, Echocardiographic Parameters, and Cardiac Autonomic Function

Sixteen consecutive patients with drug refractory advanced HF and 10 controls were included in the study. The baseline characteristics of the study group are shown in Table 1. The mean age of the HF patients was 67 ± 8 years, which was not significantly different from controls. Of the 16 HF patients, eight had ischemic and eight had nonischemic cardiomyopathy. Thirteen (81%) patients were in NYHA class III, while the remaining three were in class IV. Nearly half of the HF patients had diabetes mellitus, compared with none of the controls. Ninety-four percent of the patients were receiving beta blocker and angiotensin-converting enzyme (ACE) or angiotensin II receptor inhibitor, and remained on a stable dose during the study duration. As expected, HF patients had significantly larger LV size (LVESV index 87 mL/m^2), impaired LV systolic (mean LVEF $23 \pm 7\%$) and diastolic dysfunction, higher pulmonary artery systolic pressure (mean $44 \pm 16 \text{ mmHg}$), and abnormal intra- and interventricular mechanical dyssynchrony compared with controls (Table 1).

In the HF patient group, SDNN and SDANN were $82 \pm 30 \text{ ms}$ and $79 \pm 23 \text{ ms}$, respectively, consistent with blunted HRV, and were significantly lower than in the control group ($113 \pm 36 \text{ ms}$, $P = 0.02$ and $110 \pm 23 \text{ ms}$, $P = 0.006$). Baseline initial and delayed H/M ratio were significantly lower in HF patients than in controls (2.1 ± 0.7 vs 2.6 ± 0.3 , $P = 0.03$; 1.8 ± 0.7 vs 2.5 ± 0.3 , $P = 0.01$), while baseline H/M washout rate was significantly higher in HF patients than in controls ($55 \pm 25\%$ vs $25 \pm 12\%$, $P < 0.001$). There was no significant difference in mean plasma concentration of NE between HF patients and control groups ($593 \pm 416 \text{ pg/mL}$ vs $502 \pm 134 \text{ pg/mL}$, $P = 0.84$). The range of plasma concentration of NE was from 195 to 1,728 pg/mL in HF patients and from 281 to 692 pg/mL in controls.

Improvement in Clinical, Cardiac Contractile, and Autonomic Function after CRT

Of 16 patients who received CRT for advanced HF, one required a left ventricular assist device 3 months after CRT for stage IV HF and subsequently died. This patient had the highest baseline NE plasma level of 1,728 pg/mL, the lowest delayed H/M ratio (1.01), the highest H/M washout (93%), the lowest SDNN (42 ms) and SDANN (38 ms). The remaining 15 patients completed 6-month clinical, echocardiography and 24-hour ambulatory ECG follow-up. A subset of 12 patients underwent ^{123}I -MIBG imaging. The imaging was unable to be obtained in the remaining four study patients within a week of device implantation.

With CRT, HF patients demonstrated significant improvements in NYHA class (Fig. 1) and 6-minute walk distance from baseline to 3 and 6 months follow-up (Fig. 2). Figure 1 shows the change of NYHA class from baseline to 3 and 6 months follow-up in each patient. Global LV contractile function (LVEF) increased significantly, while LVEDV index, LVESV index and mitral regurgitation severity decreased significantly from baseline to both follow-up time

points (** $P < 0.01$, * $P < 0.05$). The pulmonary artery systolic pressure decreased significantly from baseline 44 ± 16 mmHg to 32 ± 8 mmHg in 6-month ($P = 0.03$). Concomitantly, there was significant improvement in both interventricular and intraventricular resynchronization at 3 and 6 months (Fig. 2).

In HF patients, SDNN and SDANN increased significantly from baseline to 3 and 6 months after CRT (* $P < 0.05$) and approached values in normal controls (Fig. 3, $P = \text{NS}$). Figure 4 shows baseline and follow-up ^{123}I -MIBG measurements. The delayed H/M ratio increased significantly from baseline to follow-up (from 1.8 ± 0.7 to 2.1 ± 0.7 , $P = 0.04$), while the H/M washout rate decreased significantly from baseline to follow-up (from $54 \pm 22\%$ to $34 \pm 24\%$, $P = 0.01$). Seven of 12 (58%) patients had increased delayed H/M ratio $> 10\%$ and/or reduced (improved) MIBG washout rate $> 10\%$ after CRT. Of the remaining four patients who did not achieve significant changes in MIBG imaging, three had no improvement in NYHA class. There was no significant change in mean NE level after CRT (from 593 ± 417 pg/mL to 438 ± 111 pg/mL, $P = 0.63$).

Pearson's correlation analysis was performed to determine the changes of NYHA class, 6-minute walk distance, LVEF and LVESV index after CRT, in association to the baseline clinical, echocardiographic, and cardiac autonomic parameters. We found the improvement in NYHA by CRT was significantly associated with baseline ^{123}I -MIBG H/M washout rate ($r = 0.65$, $P = 0.03$, Fig. 5A), but not other continuous variables including age, 6-minute walk distance, QRS duration, LVEDV and LVESV indices, PA systolic pressure, LV diastolic function, inter and intraventricular mechanical dyssynchrony, SDNN, and SDANN. The improvement in LVESV index was associated with baseline severity of intraventricular dyssynchrony (the SD of differences in timing intervals from QRS onset to peak negative strain of 12 basal and mid LV segments, $r = -0.67$, $P = 0.006$, Fig. 5B), the ^{123}I -MIBG delayed H/M ratio ($r = -0.67$, $P = 0.02$, Fig. 5C) and H/M washout rate ($r = 0.65$, $P = 0.03$, Fig. 5D). Consistently, the improvement in LVEF was also correlated with baseline delayed H/M ratio ($r = 0.75$, $P = 0.008$), and H/M washout rate ($r = -0.72$, $P = 0.01$), but not correlated with intraventricular dyssynchrony.

Discussion

In this prospective study of advanced HF patients undergoing clinically indicated CRT, CRT was associated with improvements in cardiac symptoms and function, which were accompanied by improved cardiac autonomic activity as measured by ^{123}I -MIBG and HRV. Moreover, baseline cardiac sympathetic reserve by ^{123}I -MIBG was strongly associated with clinical response to CRT and reversal of LV structural remodeling.

HF and Cardiac Autonomic Dysfunction

Adrenergic activation is recognized as an important factor in the pathogenesis and outcome of HF.^{3,18-20} Heightened sympathetic tone in HF leads to substantially elevated plasma NE level and impaired reuptake and storage function of this primary neurohormonal transmitter at the presynaptic level, contributing to disease progression and an unfavorable prognosis.^{19,21-23} The ^{123}I -MIBG, an NE analog, shares a similar uptake, storage and release mechanisms in the adrenergic nerve endings as NE, and its imaging is a reliable imaging technique to assess sympathetic nerve distribution and function.^{13,14} In this study, we found significantly lower delayed H/M ^{123}I -MIBG ratio and higher H/M washout rate in HF patients than in controls at baseline. This striking decrease in ^{123}I -MIBG uptake and retention in our study is in agreement with prior reports in HF patients and is consistent with a downregulation of the uptake-1 carrier protein induced by overexposure to the neurotransmitter at the synaptic level.^{22,24} In further support of altered sympathetic activity, we also found blunted HRV in our HF patients compared with controls, similar to other studies.^{12,22} The imbalance in cardiac autonomic

control results from combination of sympathetic and parasympathetic dysregulation in HF and potentially predispose to cardiac arrhythmic events and mortality.^{25,26}

CRT Rebalances Cardiac Autonomic Function in Parallel to Improved Cardiac Contractile Function

Consistent with previous clinical trials of CRT,^{8-11,27} significant improvements in symptoms and exercise tolerance were observed following CRT. These beneficial clinical effects were accompanied by evidence of reverse ventricular remodeling, which included a significant increase in LVEF and significant reductions in LV end-systolic and end-diastolic volumes, mitral regurgitation, and PA systolic pressure following CRT. In parallel, improvements in biventricular mechanical resynchronization were achieved, with significant reductions in echocardiographic measurements of interventricular and intraventricular dyssynchrony. The most important finding of this study was the improvement of cardiac sympathetic function after CRT. As demonstrated in the previous studies in animal models,^{28,29} drug treatment reversed sympathetic denervation through the induction of cardiac nerve sprouting. At 6 months following CRT, we found that clinical and cardiac functional improvements were paralleled by significant improvements in NE reuptake function as measured by ¹²³I-MIBG uptake and retention. The increase in H/M ratio post CRT in this study is similar to increases reported in HF studies examining the effects of beta blocker, ACE inhibitor, or aldosterone inhibitor therapies.³⁰⁻³² Further, HRV measured as SDNN and SDANN were markedly abnormal at baseline. CRT restored these markers possibly due to a combination of improved sympathetic function and vagal cardiac reflex response. We cannot be certain that the findings both in HRV and I-MIBG may have been related to increased baroreflex sensitivity and other cardiovagal reflexes as we did not measure primarily cardiovagal responses in this study. The improvements in NYHA class and LVESV following CRT were, indeed, strongly associated with more favorable cardiac sympathetic reserve as measured by ¹²³I-MIBG delayed H/M ratio and H/M washout rate. Those that did not achieve improvement in NYHA class had less upregulation in sympathetic reserve after CRT. To our knowledge, no published study has previously addressed the effects of CRT on cardiac autonomic modulation in HF measured by combined ¹²³I-MIBG scintigraphy and HRV. Study results therefore uniquely suggest that the nonpharmacologic approach to HF treatment can improve cardiac sympathetic activity similar to pharmacologic therapy with beta blocker or renin-angiotensin-aldosterone axis inhibition.

What is the mechanism underlying the clinical improvement of responders? Do responders have a “better” sympathetic profile than nonresponders? In those who achieved clinical and cardiac structural improvements after CRT in this study, less presynaptic uptake-1 downregulation may lead to a more easily activated sympathetic reserve. The latter may be recruited from “hibernating” status by improving myocardial efficiency during resynchronization. On the other hand, in those who had less clinical benefit from CRT, we hypothesize that a striking decrease in baseline ¹²³I-MIBG activity could be due to a combination of structural deficits in the sympathetic neurons in scarred myocardium as well as severe chronic sympathetic hyperactivity, resulting in reduced ability to reactivate or recruit sympathetic reserve, perhaps in a similar fashion to a denervated state. This hypothesis needs to be further explored in a larger study.

The mean plasma NE level in medically treated HF patients before CRT was in the normal range and was neither significantly different from controls at baseline, nor significantly changed after CRT. This was probably because a wide range of NE levels measured in both HF patients and controls. The alternative explanation is that these patients were on optimal pharmacological therapy. Concomitant use of beta blocker and ACE/angiotensin II receptor inhibitor may suppress elevated NE level or attenuate the increase in NE as previously reported.^{33,34} Whether NE level is affected by CRT is controversial from limited studies; it was observed

decrease, no change, or selected decrease in patients with a baseline NE > 800 ng/mL.³⁵⁻³⁹ We observed a consistent improvement in HRV and MIBG, but not in NE level. One possible explanation for this discrepancy is that the uptake and release of NE in the sympathetic neuron level may not coincide with circular NE level. In addition, CRT inhibit arterial baroreflex-mediated sympathoexcitation occurring in HF, and, hence, reduces adrenergic nerve outflow measured by microneurography,^{40,41} an evidence of neural, other than hormonal, regulation.

Limitations

The limited sample size makes analysis of the study less robust. Nevertheless, significant differences were noted between the groups. A larger scale ¹²³I-MIBG imaging study is needed to confirm these findings. Second, there is no consensus in the literature on the optimal method for selection of regions of interest over the heart and mediastinum. In this study, we used methodology from prior studies of HF patients in which the LV cavity was excluded from the myocardial region of interest to reflect more closely myocardial activity.^{16,42} Third, medications used during the study may affect ¹²³I-MIBG uptake, HRV, echocardiographic measurements, and circulating plasma catecholamine levels. However, patients were maintained on a stable dose of drug throughout the duration of the study. Further, several previous studies suggest that beta blockers and ACE inhibitors do not directly inhibit MIBG uptake.¹⁶ Fourth, intermittent atrial pacing and rate response algorithms may alter sinoatrial node function and impact on the interpretation of HRV after CRT other than autonomic mechanism, although the same atrial pacing algorithm was programmed throughout the study in each patient.¹²

Conclusion

This is the first study to demonstrate that following CRT in advanced HF patients, improvements in cardiac symptoms and LV function are accompanied by rebalance in cardiac autonomic function as measured by ¹²³I-MIBG and HRV. CRT restores cardiac sympathetic response and possibly reverses denervation hypersensitivity. The correlation between baseline ¹²³I-MIBG parameters (the cardiac sympathetic reserve) and CRT clinical response suggests the need for further studies to address the potential role of ¹²³I-MIBG as a predictor of CRT response.

Acknowledgments

The authors thank Tracy Webster, RN, Connie Dalzell, RN, Connie Meiners, RN, and Linda Hyberger at the Mayo Clinic Heart Rhythm Division, and Teresa Decklever, CNMT at the Mayo Nuclear Cardiology Laboratory for their contributions to this study.

This study received funding from Scientist Development Grant from AHA Greater Midwest Affiliate AHA 0435347Z and Award for Research in Cardiology Grant from the Mayo Clinic and Foundation.

Dr. Shen is the PI of an investigator initiated, multicenter research trial funded by Medtronic; Dr. Miyazaki has received research grants from Guidant, St. Jude Medical, and Medtronic; Dr. Hayes serves on the medical advisory boards of Boston Scientific, Sorin, and St. Jude Medical.

References

1. Liang C, Fan T, Sullegarger J, Sakamoto S. Decreased adrenergic neuronal uptake activity experimental right heart failure. A chamber-specific contributor to beta-adrenoceptor down regulation. *J Clin Invest* 1989;84:1267–1275. [PubMed: 2551925]
2. Himura T, Felten S, Kashiki M, Lewandowski T, Delenhanty J, Liang C. Cardiac noradrenergic nerve terminal abnormalities in dogs with experimental congestive heart failure. *Circulation* 1993;88:1299–1309. [PubMed: 8102598]

3. Zucker I, Wang W, Pliquett R, Lie J, Patel K. The regulation of sympathetic outflow in heart failure. The roles of angiotensin II, nitric oxide, and exercise training. *Ann N Y Acad Sci* 2001;940:431–443. [PubMed: 11458699]
4. Lombardi F, Porta A, Marzegalli M, Favale S, Santini M, Vicenti A, De Rosa A. Heart rate variability patterns before ventricular tachycardia onset in patients with an implantable cardioverter defibrillator. Participating investigators of ICD-HRV Italian Study Group. *Am J Cardiol* 2000;86:959–963. [PubMed: 11053707]
5. Meredith I, Broughton A, Jennings G, Esler M. Evidence of a selective increase in cardiac sympathetic activity in patients with sustained ventricular arrhythmias. *N Engl J Med* 1991;325:618–624. [PubMed: 1861695]
6. Packer M, Coats A, Fowler M, Katus H, Krum H, Mohacsi P, Rouleau J, Tendera M, Castaigne A, Roecker E, Schultz M, DeMets D. Effect of carvedilol on survival in severe chronic heart failure. *N Engl J Med* 2001;344:1651–1658. [PubMed: 11386263]
7. SOLVD. Effect of further enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. *N Engl J Med* 1991;325:293–302. [PubMed: 2057034]
8. Abraham W, Fisher W, Smith A, Delurgio D, Leon A, Loh E, Kocovic D, Packer M, Clavell A, Hayes D, Ellestad M, Trupp R, Underwood J, Pickering F, Truex C, McAtee P, Messenger J. Cardiac resynchronization in chronic heart failure. *N Engl J Med* 2002;346:1845–1853. [PubMed: 12063368]
9. Cazeau S, Leclercq C, Lavergne T, Walker S, Varma C, Linde C, Garrigue S, Kappenberger L, Haywood G, Santini M, Bailleul C, Daubert J. Effects of multisite biventricular pacing in patients with heart failure and intraventricular conduction delay. *N Engl J Med* 2001;344:873–880. [PubMed: 11259720]
10. Young J, Abraham W, Smith A, Leon A, Lieberman R, Wilkoff B, Canby R, Schroeder J, Liem L, Hall S, Whealan K. Combined cardiac resynchronization and implantable cardioversion defibrillation in advanced chronic heart failure: The MIRACLE ICD Trial. *JAMA* 2003;289:2685–2694. [PubMed: 12771115]
11. Cleland G, Daubert J, Erdmann E, Freemantle N, Gras D, Kappenberger L, Tavazzi L. The effect of cardiac resynchronization on morbidity and mortality in heart failure. *N Engl J Med* 2005;352:1539–1549. [PubMed: 15753115]
12. Adamson P, Kleckner K, VanHout W, Srinivasan S, Abraham W. Cardiac resynchronization therapy improves heart rate variability in patients with symptomatic heart failure. *Circulation* 2003;108:266–269. [PubMed: 12860899]
13. Sisson J, Wieland D, Sherman P, Mangner T, Tobes M, Jacques S. Metaiodobenzylguanidine as an index of the adrenergic nervous system integrity and function. *J Nucl Med* 1987;28:1620–1624. [PubMed: 3655914]
14. Wieland D, Brown L, Rogers W, Worthington K, Wu J, Clinthorne N, Otto C, Swanson D, Beierwaltes W. Myocardial imaging with a radioiodinated norepinephrine storage analog. *J Nucl Med* 1981;22:22–31. [PubMed: 7452352]
15. Electrophysiology TFOtESoCtNASoPa. Heart rate variability: Standards of measurement, physiological interpretation, and clinical use. *Circulation* 1996;93:1043–1065. [PubMed: 8598068]
16. Somsen G, Verberne H, Fleury E, Righetti A. Normal values and within-subject variability of cardiac I-123 MIBG scintigraphy in healthy individuals: Implications for clinical studies. *J Nucl Cardiol* 2004;11:126–133. [PubMed: 15052243]
17. Oh, J.; Seward, J.; Tajik, A. *The Echo Manual*. Vol. 2nd edition. Lippincott Williams & Wilkins; Philadelphia, PA: 1999.
18. Association, AH. American Heart Association 2002 Heart and Stroke Statistical Update. American Heart Association; Dallas, TX: 2002.
19. Cohn J, Levine T, Olivari M, Garberg V, Lura D, Francis G, Simon A, Rector T. Plasma norepinephrine as a guide to prognosis in patients with chronic congestive heart failure. *N Engl J Med* 1984;311:819–823. [PubMed: 6382011]
20. Kaye D, Lefkowitz J, Jennings G, Bergin P, Broughton A, Esler M. Adverse consequences of high sympathetic nervous activity in the failing human heart. *JACC* 1995;26:1257–1263. [PubMed: 7594040]

21. Packer M. The neurohormonal hypothesis: A theory to explain the mechanism of disease progression in heart failure. *JACC* 1992;20:248–254. [PubMed: 1351488]
22. Yamada T, Shimonagata T, Fukunami M, Kumagai K, Ogita H, Hirata A, Asai M, Makino N, Kioka H, Kusuoka H, Hori M, Hoki N. Comparison of the prognostic value of cardiac iodine-123 metaiodobenzylguanidine imaging and heart rate variability in patients with chronic heart failure: A prospective study. *JACC* 2003;41:231–238. [PubMed: 12535815]
23. Inamura Y, Ando H, Mitsuoka W, Egashira S, Masaki H, Ashihara T, Fukuyama T. Iodine-123 metaiodobenzylguanidine images reflect intense myocardial adrenergic nervous activity in congestive heart failure independent of underlying cause. *JACC* 1995;26:1594–1599. [PubMed: 7594091]
24. Ogita H, Shimonagata T, Fukunami M, Yamada T, Asano Y, Hirata A, Asai M, Kusuoka H, Hori M, Hoki N. Prognostic significance of cardiac (123) I metaiodobenzylguanidine imaging for mortality and morbidity in patients with chronic heart failure: A prospective study. *Heart* 2001;86:656–660. [PubMed: 11711461]
25. Nolan J, Batin P, Andrews R, Lindsay S, Brooksby P, Mullen M, Baig W, Flapan A, Cowley A, Prescott R, Neilson J, Fox K. Prospective study of heart rate variability and mortality in chronic heart failure: Results of the United Kingdom heart failure evaluation and assessment of risk trial (UK-heart). *Circulation* 1998;98:1510–1560. [PubMed: 9769304]
26. LA Rovere M, Pinna G, Maestri R, Mortara A, Capomolla S, Febo O, Ferrari R, Franchini M, Gnemmi M, Opasich C, Riccardia P, Traversi E, Cobelli F. Short-term heart rate variability strongly predicts sudden cardiac death in chronic heart failure patients. *Circulation* 2003;107:565–570. [PubMed: 12566367]
27. Stellbrink C, Breithardt O, Franke A, Sack S, Bakker P, Auricchio A, Pochet T, Salo R, Kramer A, Spinelli J. Impact of cardiac resynchronization therapy using hemodynamically optimized pacing on left ventricular remodeling in patients with congestive heart failure and ventricular conduction disturbances. *J Am Coll Cardiol* 2001;38:1957–1965. [PubMed: 11738300]
28. Liang C, Yatani A, Himura Y, Kashiki M, Stevens S. Desipramine attenuates loss of cardiac sympathetic neurotransmitters produced by congestive heart failure and NE infusion. *Am J Physiol-Heart Circ Physiol* 2003;284:H1729–H1736. [PubMed: 12543636]
29. Cha Y, Redfield M, Shah S, Shen W, Fishbein M, Chen P. Effects of omapatrilat on cardiac nerve sprouting and structural remodeling in experimental congestive heart failure. *Heart Rhythm* 2005;2:984–990. [PubMed: 16171755]
30. Toyama T, Hoshizaki H, Seki R, Isobe N, Adachi H, Naito S, Oshima S, Taniguchi K. Efficacy of carvedilol treatment on cardiac function and cardiac sympathetic nerve activity in patients with dilated cardiomyopathy: Comparison with metoprolol therapy. *J Nucl Med* 2003;44:1604–1611. [PubMed: 14530474]
31. Kasama S, Toyama T, Kumakura H, Takayama Y, Ichikawa S, Suzuki T, Kurabayashi M. Addition of valsartan to an angiotensin-converting enzyme inhibitor improves cardiac sympathetic nerve activity and left ventricular function in patients with congestive heart failure. *J Nucl Med* 2003;44:884–890. [PubMed: 12791814]
32. Kasama S, Toyama T, Kumakura H, Takayama Y, Ichikawa S, Suzuki T, Kurabayashi M. Spironolactone improves cardiac sympathetic nerve activity and symptoms in patients with congestive heart failure. *J Nucl Med* 2002;43:1279–1285. [PubMed: 12368364]
33. Latini R, Masson S, Anand I, Judd D, Maggioni A, Shiang Y, Bevilacqua M, Salio M, Cardano P, Dunselman P, Holwerda N, Tognoni G, Cohn J. Effects of Valsartan on circulating brain natriuretic peptide and norepinephrine in symptomatic chronic heart failure: The Valsartan heart failure trial (Val-HeFT). *Circulation* 2002;106:2454–2458. [PubMed: 12417542]
34. Azevedo E, Kubo T, Mak S, Al-Hesayen A, Schofield A, Allan R, Kelly S, Newton G, Floras J, Parker J. Nonselective versus selective beta-adrenergic receptor blockade in congestive heart failure: Differential effects on sympathetic activity. *Circulation* 2001;104:2194–2199. [PubMed: 11684630]
35. Adamson P, Kleckner K, Warren L, Srinivasan S, Abraham W. Cardiac resynchronization therapy improves heart rate variability in patients with symptomatic heart failure. *Circulation* 2003;108:266–269. [PubMed: 12860899]

36. Braun M, Rauwolf T, Zerm T, Schulze M, Schnabel A, Strasser R. Long term biventricular resynchronisation therapy in advanced heart failure: Effect on neurohormones. *Heart* 2004;91:601–605. [PubMed: 15831642]
37. Boriani G, Regoli F, Saporito D, Martignani C, Toselli T, Biffi M, Francolini G, Diemberger I, Bacchi L, Rapezzi C, Ferrari R, Branzi A. Neurohormones and inflammatory mediators in patients with heart failure undergoing cardiac resynchronization therapy: Time courses and prediction of response. *Peptides* 2006;27:1776–1786. [PubMed: 16621149]
38. Seifert M, Schlegel M, Hoersch W, Fleck E, Doelger A, Stockburger M, Butter C. Functional capacity and changes in the neurohormonal and cytokine status after long-term CRT in heart failure patients. *Int J Cardiol* 2007;121:68–73. [PubMed: 17582527]
39. Saxon L. TEE evidence of right atrial tachycardia with mechanical alternans, interatrial and atrioventricular 2:1 block. *Pacing Clin Electrophysiol* 1999;829–830. [PubMed: 10353149]Abstract
40. Grassi G, Vincenti A, Brambilla R, Trevano F, Dell'Oro R, Ciro A, Trocino G, Vincenzi A, Mancina G. Sustained sympathoinhibitory effects of cardiac resynchronization therapy in severe heart failure. *Hypertension* 2004;44:727–731. [PubMed: 15381677]
41. Hamdan M, Jason M, Zagrodzky J, Joglar J, Sheehan C, Ramaswamy K, Erdner J, Page R, Smith M. Biventricular pacing decreases sympathetic activity compared with right ventricular pacing in patients with depressed ejection fraction. *Circulation* 2000;102:1027–1032. [PubMed: 10961968]
42. Toyama T, Hoshizaki H, Seki R, Isobe N, Adachi H, Naito S, Oshima S, Taniguchi K. Efficacy of carvedilol treatment on cardiac function and cardiac sympathetic nerve activity in patients with dilated cardiomyopathy: Comparison with metoprolol therapy. *J Nucl Cardiol* 2003;44:1604–1611.

Figure 1.

Shown are the changes in NYHA class after CRT in each individual patient. One patient did not survive at 6-month follow-up.

Figure 2.

Figure depicts the delta changes of NYHA function class, distance of 6-minute walk, LV end-diastolic volume (LVEDV) index, LV end-systolic volume (LVESV) index, LV ejection fraction (LVEF), the degree of mitral regurgitation (MR), interventricular conduction delay by tissue Doppler, and intraventricular conduction delay by strain rate in 3-month and 6-month follow-up after CRT. *P < 0.05; **P < 0.01 compared with baseline.

Figure 3.

The figure shows the standard deviation of all normal to normal intervals (SDNN), the SD of the averages NN intervals in all 5-minute segments (SDANN) expressed as Mean $\pm$ SD at baseline, 3-month and 6-month follow-up after CRT. *P < 0.05 compared with baseline; #P < 0.05 compared with control baseline.

Figure 4.

The histogram shows the effect of CRT on ^{123}I -MIBG imaging after CRT. The initial and delayed H/M ratios were lower and H/M washout rate was higher in patients with HF compared with controls at baseline. The delayed H/M ratio and H/M washout rate were significantly improved in 6-month after CRT. * $P < 0.05$; ** $P < 0.01$ compared to baseline; ### $P < 0.01$ compared with control baseline.

Figure 5.

The figure shows significant correlation of change in NYHA class after CRT with baseline ^{123}I -MIBG H/M washout (A), and correlations of change in LV end-systolic volume (LVESV) index after CRT with baseline intraventricular dyssynchrony (the standard deviation of differences in timing intervals from QRS onset to peak negative strain of 12 basal and mid LV segments) (B), baseline ^{123}I -MIBG delayed H/M ratio (C), and H/M washout rate (D).

TABLE 1

A Comparison of Baseline Characteristics in Heart Failure and Controls

	CRT Group N = 16	Control Group n = 10	P
Age (years)	67 ± 8	64 ± 6	0.18
Male gender (%)	75	60	0.66
Ischemic cardiomyopathy n (%)	8 (50)	0 (0)	
Diabetes n (%)	7 (44)	0 (0)	0.02
Hypertension n (%)	8 (50)	3 (30)	0.4
Beta blocker n (%)	15 (94)	0 (0)	< 0.001
ACEI/ARB n (%)	15 (94)	0 (0)	< 0.001
Aldactone n (%)	6 (38)	0 (0)	0.05
Statins n (%)	11 (69)	0 (0)	0.007
Distance of 6-minute walk (m)	324 ± 87	472 ± 85	< 0.001
QRS duration (ms)	162 ± 18	106 ± 25	0.005
LBBB n (%)	10 (63)	0 (0)	0.002
Echocardiography EF (%)	23 ± 7	60 ± 4	< 0.001
LVEDV index (mL/m ²)	114 ± 27	45 ± 6	< 0.001
LVESV index (mL/m ²)	87 ± 25	18 ± 2	< 0.001
Mitral regurgitation grade	1.8 ± 1.5	0.4 ± 0.5	0.02
PASP (mmHg)	44 ± 16	27 ± 3	0.007
LV diastolic dysfunction	2.5 ± 1.1	1.5 ± 1.4	0.007
Interventricular dyssynchrony (ms)	38 ± 20	15 ± 11	0.003
Intraventricular dyssynchrony by strain			
SD of 12 segments (ms)	114 ± 51	51 ± 10	< 0.001
Max difference in 12 segments (ms)	344 ± 138	151 ± 28	< 0.001

LVEDV = left ventricular end-diastolic volume; LVESV = left ventricular end-systolic volume; PASP = pulmonary artery systolic pressure.