Improvement in cardiac sympathetic nerve activity in responders to resynchronization therapy

Haran Burri1*, Henri Sunthorn1, Aernout Somsen2, Eric Fleury1, Carine Stettler1, Dipen Shah1, and Alberto Righetti1

1Cardiology Service, University Hospital of Geneva, 23, Micheli-du-Crest, 1211 Geneva, Switzerland; and 2Department of Cardiology, Onze Lieve Vrouwe Gasthuis, Amsterdam, The Netherlands

Received 9 November 2007; accepted after revision 8 January 2008

Aims To assess changes in cardiac adrenergic activity with cardiac resynchronization therapy (CRT), and to investigate whether these changes are related to improvement in left ventricular ejection fraction (LVEF).

Methods and results Sixteen patients (13 males, age 66 ± 7 years) were studied at baseline and after 6 months of CRT (mean follow-up 9.2 ± 3.2 months). LVEF was assessed by nuclear angiography. Responders were defined as patients showing ≥5% absolute increase in LVEF + improvement in ≥1 NYHA class + absence of heart failure hospitalization. Cardiac sympathetic nerve activity was studied by 123I-metaiodobenzyl-guanidine (123I-MIBG) scintigraphy. Responders (n = 8) showed lower 123I-MIBG washout at follow-up when compared with non-responders (P = 0.002), indicating lower cardiac sympathetic nerve activity. The decrease in 123I-MIBG washout at follow-up when compared with baseline was only seen in the responder group (P = 0.036). There was a moderate correlation between increase in LVEF and decrease in 123I-MIBG washout (r = 0.52, P = 0.04).

Conclusion CRT induces a reduction in cardiac sympathetic nerve activity in responders, that parallels an improvement in LVEF, whereas non-responders do not show any significant changes.

KEYWORDS Cardiac resynchronization therapy; MIBG; Nervous system; Sympathetic; Ventricular function

Introduction Cardiac resynchronization therapy (CRT) has been shown to improve sympatho-vagal balance in patients with advanced heart failure.1–3 It is not known whether this improvement is due to changes in circulating plasma catecholamines, central sympatho-vagal tone, or to direct cardiac innervation. The former hypothesis seems unlikely as studies have not shown any changes in the levels of circulating dopamine, epinephrine, or norepinephrine.1,4 Peripheral sympathetic nerve activity has been shown to be acutely reduced by CRT.5,6 Specific cardiac sympathetic nerve activity can be assessed in vivo by 123I-metaiodobenzyl-guanidine (123I-MIBG) scintigraphy. 123I-MIBG shares the same presynaptic uptake, storage, and release mechanisms as norepinephrine, but is biologically inactive. Increased MIBG washout (see methods section) represents increased sympathetic nerve activity and has been associated with increased risk of sudden death and admission for heart failure in patients with systolic heart failure.7,8

CRT pacemakers have been shown to reduce mortality, both owing to heart failure, as well as to sudden death.9 The reduction in sudden death by CRT is intriguing, and may be due to substrate modification because of reverse remodelling (reduction in ventricular volumes and improvement in systolic function), as well as to changes in sympathetic activity. Our aim was to investigate whether CRT affects cardiac sympathetic nerve activity, and whether changes are related to CRT response.

Materials and methods Patient population

We studied 16 patients with a standard indication for CRT (LVEF ≤ 0.35, drug-refractory NYHA class III-IV heart failure and QRS > 120 ms). Patient demographics are shown in Table 1. The two patients with chronic atrial fibrillation had both >90% ventricular pacing at follow-up (with the baseline rate programmed at 70 bpm). All patients provided informed consent to the study, which was approved by the institutional ethics committee. The patients were studied at baseline (at CRT implantation) and after 6 months’ follow-up with a clinical assessment and the same nuclear exams comprising a radionuclide angiogram for
measurement of LVEF, and \(^{123}\text{I}\)-MIBG scintigraphy for measurement of sympathetic nerve activity. Doses of angiotensin-converting enzyme-inhibitor (ACE-I)/angiotensin-receptor blocker (ARB) were increased during follow-up in three patients (by 50% in two patients, and doubled in one patient). Doses of beta-blockers were increased in four patients (by 50% in one patient, and doubled in three patients). One of these patients had an increase in both drugs.

**Device implantation and programming**

All leads were placed transvenously. There were 13 patients with a biventricular ICD, and three with a biventricular pacemaker. Atrial leads were positioned in the right atrial appendage. Right ventricular leads were placed either at the mid-septum (n = 11) or at the apex (n = 5) according to the implanter’s preference. Left ventricular leads were positioned via the coronary sinus in a postero-lateral (n = 5), lateral (n = 9), or antero-lateral (n = 2) tributary. Atrioventricular intervals were optimized by echocardiography using the Ritter method\(^{10}\) with simultaneous biventricular pacing.

**Radionuclide angiography**

Images were acquired within 2 days after device implantation. A blood sample was drawn to label red blood cells with 1 GBq of technetium-99 m. Images were acquired during biventricular pacing at 80 bpm in order to avoid changes in LVEF due uniquely to heart rate. The ECG was monitored continuously for R-wave gating, with elimination of extrasystolic and post-extrasystolic cycles. Multi-gated equilibrium blood pool planar scintigrams at 32 frames/cycle (200-250 Kcounts/frame in a 128 × 128 matrix) were acquired using a ADAC-Phillips double-head gamma camera until the number of counts was at least \(6 \times 10^6\) in the ‘best-septal’ left anterior oblique projection that provided optimal right and left ventricular discrimination. The right and left ventricular regions of interest in systole and diastole were drawn by a single investigator (E.F.). LVEF was computed using the formula: LVEF = (ESC – EDV)/ESC, where ESC is end-systolic counts and EDV is end-diastolic counts. We have previously reported the intra-observer reproducibility of LVEF to have 95% limits of agreement of \(\pm 3.5\%\) and correlation between repeated measurements of 0.99 (\(P < 0.001\)).\(^{11}\)

\(^{123}\text{I}\)-metaiodobenzyl-guanidine scintigraphy

\(^{123}\text{I}\)-MIBG scintigraphy was performed \(\geq 48\) h after the radionuclide angiograms (with the same gamma camera) in order to avoid any interference between the tests. After an overnight fast, the patients received 100 mg potassium iodide per os prior to the exam to block thyroid uptake. After 1 h, 185 MBq of \(^{123}\text{I}\)-MIBG was injected intravenously and planar scintigrams performed in the antero-posterior projection at 15 and 240 min. Images were acquired during biventricular pacing. A 20% energy window was centred on the 159 keV photopeak of \(^{123}\text{I}\). Data collection was performed with a \(128 \times 128\) matrix and a zoom factor of 1.46. The studies were reconstructed with the PEGASYS software package (ADAC Laboratories, Milpitas, CA, USA) and fifth order Pega Butterworth pre-reconstruction filter. Images were zoomed to 250%. Myocardial \(^{123}\text{I}\)-MIBG activity was measured manually by drawing a region of interest around the ventricles. Mediastinal activity was measured by drawing a fixed 40-pixel region drawn over the upper mediastinum. An example of a \(^{123}\text{I}\)-MIBG scintigram is shown in **Figure 1**. Myocardial and mediastinal activity are expressed as mean counts/pixel. The parameters described below were calculated.

**Heart/mediastinal (H/M) ratio**

This parameter was calculated at 15 and 240 min. This parameter of \(^{123}\text{I}\)-MIBG uptake is a reflection of sympathetic function as an increase in uptake reflects restoration of function. Normal ranges for H/M\(_{15}\) and H/M\(_{240}\) have been previously reported to be 1.9 –2.8 and 1.8–2.7, respectively.\(^{12}\)

**\(^{123}\text{I}\)-metaiodobenzyl-guanidine washout**

This parameter was calculated using the washout formula, taking into account decay of \(^{123}\text{I}\)-MIBG (T): \(100 \times [(H/T – M/T)_{15} – (H/T – M/T)_{240}]/(H/T – M/T)_{15}\). A decrease in washout reflects a reduction in sympathetic activity. Abnormal washout has previously been defined as \(> 27\%\) and has been associated with increased risk of sudden death in patients with systolic heart failure.\(^7,8\)

All the data were processed by a single investigator (E.F.), who was blinded to the patient’s clinical improvement. All acquisitions (32 recordings in 16 patients) were reprocessed a second time (with blinding to the results of the first measurements) in order to evaluate intra-observer reproducibility.

**Definition of response**

Responders to CRT were defined as patients who improved their LVEF by \(\geq 5\%\) in absolute terms (as this has been shown to be a strong predictor of mortality in patients with heart failure).\(^{13}\) In addition, patients had to improve by \(\geq 1\) NYHA class and not be hospitalized for heart failure during follow-up.
Statistical analysis

The Shapiro-Wilk test indicated that the $^{123}$I-MIBG data did not have a Gaussian distribution. The Wilcoxon’s test was used for comparing continuous variables at baseline and follow-up. The Mann–Whitney test was used from comparing continuous variables between two unrelated groups. The Kruskall–Wallis test was used from comparing continuous data of multiple unrelated groups. Linear regression and Spearman’s correlation coefficient were used for correlating data. Reproducibility was assessed using the Bland-Altman method. Data are expressed as mean ± SD. A two-sided $P$-value of <0.05 was considered statistically significant.

Results

Mean follow-up was 9.2 ± 3.2 months. NYHA functional class improved from 3.3 ± 0.4 to 2.3 ± 0.7 at follow-up ($P = 0.001$), with 12 of 16 (75%) of patients improving by ≥1 NYHA class. Two patients were admitted for heart failure during follow-up. There were no deaths during the follow-up period. LVEF improved from 24.7 ± 8.2 to 30.0 ± 14.7% ($P = 0.034$) with an absolute increase of 5.3 ± 9.6%. In 8 of 16 (50%) patients, LVEF improved by ≥5% (in absolute terms). All these eight patients were considered to be responders (as they all reported improvement in NYHA class and none were admitted for heart failure).

Intra-observer reproducibility was excellent for all $^{123}$I-MIBG parameters: 95% limits of agreement and correlation for repeat measurements were −0.08 to 0.08 and $r = 0.98$, respectively, for H/M$_{25}$, −0.05 to 0.03 and $r = 0.99$ for H/M$_{240}$, −9.4 to 13.1% and $r = 0.92$ for washout. There was no significant correlation between baseline LVEF and any of the baseline $^{123}$I-MIBG parameters. None of the $^{123}$I-MIBG parameters showed any significant change at follow-up when compared with baseline for the group as a whole. However, when the groups were analysed separately according to response to CRT, only responders showed a significant decrease in washout at follow-up when compared with baseline ($P = 0.036$; Figure 2). Responders also had a significantly lower washout at follow-up when compared with non-responders ($P = 0.002$; Figure 2). None of the $^{123}$I-MIBG parameters were different between the groups at baseline (Figure 2). There was a moderate, but significant correlation between improvement in washout and improvement in LVEF at follow-up ($r = −0.52$, $P = 0.038$; Figure 3). However, the significance of the correlation became borderline ($r = −0.51$, $P = 0.051$) when the patient with greatest LVEF improvement (33%) was excluded from the analysis.

Twelve patients (75%) who improved by ≥1 NYHA class had a lower $^{123}$I-MIBG washout at follow-up than patients who did not show clinical response (45 ± 13% vs. 54 ± 4%, $P = 0.042$). None of the other $^{123}$I-MIBG parameters showed any difference between the groups.

There were no differences in changes in $^{123}$I-MIBG parameters between patients with non-ischaemic vs. ischaemic cardiomyopathy. However, the former group tended to have a greater improvement in LVEF at follow-up (increase in absolute terms of $9.0 ± 10.5\%$ vs. $0.6 ± 6.4\%$, $P = 0.06$). We compared changes in $^{123}$I-MIBG parameters in patients according to RV (septal vs. apical) and LV (postero-lateral vs. lateral vs. antero-lateral) lead position, and found no significant differences between groups ($P > 0.06$ and $P > 0.41$, respectively). There were no changes in $^{123}$I-MIBG parameters in the six patients who had increase in ACE-I/ARB and/or beta-blocker dosage at follow-up, when compared with those without changes in drug dosage.

Discussion

Our study shows for the first time that responders to CRT have a reduction in cardiac sympathetic nerve activity at follow-up with a reduction in $^{123}$I-MIBG washout, whereas non-responders do not show any significant changes. There was a significant (albeit moderate) correlation between improvement in $^{123}$I-MIBG washout and improvement in LVEF because of CRT. Our study does not allow to ascertain whether a causal relationship exists between these two
parameters, or whether they are simply improved in parallel. Importantly, cardiac sympathetic activity does not seem to be directly related to LVEF, as there was no significant correlation between LVEF and any $^{123}$I-MIBG parameters at baseline, which is in agreement with previous data.\(^\text{15}\)

To our knowledge, there are only two existing publications of CRT and cardiac sympathetic nerve activity studied by $^{123}$I-MIBG. Erol-Yilmaz et al.\(^\text{16}\) studied 13 patients, and also reported a significant decrease in $^{123}$I-MIBG washout after 6 months' follow-up, but the study did not analyse changes according to CRT response. Contrary to our study, they reported an improvement in $^{123}$I-MIBG washout (and borderline changes in $H/M_{240}$) for the entire patient group. Baseline values of $^{123}$I-MIBG parameters were very similar when compared with our patient population, but the response rate in their study was higher (75% of patients increased LVEF by $\geq 5\%$ evaluated by echocardiography, and 100% of patients had clinical response). LVEF response of 50% in our study was nevertheless similar when compared with previous publications (for example, 54% in a multicentre series).\(^\text{17}\) The second report is a randomized crossover study in 10 patients who showed marginal improvement in $H/M_{15}$ and $H/M_{240}$ during 2 weeks with CRT when compared with 2 weeks without CRT, although there were no changes in washout rate.\(^\text{18}\) However, as opposed to our study, patients had already been treated with CRT since $\geq 6$ months (and were therefore less sick at baseline), and the 2-week periods may have been too short to show significant changes in washout rate.

A link between CRT response and effect on sympathetic innervation has previously been described by Najem et al.\(^\text{6}\)

Only patients who were clinical responders showed an acute increase in muscle sympathetic nerve activity when CRT was inactivated, whereas non-responders showed no change.

**Study limitations**

The main limitation of our study was the limited number of patients that was principally due to the high cost of $^{123}$I-MIBG (~2000 €/patient at our institution). Therefore, our study may have been underpowered to show differences in certain $^{123}$I-MIBG parameters between responders and non-responders. We only studied global $^{123}$I-MIBG uptake by planar images, and did not perform tomographic acquisitions to evaluate regional changes in innervation. However, the low uptake in $^{123}$I-MIBG in our patient population would have made it difficult to study regional changes by SPECT (which also has lower reproducibility than planar images).\(^\text{19}\) The $^{123}$I-MIBG scans and radionuclide angiograms were performed after device implantation. This may have mitigated changes in parameters at follow-up in patients with an acute response to CRT. Increase in doses of ACE-I/ARB and beta-blockers during follow-up may have interfered with $^{123}$I-MIBG uptake and confounded results, although there were no significant differences in $^{123}$I-MIBG parameters in patients with or without changes in drug dosage.

**Conclusions**

Our study shows for the first time that cardiac sympathetic nerve activity is reduced in responders to CRT, whereas non-responders do not show any significant changes. It may be speculated that the favourable effect of CRT on cardiac innervation may contribute to the improvement in outcome\(^\text{9}\) observed in patients responding to this treatment.

**Conflict of interest:** Haran Burri, MD, has served as a consultant and has been on the speaker’s bureau for Medtronic and Boston Scientific.

**Funding**

The study was funded by a research grant by Medtronic.

**References**


