Prognostic effect and modulation of cardiac sympathetic function in heart failure patients treated with cardiac resynchronization therapy

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Background. Cardiac autonomic dysfunction as assessed by ¹²³I-metaiodobenzylguanidine (¹²³I-mIBG) scintigraphy is associated with poor prognosis in heart failure (HF) patients. Although cardiac resynchronization therapy (CRT) has emerged as an effective therapy in improving outcomes on HF patients, its effect on cardiac sympathetic nervous function is still not fully understood. We aimed to study the value of pre-implantation ¹²³I-mIBG late heart-to-mediastinum ratio (HMR) as a predictor of response and outcomes after CRT and to correlate modification in this parameter with CRT response and functional improvement.

Methods and Results. BETTER-HF (Benefit of exercise training therapy and cardiac resynchronization in HF patients) is a prospective randomized clinical trial including HF patients submitted CRT (mean LVEF $24 \pm 8\%$, 74% NYHA class $\geq$ III) who underwent a clinical, echocardiographic, and scintigraphic assessment before and 6 months after CRT. One-hundred and twenty-one patients were included. Echocardiographic response was observed in 54% and composite outcome of cardiac mortality, cardiac transplant or heart failure hospitalization in 24% of patients. Baseline late HMR was an independent predictor of CRT response (regression coefficient 2.906, 95% CI 0.293-3.903, P .029) and outcomes (HR 0.066 95% CI 0.005-0.880, P .040). At follow-up, ¹²³I-mIBG imaging showed positive changes in cardiac sympathetic nerve activity only in responders to CRT (1.36 ± 0.14 prior vs. 1.42 ± 0.16 after CRT, P .039). There was a significant correlation between improvement in late HMR and improvement in peak oxygen consumption (r 0.547, P < .001).

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Conclusion. In our study, baseline cardiac denervation predicted response and clinical outcomes after CRT implantation. Cardiac sympathetic function was improved only in patients who responded to CRT and these positive changes were correlated with improvement in functional capacity. (J Nucl Cardiol 2020;27:283–90.)

Key Words: Heart failure • cardiac innervation • diagnostic and prognostic application

Abbreviations

HF	Heart failure
¹²³ I-mIBG	¹²³ I-metaiodobenzylguanidine
HMR	Heart-to-mediastinum ratio
CRT	Cardiac resynchronization therapy
LVEF	Left ventricular ejection fraction
LVESV	Left ventricle end-systolic volume
VO ₂	Oxygen consumption
BNP	Brain natriuretic peptide
Hs-CRP	High-sensitive C-reactive protein

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INTRODUCTION

Sympathetic activation is a key pathophysiological mechanism in chronic heart failure (HF).^{1,2} Specific cardiac sympathetic nerve activity can be assessed by ¹²³I-metaiodobenzylguanidine (¹²³I-mIBG) scintigraphy, since it shares the same presynaptic uptake, storage, and release mechanisms as norepinephrine, but is biologically inactive. The semi-quantified parameters of ¹²³I-mIBG myocardial uptake and washout, i.e., late heart-to-mediastinum ratio (HMR), were proven to be of prognostic value in HF patients.^{3,4}

In the last two decades, cardiac resynchronization therapy (CRT) has been shown to improve left ventricular ejection fraction (LVEF), reduce heart failure hospitalizations, and decrease all-cause mortality in patients with HF and electrical dyssynchrony.^{5–7} However, its effect on cardiac sympathetic nervous function is still not fully well known.

Our purpose was to investigate the value of baseline cardiac sympathetic activity, assessed by ¹²³I-mIBG late HMR, as a predictor of response and outcomes in HF patients undergoing CRT implantation. Additionally, we sought to correlate changes in ¹²³I-mIBG late HMR after device implantation with CRT response and functional improvement at 6-month follow-up.

METHODS

Study Design

BETTER-HF (NCT02413151) is a prospective cohort of consecutive patients with HF and reduced ejection fraction (HFrEF) submitted to cardiac resynchronization therapy (CRT) enrolled between April 2011 and February 2015 in a single centre. Heart failure patients in NYHA class III–IV with LV dysfunction (LVEF < 35%), QRS duration wider than 120

millisecond, and dyssynchrony, referred for CRT implantation were included. Patients who refused participation and who did not sign the informed consent were excluded.

The protocol of the study has been detailed in a prior publication.⁸ Patients were subjected to a baseline assessment before CRT, including clinical evaluation, blood analysis, and transthoracic echocardiogram and were reevaluated at 6 months after CRT. ¹²³I-mIBG scintigraphy was performed in all patients at baseline. When feasible due to distance of resident and costs, patients were submitted to ¹²³I-mIBG scintigraphy reevaluation at 6 months after enrolment.

All patients signed a written informed consent form before the performance of any procedure. The study was approved by the Institutional Review Board and Ethics Committee.

¹²³I-MIBG CARDIAC SCINTIGRAPHY ACQUISITION AND PROCESSING

¹²³I-mIBG scintigraphy was performed by obtaining planar images in an anterior projection using a single-headed Siemens e.Cam camera fitted with a low-energy high-resolution collimator. Counts were acquired for 240 seconds into a 128 x 128 pixel matrix 15 minutes (early) and 4 hours (late) after the intravenous injection of 185 MBq of ¹²³I-mIBG. The main energy window was centered to 15% of the 159-keV ¹²³I photo peak. No scatter correction was applied. Thyroid blockade with potassium iodide was performed > 30 minutes before ¹²³I-mIBG injection. Cardiovascular drugs, namely beta-blockers, were maintained at both acquisitions. Antidepressants were interrupted, whenever possible. Images were processed on a WS Siemens Syngo workstation.

Early and late heart-to-mediastinum ratio (HMR) values were calculated after measuring the mean count of ¹²³I-mIBG uptake per pixel in two separate visually drawn regions of interest: around the entire heart (H) and over the midline upper mediastinum to reflect the location with lowest activity (M). The washout rate was expressed as a percentage and calculated according to this formula: ((Early M-early H) – (late M-late H))/(early M-early H) * 100.

In order to confirm reproducibility of this imaging technique, all the scans were evaluated by two separate readers with the average value for each parameter taken for the main analysis.

Previous analysis of this population showed good inter-observer agreement of HMR, as measured by the

intraclass correlation coefficient, indicating good to excellent reproducibility.⁸

Echocardiographic Acquisition and Processing

A GE Vivid 9 ultrasound system was used to acquire parasternal long- and short-axis views, as well as apical two-, three-, and four-chamber views. Echocardiographic parameters, including left ventricle end-diastolic and end-systolic volumes and left ventricle ejection fraction, were determined according to the American Society of Echocardiography's recommendations.^{9,10}

Definitions

Echocardiographic response to CRT was defined as left ventricle end-systolic volume (LVESV) decrease $\geq 15\%$.¹¹ Composite outcome was defined as cardiac mortality, cardiac transplant or heart failure hospitalization. Functional capacity was assessed with cardiopulmonary exercise test and peak oxygen consumption (VO₂) was defined as the highest 30-second average value of VO₂ achieved during exercise.

Statistical Analysis

Data were expressed as mean $\pm$ standard deviation (SD) for continuous variables and as frequencies and percentages for categorical variables. Data distribution was tested for normality using the Kolmogorov-Smirnov test or Shapiro-Wilk as appropriate. Comparisons of baseline characteristics and response were performed using the Chi-square test or Fisher's exact test, when appropriate, for categorical variables, and the Student's *t* test or the Mann-Whitney test for continuous variables. Logistic regression analysis was used to identify predictors of CRT response, and Cox proportional hazards regression analysis was performed to identify predictors of composite endpoint. The relationship between the change in late HMR and the change in other variables was examined by the determination of standardized correlation coefficients. All the statistical tests were two-sided, and a *P* value $< .05$ was considered significant. The SPSS version 21 software (SPSS Inc., Chicago, IL) was used for computation.

RESULTS

Baseline Characteristics

The study included 121 patients, average age of 67 ± 11 years, the majority of whom were men (70.4%).

Baseline characteristics of the population are shown in Table 1. Most had non-ischemic cardiomyopathy (72.2%), suffered from severe HF (73.5% with NYHA class $\geq$ III), and had poor LV function (mean LVEF $24.2 \pm 6.7\%$).

Baseline Cardiac Sympathetic Innervation and CRT Response

Mean baseline late HMR was $1.38 (\pm 0.18)$, early HMR $1.47 (\pm 0.17)$, and wash out rate $49\% (\pm 18)$.

CRT response ($\geq 15\%$ reduction in LVESV) was observed in 53.7% of patients at 6-month follow-up. There were no significant differences regarding age, gender, NYHA class nor comorbidities in the two groups (Table 1).

In a multivariable analysis adjusting for age, gender, aetiology, and left bundle branch morphology, late HMR was an important independent predictor of response to CRT (regression coefficient 2.906, 95% CI 0.293-3.903, *P* .029).

Baseline Cardiac Sympathetic Innervation and Long-Term Outcome

During follow-up (mean 25.5 ± 12.9 months), composite endpoint was documented in 29 patients (24.4%), corresponding to 11.5% per year.

Univariate analysis identified baseline estimated glomerular filtration rate, serum levels of brain natriuretic peptide (BNP) and high-sensitive C-reactive protein (hs-CRP), smoking habits, electrical dyssynchrony and late HMR as predictors of composite endpoint (Table 2). Multivariate Cox proportional hazards regression analysis using these significant predictors showed that late HMR was an independent powerful determinant of composite outcome (HR 0.066, 95% CI 0.005-0.880, *P* .040).

Cardiac Sympathetic Innervation Changes, CRT Response, and Functional Improvement

Changes in different parameters induced by CRT are shown in Table 3. Significant improvement in NYHA class, LVEF, and LV end-systolic volume index were observed after CRT. ¹²³I-mIBG parameters at 6-month follow-up were available in 55 patients. When the entire cohort was analyzed, ¹²³I-mIBG parameters did not show any significant change at follow-up when compared to baseline. However, when the groups were analyzed separately according to response to CRT, only echocardiographic responders showed a significant increase in late HMR at follow-up when compared to baseline (1.36 ± 0.14 prior to CRT vs. 1.42 ± 0.16 six

Table 1. Baseline characteristics according to CRT response

Baseline characteristics	All patients n = 121	Responders n = 65	Non-responders n = 56	P
Age, years mean (SD)	67 (± 11)	68 (± 12)	63 (± 10)	.103
Male gender, n (%)	85 (70)	48 (73)	37 (67)	.538
Ischaemic aetiology, n (%)	34 (28)	18 (28)	16 (29)	.929
NYHA class ≥ III, n (%)	90 (74)	46 (71)	44 (79)	.581
Obesity, n (%)	34 (28)	20 (31)	14 (25)	.609
Hypertension, n (%)	105 (87)	57 (89)	48 (86)	.592
Dyslipidemia, n (%)	84 (69)	42 (64)	42 (75)	.176
Diabetes, n (%)	46 (38)	23 (35)	23 (41)	.495
History of smoking habits, n (%)	29 (25)	12 (19)	17 (30)	.198
Beta-blockers, n (%)	107 (89)	57 (88)	50 (89)	.917
ACE-I or ARA, n (%)	110 (91)	59 (91)	51 (91)	.875
Left bundle branch block, n (%)	86 (71)	45 (69)	41 (73)	.566
QRS duration, ms mean (SD)	145 (± 24)	145 (± 24)	142 (± 20)	.48
BNP, pg·mL ⁻¹ mean (SD)	490 (± 404)	515 (± 481)	480 (± 312)	.132
hs-CRP, mg·L ⁻¹ mean (SD)	3.2 (± 2.8)	2.0 (± 0.9)	4.4 (± 4.0)	.73
eGFR, mL·min ⁻¹ /1.73 m ² mean (SD)	78 (± 37)	77 (± 45)	80 (± 26)	.451
Peak VO ₂ , mL·kg ⁻¹ ·min ⁻¹ mean (SD)	14.8 (± 5.8)	14.4 (± 6.3)	15.2 (± 5.7)	.202
LVEF, % mean (SD)	24 (± 7)	24 (± 7)	24 (± 9)	.065
LVEDV index, mL·m ⁻² mean (SD)	127 (± 40)	129 (± 73)	122 (± 38)	.448
LVESV index, mL·m ⁻² mean (SD)	95 (± 36)	99 (± 39)	89 (± 33)	.895
Early HMR	1.47 (± 0.17)	1.48 (± 0.17)	1.46 (± 0.18)	.202
Late HMR	1.38 (± 0.18)	1.41 (± 0.14)	1.37 (± 0.16)	.047
Wash out rate (%)	49 (± 18)	50 (± 19)	47 (± 24)	.581

NYHA, New York Heart Association; ACE-I, angiotensin-converting enzyme inhibitors; ARA, angiotensin II receptor blockers; BNP, brain natriuretic peptide; hs-CRP, high-sensitivity C-reactive protein; eGFR, estimated glomerular filtration rate; peak VO₂, peak oxygen consumption; LVEF, left ventricular ejection fraction; LVEDV, LV end-diastolic volume; LVESV, LV end-systolic volume; HMR, heart-to-mediastinum ratio

months after CRT, *P* .039), whereas non-responders did not show significant differences. There were no significant changes in early HMR nor washout rate.

Baseline clinical variables were not predictors of late HMR modifications.

Pearson's correlation analysis was performed to analyze the association between late HMR changes and modifications in clinical, laboratory, echocardiographic variables (Table 4). There was a moderate significant correlation between improvement in late HMR and improvement in hs-CRP (*r* = 0.356, *P* .012) and in peak VO₂ at 6 months (*r* 0.547, *P* < .001, Figure 1).

DISCUSSION

The findings of the current study can be summarized as follows: (1) baseline late HMR could predict response and outcomes in HF patients undergoing CRT; (2) CRT responders improved cardiac sympathetic nerve

dysfunction, whereas non-responders did not show any significant changes and (3) after CRT there was a significant correlation between improvement in late HMR and improvement in peak VO₂.

Baseline Cardiac Denervation, CRT Response, and Outcomes

Adrenergic activation is recognized as an important factor in the pathogenesis and outcome of HF.^{12,13} In response to a deterioration of cardiac function, increased neuronal release of norepinephrine (NE) is accompanied by a decrease in presynaptic NE reuptake due to downregulation of the cardiac NE transporter. If continued, reactive desensitization of the myocardial beta-adrenergic receptors in the synaptic cleft develops and cardiac pump failure is further exacerbated. Cardiac ¹²³I-mIBG scintigraphy provides information on the

Table 2. Univariate and multivariate analysis of predictors of composite endpoint

Dependent variable	Univariable analysis		Multivariable analysis	
	HR (95% CI)	P	HR (95% CI)	P
Age	1.026 (0.992–1.061)	.132	-	
Female gender	0.297 (0.151–1.042)	.061	-	
Obesity	1.586 (0.645–3.901)	.315	-	
Diabetes mellitus	1.076 (0.498–2.325)	.853	-	
Hypertension	2.058 (0.879–4.819)	.107	-	
Dyslipidemia	0.773 (0.341–1.754)	.539	-	
History of smoking habits	0.429 (0.198–0.928)	.032	0.486 (0.199–1.189)	.114
Beta-blockers	3.318 (0.448–24.548)	.24	-	
ACE-I or ARA	1.000 (0.235–4.259)	.998	-	
NYHA class	0.871 (0.419–1.807)	.71	-	
LBBB and QRS $\geq$ 150 ms	0.830 (0.743–0.987)	.042	0.855 (0.621–1.256)	.367
BNP	1.001 (1.000–1.001)	< .001	1.000 (0.999–1.001)	.442
hs-CRP	1.020 (1.006–1.034)	.005	1.015 (0.998–1.031)	.081
eGFR	0.981 (0.967–0.994)	.006	0.983 (0.970–0.997)	.017
LVEF	0.989 (0.922–1.017)	.2	-	
LVEDV index	1.005 (0.996–1.015)	.255	-	
LVESV index	1.004 (0.993–1.015)	.517	-	
Early HMR	0.614 (0.016–1.654)	.125	-	
Late HMR	0.034 (0.003–0.420)	.008	0.066 (0.005–0.880)	.04
Wash out rate	1.019 (0.994–1.044)	.14	-	

HR, Hazards ratio; CI, confidence intervals; NYHA, New York Heart Association; ACE-I, angiotensin-converting enzyme inhibitors; ARA, angiotensin II receptor blockers; LBBB, left bundle branch block; BNP, brain natriuretic peptide; hs-CRP, high-sensitivity C-reactive protein; eGFR, estimated glomerular filtration rate; peak VO₂, peak oxygen consumption; LVEF, left ventricular ejection fraction; LVEDV, LV end-diastolic volume; LVESV, LV end-systolic volume; HMR, heart-to-mediastinum ratio

Table 3. Changes in clinical and functional parameter induced by CRT

	Pre	Post	P
NYHA class $\geq$ III (%)	73.8	13.5	< .001
BNP	490 ($\pm$ 404)	446 ($\pm$ 365)	.225
hs-CRP	3.2 ($\pm$ 2.8)	3.7 ($\pm$ 1.5)	.292
LVEF (%)	24 ($\pm$ 7)	37 $\pm$ 11	.001
LVEDV index	127 ($\pm$ 40)	106 ($\pm$ 43)	.01
LVESV index	95 ($\pm$ 36)	71 ($\pm$ 37)	< .001
Early HMR	1.47 ($\pm$ 0.17)	1.49 ($\pm$ 0.17)	.456
Late HMR	1.38 ($\pm$ 0.18)	1.41 ($\pm$ 0.19)	.159
Wash out rate (%)	49 ($\pm$ 18)	47 ($\pm$ 16)	.602

NYHA, New York Heart Association; BNP, brain natriuretic peptide; hs-CRP, high-sensitivity C-reactive protein; LVEF, left ventricular ejection fraction; LVEDV, LV end-diastolic volume; LVESV, LV end-systolic volume; HMR, heart-to-mediastinum ratio

function and integrity of presynaptic nerve endings, since it uses the same myocardial uptake and release mechanisms as norepinephrine.^{14,15}

Abnormal ¹²³I-mIBG uptake and washout have been shown to predict HF progression and death.¹⁶ The ADMIRE-HF trial (961 patients, LVEF $\leq$ 35%, and

Table 4. Correlation between late HMR changes and modifications in clinical, laboratory, echocardiographic variables

Dependent variable	Pearson correlation	
	<i>r</i>	<i>P</i>
NYHA class change	− 0.181	.244
BNP change	− 0.265	.103
Hs-CRP change	− 0.356	.012
eGFR change	− 0.063	.666
Peak VO ₂ change	0.547	< .001
LVEF change	0.074	.597
LVEDV index change	0.025	.865
LVESV index change	0.032	.825

NYHA, New York Heart Association; BNP, brain natriuretic peptide; *hs-CRP*, high-sensitivity C-reactive protein; *eGFR*, estimated glomerular filtration rate; *peak VO₂*, peak oxygen consumption; *LVEF*, left ventricular ejection fraction; *LVEDV*, LV end-diastolic volume; *LVESV*, LV end-systolic volume

Figure 1. Relationship between changes induced by CRT in peak oxygen consumption (VO₂) and late heart-to-mediastinum ratio (HMR) values.

NYHA class II-III) demonstrated that a higher late HMR was a strong independent predictor of prognosis.³ However, these data did not include patients after CRT implantation.

Some group reports have described an association between baseline ¹²³I-mIBG parameters and response to CRT. Nishioka et al¹⁷ demonstrated that late HMR and washout rate were associated with CRT clinical response

(improving to NYHA class I or II) in 30 chronic HF patients.

Cha et al¹⁸ demonstrated in 45 consecutive patients who received CRT (NYHA class II-III, mean LVEF 26 ± 5%) that baseline ¹²³I-mIBG parameters were associated with a greater LV reverse remodeling.

Our study with 121 patients also demonstrated that baseline late HMR was an independent predictor of response to CRT at 6-month follow-up. Additionally, we also found that baseline late HMR was an independent predictor of composite outcome in HF patients who implant CRT.

These results are in line with Curcio et al study¹⁹ (26 patients, mean LVEF 29 ± 4%), in which late HMR showed a good performance for prediction of HF repeated hospitalizations.

These results suggest that baseline ¹²³I-mIBG parameters may improve selection of patients to CRT implant.

Cardiac Denervation Changes, CRT Response, and Functional Capacity Improvement

Our results showed that, at 6-month after implantation, cardiac sympathetic denervation significantly improved in responders, whereas non-responders did not show significant changes.

Erol-Yilmaz et al²⁰ studied 13 patients and also reported a significant improvement in ¹²³I-mIBG parameters after 6-month follow-up, but the study did not analyze changes according to CRT response. Burri et al²¹ analyzed changes in ¹²³I-mIBG parameters according to response, defined as an increase of > 5% in LVEF and improvement in NYHA class by ≥ 1. In 8 of 13 patients who responded to CRT, washout rate significantly reduced and late HMR showed a statistically non-significant tendency to improve. In another study, Shinoahara et al²² defined response to CRT as a decrease in LVESV ≥ 15%, and non-ischemic HF patients who were responders (19 patients) showed a significant increase in late HMR, whereas non-responders did not. Washout rate did not change in either group.

In this same study,²² improvement in cardiac sympathetic nervous dysfunction was associated with reduction in systemic inflammation. We also demonstrated an association between improvement in hs-CRP and late HMR modification. Moreover, there was a significant correlation between improvement in late HMR and improvement in peak VO₂ because of CRT. This suggests that the alteration in cardiac adrenergic function may participate in the improvement in exercise tolerance conferred after CRT implantation. Results from previous studies²³⁻²⁵ proposed that the correlation between

increased sympathetic tone and exercise impairment is not restricted to sympathetic tone at the level of the peripheral muscle and the modification in cardiac sympathetic tone contributes to the observed changes in exercise tolerance. However, it is not possible to exclude that the explanation for the observed correlation between peak VO₂ and late HMR may be because both parameters have been related to disease severity and prognosis^{26,27} and the relation between the two thus represents two different parameters of the same phenomenon.

NEW KNOWLEDGE GAINED

This study highlights the potential role of cardiac autonomic dysfunction assessed by ¹²³I-mIBG imaging in CRT. Baseline late HMR was a predictor of response and clinical outcomes in HF patients undergoing CRT. Moreover, only CRT responders showed improvement in cardiac sympathetic nerve dysfunction and there was a significant correlation between changes in late HMR and modifications in peak VO₂ after CRT.

LIMITATIONS

¹²³I-mIBG scintigraphy results are highly dependent on acquisition and processing conditions, so this might preclude the extrapolation of this information to other settings, despite previous analysis of this population showed good to excellent reproducibility.⁸ Also, most of the subjects in the present study were treated with one or more drugs such as beta-blockers, angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers which may influence myocardial uptake of ¹²³I-mIBG. Another limitation may involve the fact that only planar images were used. Usually, the use of ¹²³I-mIBG tomographic images allows a better separation of the heart from other thoracic structures. However, available data show that it is difficult to reconstruct SPECT data when global ¹²³I-mIBG uptake is severely reduced, like in severely dilated cardiomyopathy.²⁸ Finally, the limited sample size makes analysis of the study less robust.

CONCLUSION

Baseline cardiac sympathetic nervous dysfunction assessed by ¹²³I-mIBG imaging predicted CRT response and outcomes in advanced HF patients. Cardiac autonomic positive modulation occurred only in patients who responded to CRT with significant reverse remodeling. This autonomic change correlated with objective increase in functional capacity.

These results may help deciding whose patients will respond to CRT in cases of doubt regarding decision of implantation.

Disclosures

Rita Ilhão Moreira, Ana Abreu, Guilherme Portugal, Luís Oliveira, Mário Oliveira, Inês Rodrigues, Madalena Coutinho Cruz, Pedro Silva Cunha, Vanessa Santos, Helena Santa Clara, Rui Cruz Ferreira, Miguel Mota Carmo have no conflicts of interest to declare.

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