ORIGINAL ARTICLE

Relationship of left ventricular global longitudinal strain with cardiac autonomic denervation as assessed by ^{123}I-*m*IBG scintigraphy in patients with heart failure with reduced ejection fraction submitted to cardiac resynchronization therapy

Assessment of cardiac autonomic denervation by GLS in patients with heart failure with reduced ejection fraction submitted to CRT

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Background. **Heart failure (HF) is associated with cardiac autonomic denervation (AD), which can be non-invasively assessed by ^{123}I-*meta*iodobenzylguanidine (^{123}I-*m*IBG) scintigraphy and has prognostic implications. We aimed to study the relationship between myocardial contractility assessed by global longitudinal strain (GLS) and AD assessed by ^{123}I-*m*IBG scintigraphy in advanced HF.**

Methods/Results. **BETTER-HF is a prospective randomized clinical trial including HF patients (pts) submitted to cardiac resynchronization therapy (CRT) who are submitted to a clinical, echocardiographic, and scintigraphic assessment before and 6 months after CRT. 81 pts were included. An echocardiographic response (absolute increase in left ventricular ejection fraction ≥ 10%) was observed in 73.7% of pts. A higher baseline late heart-to-mediastinum ratio (HMR) was associated with a better echocardiographic response. There was a significant association between late HMR and GLS at baseline and 6 months. At baseline, GLS had an**

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AUC of 0.715 for discrimination for a late HMR < 1.6. A GLS cut-off of − 9% maximized the likelihood of correctly classifying a pt as having severe AD (HMR < 1.6).

Conclusion. **Myocardial contractility as assessed by GLS is moderately correlated with AD as assessed by ^{123}I-*m*IBG scintigraphy and has a good discrimination for the identification of severe cardiac denervation. GLS may allow for a more readily accessible estimation of the degree of AD in advanced HF pts. (J Nucl Cardiol 2017)**

Key Words: Heart failure • *m*IBG imaging • diagnostic and prognostic application • left ventricular function

Abbreviations

^{123}I-*m*IBG	^{123}I-*meta*iodobenzylguanidine
CRT	Cardiac resynchronization therapy
GLS	Global longitudinal strain
HMR	Heart-to-mediastinum ratio
HFrEF	Heart failure with reduced ejection fraction
ICC	Intraclass correlation coefficient
LVEF	Left ventricular ejection fraction
WR	Washout rate

INTRODUCTION

Heart failure (HF) is a very prevalent clinical entity, affecting 1-12% of the adult population in developed countries[1] and ≥ 10% among individuals older than 70 years.[2] Despite recent improvements in treatments and their implementation in patients (pts) with HF with reduced ejection fraction (HFrEF), the mortality and hospitalization rate have remained high.[3]

Sympathetic nervous system overactivity is a hallmark of HF[4] and is initially beneficial as it intends to preserve cardiac output and other hemodynamic parameters. However, chronically elevated catecholamine levels dampen cardiovascular reflexes and downregulate adrenergic nerve terminals in the myocardium, thus promoting the desensitization of the heart to sympathetic stimulation.[5] This cardiac denervation contributes directly to disease progression and is related to a worse outcome.[6]

^{123}I-*meta*iodobenzylguanidine (^{123}I-*m*IBG) cardiac scintigraphy is an imaging method that uses a radioactive tracer, ^{123}I-*m*IBG, which binds to cardiac presynaptic adrenergic receptors and is not affected by intracellular metabolism thus permitting an in vivo assessment of cardiac autonomic innervation.[7] It is a safe method[8] that has been demonstrated to predict mortality and cardiac events independently of other prognostic markers,[9–11] stratify the risk of sudden cardiac death and ventricular arrhythmias[12–14], and assess response to medical[15–18] and device therapy.[19–23] It has been proposed to aid in the clinical management and assessment of prognosis of HF pts, but the fact that it is not easily accessible and the need for radiation exposure precludes its widespread use.

Quantification of the left ventricular ejection fraction (LVEF) by the modified biplane Simpson's rule has been historically used to stratify pts into the two categories of HF: preserved and reduced ejection fraction.[24] Recently, other parameters to determine left ventricular function have been developed. Global longitudinal strain (GLS) as assessed by speckle tracking measures left ventricular wall deformation and has proven to have added prognostic value over LVEF in the setting of HF.[25,26]

To overcome the shortcomings of ^{123}I-*m*IBG scintigraphy, we hypothesized that myocardial contractility would reflect local autonomic denervation (AD) and as such, would allow for estimation of cardiac autonomic dysfunction. Our aim was to study the relationship between myocardial contractility as assessed by GLS and autonomic dysfunction as assessed by ^{123}I-*m*IBG scintigraphy in pts with HFrEF.

METHODS

Study Design

BETTER-HF (NCT02413151) is a prospective, interventional, randomized, single center clinical trial of the effect of prolonged cardiac rehabilitation on autonomic function and clinical and echocardiographic response of pts with HFrEF submitted to cardiac resynchronization therapy (CRT).

One hundred and twenty-one adult (> 18 years) HFrEF pts referred for CRT were prospectively enrolled between April 2011 and February 2015. Pts were subjected to a baseline assessment before CRT, including clinical evaluation, blood analysis, and transthoracic echocardiogram and were reevaluated at 6 months after CRT. ^{123}I-*m*IBG scintigraphy was performed in all pts at baseline. Of these, 81 had baseline GLS measurement as part of the echocardiographic assessment. When feasible due to distance and cost of transportation, pts were submitted to ^{123}I-*m*IBG scintigraphy reevaluation at 6 months after enrollment (N = 55). Of these, 40 pts had GLS measurement at 6 months.

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

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 were determined according to the American Society of Echocardiography's recommendations.[24,27] Left atrial volume was assessed by the biplane method of disks. LVEF was measured using the biplane Simpson's method. Estimation of GLS was performed offline following acquisition of apical two-, three-, and four-chamber views, using a semi-automatic algorithm in the EchoPAC BT12 software, based on regional assessment of 18 segments, the mean of which was used to calculate GLS. The variability of GLS measurement in HFrEF pts has previously been assessed, showing good intra- and inter-observer reproducibility of this measurement.[28]

^{123}I-*m*IBG Cardiac Scintigraphy Acquisition and Processing

^{123}I-*m*IBG 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 × 128 pixel matrix 15 minutes (early) and 4 hours (late) after the intravenous injection of 185 MBq of ^{123}I-*m*IBG. The main energy window was centered to 15% of the 159-keV ^{123}I photopeak. No scatter correction was applied. Thyroid blockade with potassium iodide was performed > 30 minutes before ^{123}I-*m*IBG injection. Cardiovascular drugs, namely β-blockers, were maintained at both acquisitions. Antidepressants were interrupted, whenever possible, not to cause any interference. Images were processed on a WS Siemens Syngo workstation.

Early and late heart-to-mediastinum ratio (HMR) were calculated after measuring the mean count of ^{123}I-*m*IBG 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 (WR) was expressed as a percentage and calculated according to this formula:

$$((\text{Early M} - \text{early H}) - (\text{late M} - \text{late H}))/(\text{early M} - \text{early H}) * 100.$$

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.

Definitions

Echocardiographic response to CRT was defined as an absolute increase in LVEF of ≥ 10%.[29] Severe cardiac denervation was defined as a late HMR < 1.6.

Statistical Analysis

Continuous variables were expressed as mean and standard deviation when they followed a normal distribution, and as median and interquartile range otherwise. Qualitative variables were expressed as frequency and percentage. Comparison between continuous variables was performed with the non-parametric Wilcoxon signed-rank test and between qualitative variables with the χ^2 test. Inter-rater agreement of ^{123}I-*m*IBG scintigraphy was evaluated by the intraclass correlation coefficient (ICC). Intra-observer variability was not assessed in this population since the interpretation of the exam was only performed once by each reader. However, the intra-observer agreement regarding this imaging modality is known to be high in HF pts.[30] We employed logistic regression analysis to assess the impact of cardiac denervation as assessed by ^{123}I-*m*IBG scintigraphy on echocardiographic response to CRT as defined above (LVEF variation ≥ 10%). In addition, we tested for the interaction of baseline LVEF to control for its effect on response to CRT. The relation between scintigraphic and echocardiographic variables and AD at baseline and 6 months was explored with the use of the Pearson correlation coefficient. A subanalysis was performed to assess for a more significant correlation in the following pre-specified subgroups: LVEF < 25%, female gender, ischemic etiology, and age > 70 years. To analyze the discrimination of GLS for the detection of severe cardiac AD we performed a receiving-operator curve analysis for a pre-specified late heart-to-mediastinum cut-off value of 1.6. The optimum cut-off value for GLS was determined using the maximum likelihood ratio. A P value < 0.05 was considered statistically significant. All statistical analyses were performed using the software package STATA 12 (Statacorp).

RESULTS

Patient Characteristics

A total of 81 pts had available data on pre-implantation ^{123}I-*m*IBG scintigraphy and GLS and were included in this study. All pts were submitted to CRT as previously described. Mean age was 69.4 years (range 35-84 years). Pt characteristics are displayed in Table 1.

Planar Heart-to-Mediastinum Ratio

Mean HMR and WR were obtained for all pts on both early and late imaging for baseline assessment, and for a subset of 40 pts at 6 months follow-up. ICC for early HMR was 0.767 (95% CI 0.686-0.827, $P < 0.001$) and for late HMR 0.729 (95% CI 0.632-0.797, $P < 0.001$). The results for measurements of early HMR, late HMR, and WR are presented on Table 2. No significant difference was found between cardiac denervation at baseline and at 6 months follow-up (Wilcoxon signed-rank test, $P =$ NS). Regarding the association between baseline ^{123}I-*m*IBG parameters and CRT response, late HMR was the only scintigraphic parameter that predicted CRT response at 6 months (Figure 1, OR 11.6, 95% CI 1.17-114, $P = 0.036$); this

Table 1. Baseline characteristics

	Total population N = 81	Repeat imaging group N = 40
Age (years)	68.10 ± 12.94	65.81 ± 11.50
Male gender	55 (67.5)	31 (75.5)
Etiology		
Ischemic cardiomyopathy	23 (28.75)	14 (35.0)
Dilated cardiomyopathy	54 (67.5)	24 (5.0)
Valvular heart disease	3 (3.75)	2 (60.0)
NYHA functional class		
II	22 (25.75)	6 (15.0)
III	56 (70.0)	32 (80.0)
IV	2 (2.5)	2 (5.0)
Current smoking	14 (16.9)	5 (12.8)
Diabetes mellitus	35 (43.1)	18 (46.2)
Hypertension	70 (86.2)	34 (87.2)
Dyslipidemia	54 (67.2)	30 (76.9)
Obesity	24 (29.7)	10 (25.6)
Medication		
β-Blocker	71 (87.7)	35 (89.7)
ACEi or ARB	74 (90.9)	36 (92.3)
Diuretics	76 (93.8)	36 (92.3)
BNP (pg·mL)	574.78 ± 604.49	482.46 ± 411.95

No significant differences were seen between the two groups
ACEi, angiotensin converting enzyme inhibitor; *ARB*, angiotensin receptor blocker; *BNP*, brain natriuretic peptides; *NYHA*, New York Heart Association

result was independent of LVEF (P for interaction = NS). 54.3% of the pts with late HMR < 1.6 showed an echocardiographic response. No significant association was found between early HMR or WR and CRT response (P = NS for both).

Echocardiographic Measurements

Echocardiographic measurements are described in Table 3. Mean LVEF at baseline was 26.3%, with an increase ≥ 10% noted during follow-up in 46 pts (56.8%). We observed a significant improvement during the study period regarding LVEF, left ventricular end-systolic volume, mean E/e' ratio, and GLS ($P \leq 0.05$ for all).

Correlation Between Echocardiographic Parameters and Cardiac Denervation

Conventional echocardiographic measures including LVEF, E/A ratio, E/e' ratio, and tricuspid annular plane systolic excursion were not significantly correlated with any scintigraphic measures of cardiac denervation (P = NS for all). There was a significant association

Table 2. Early and late heart-to-mediastinum ratio and washout rate

Timing	Baseline N = 81	6 months FU N = 40	P values
Early HMR	1.53 ± 0.15	1.50 ± 0.16	0.07
Late HMR	1.43 ± 0.18	1.46 ± 0.15	0.33
Washout rate	45.68 ± 24.01	40.53 ± 20.29	0.71

FU, follow-up; *HMR*, heart-to-mediastinum ratio; *SD*, standard deviation

between late HMR and GLS, both at baseline (Coeff: $R - 0.282$, $P = 0.01$, Figure 2A) and at 6 months (Coeff: $R - 0.363$, $P = 0.021$, Figure 2B). No significant correlation was found between GLS and early HMR or WR (Table 4).

To investigate whether GLS could be more useful in assessing cardiac denervation in specific subsets of pts, we additionally performed correlation analysis for pre-specified subgroups. Performance of GLS in predicting

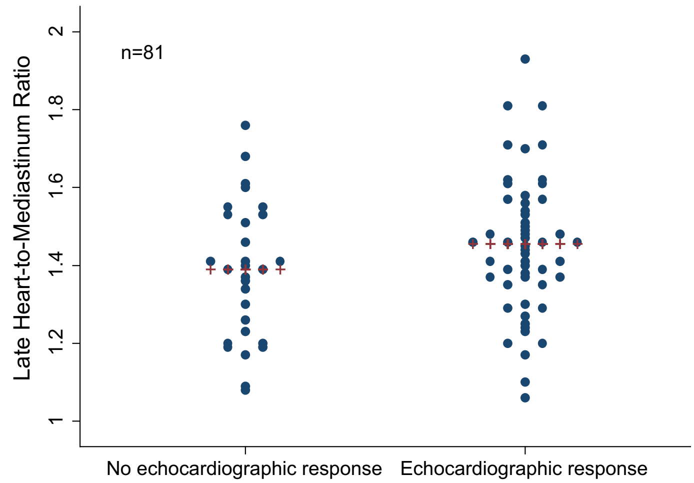

Figure 1. Association between late heart-to-mediastinum ratio and echocardiographic response. Echocardiographic response to cardiac resynchronization therapy (CRT) was defined as an absolute increase in left ventricular ejection fraction of ≥ 10%. Late heart-to-mediastinum ratio (HMR) was the only baseline scintigraphic parameter that predicted CRT response at 6 months (OR 11.6, 95% CI 1.17-114, *P* 0.036), with patients with no echocardiographic response having a lower late HMR at baseline (1.35 vs 1.44).

Table 3. Echocardiographic measurements

Timing	Baseline N = 81	6 months FU N = 81	*P* values
LVEF (%)	26.27 ± 7.09	38.48 ± 11.05	< 0.001
LVEDV (mL)	207.7 ± 63.8	203.0 ± 74.9	0.245
LVESV (mL)	159.2 ± 51.8	142.9 ± 62.5	< 0.001
Mean E/e' ratio	18.15 ± 11.17	14.93 ± 8.28	0.050
Left atrial volume (mL)	85.3 ± 46.2	80.2 ± 51.3	0.210
Global longitudinal strain	− 6.28 ± 3.28	− 8.20 ± 3.74	0.002
TAPSE (mm)	19.49 ± 6.01	19.64 ± 5.39	0.668
SPAP (mmHg)	40.6 ± 12.5	38.1 ± 11.2	0.064

FU, follow-up; *LVEDV*, left ventricular end-diastolic volume; *LVEF*, left ventricular ejection fraction; *LVESV*, left ventricular end-systolic volume; *SPAP*, systolic pulmonary artery pressure; *TAPSE*, tricuspid annular plane systolic excursion

cardiac denervation was better in pts with LVEF < 25% (Coeff: $R - 0.405$, $P = 0.019$), ischemic etiology (Coeff: $R - 0.413$, $P = 0.050$) and female gender (Coeff: $R - 0.426$, $P = 0.026$); age did not affect the association between GLS and late HMR.

Regarding the discrimination of GLS for the prespecified cut-off value of late HMR for cardiac denervation, GLS had an area under the curve of 0.721 (bootstrap) for discrimination of a late HMR < 1.6 on the baseline assessment (Figure 3). A GLS cut-off value of—9% maximized the likelihood of correctly classifying a pt as having severe cardiac denervation (likelihood ratio 2.83).

DISCUSSION

In our study we assessed the relationship between cardiac denervation as assessed by ^{123}I-*m*IBG cardiac scintigraphy and global cardiac deformation in advanced systolic HF pts submitted to CRT. The main findings of our study were: (1) cardiac denervation was prevalent in this high-risk population; (2) cardiac denervation predicted echocardiographic response at 6 months independently of LVEF; and (3) a significant correlation between the cardiac denervation and GLS at baseline and at 6 months.

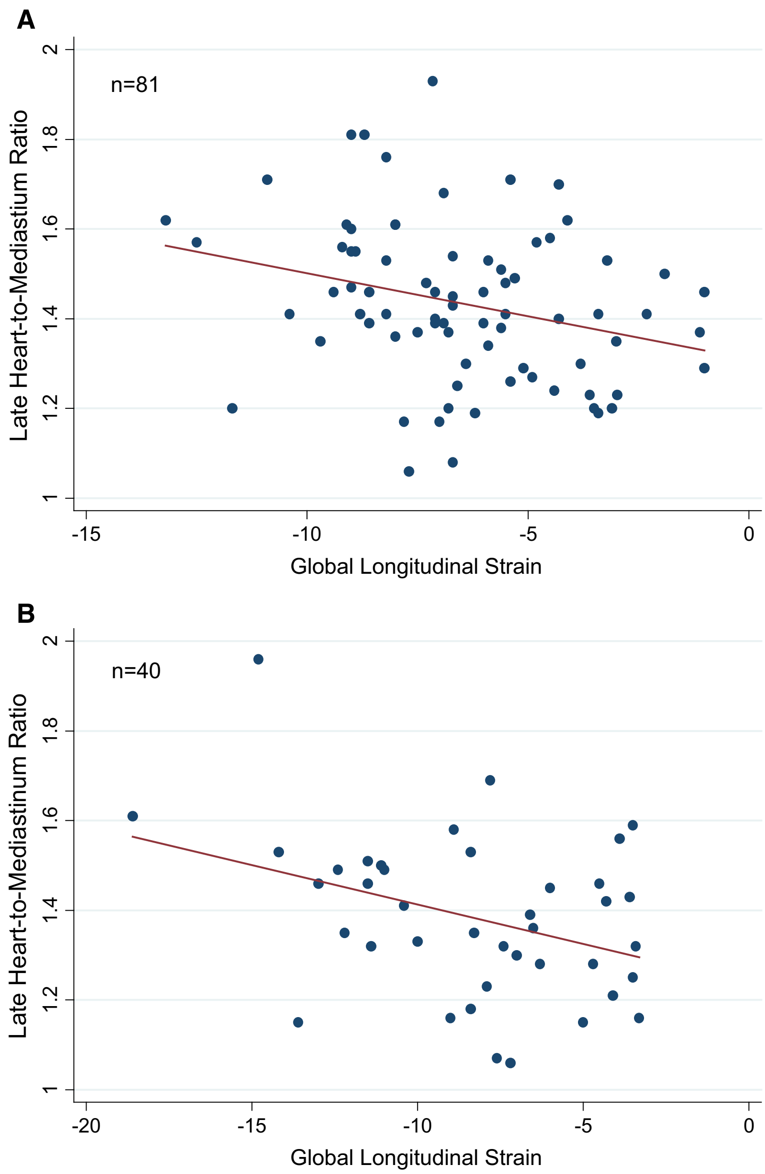

Figure 2. Correlation between late heart-to-mediastinum ratio and global longitudinal strain at baseline (**A**) and at 6-month follow-up (**B**). (**A**) A significant correlation between late heart-to-mediastinum ratio and global longitudinal strain at baseline was seen using the Pearson's correlation coefficient ($R - 0.282$, P 0.010). (**B**) A significant correlation between late heart-to-mediastinum ratio and global longitudinal strain at 6 months was seen using the Pearson's correlation coefficient ($R - 0.363$, P 0.021).

Cardiac Denervation in Advanced Systolic Heart Failure

HF is characterized by changes in myocardial sympathetic activity, which serves initially as a favorable compensatory mechanisms but ultimately leads to deleterious neurohormonal and myocardial structural alterations and increase the likelihood of arrhythmias or cardiac death.[31]

Previous studies have assessed the prevalence of cardiac denervation in advanced HF.[12,32] Multiple methodologies may be employed in the estimation of degree of cardiac denervation, either evaluating global cardiac autonomic function such as the HMR, the WR,

Table 4. Correlation between baseline echocardiographic parameters and cardiac denervation

	N = 81					
	Early HMR	***P* values**	**Late HMR**	***P* values**	**Washout rate**	***P* values**
GLS	− 0.136	0.225	− 0.282	0.011	0.166	0.139
LVEF	− 0.032	0.778	0.038	0.734	− 0.016	0.885
E/A ratio	− 0.099	0.466	− 0.025	0.857	− 0.020	0.883
E/e' ratio	0.043	0.752	0.078	0.566	− 0.056	0.682
TAPSE	0.106	0.373	0.164	0.166	0.041	0.729

GLS, global longitudinal strain; *HMR*, heart-to-mediastinum ratio; *LVEF*, left ventricular ejection fraction; *TAPSE*, tricuspid annular plane systolic excursion

or single photon emission computed tomography (SPECT)-derived regional measures such as the defect score.[13] Of note, all have been correlated to non-invasive measures of autonomic activity.[33,34]

The inter-observer agreement of HMR in our population, as measured by the ICC, indicated good to excellent reproducibility.[35]

Prognostic Value of ^{123}I-*m*IBG Scintigraphy in Advanced Heart Failure

There are several studies linking cardiac autonomic function to prognosis in advanced systolic HF pts; extensive data report on the association between measures of cardiac denervation and arrhythmic events in ICD recipients.[12,13,36,37] In addition, the landmark ADMIRE-HF trial[10] included 961 pts with LVEF $\leq$ 35% and NYHA class II or III and assessed the relationship between scintigraphic measures of cardiac denervation and HF progression, arrhythmic events, and cardiac death. A late HMR higher than 1.60 was associated with a hazard ratio of 0.49, 0.37, and 0.14, respectively. A subanalysis of the trial reinforced the prognostic value regarding arrhythmic events.[38]

^{123}I-*m*IBG scintigraphy has also been employed in the assessment of pts submitted to CRT. Data from several groups report an association between cardiac denervation and response to CRT.[19,21,22] In similarity, we also found that late HMR predicted echocardiographic response to CRT.

Response to CRT is determined by the interaction of a number of cofactors besides cardiac denervation, such as gender, type of cardiomyopathy, sinus rhythm, QRS morphology and duration, medical comorbidities, hemodynamic abnormalities, and abnormalities of left ventricle substrate.[39,40] As such, no parameter can solely account for the ability of one pt to respond to CRT and this explains the proportion of pts with cardiac denervation and an adequate echocardiographic response reported our study.

Relationship Between Cardiac Denervation and Global Longitudinal Strain

Speckle tracking is a recent technique based on 2D ultrasound acquisition, allowing for the calculation of segmental and global wall strain, and has been validated against sonomicrometry and magnetic resonance imaging.[41,42] GLS has previously been linked to prognosis both in pts with preserved[43] and reduced LV ejection fraction.[44]

We hypothesized that local myocardial deformation as assessed by 2D longitudinal strain would reflect regional autonomic activity, and as such GLS could act as a surrogate for cardiac autonomic dysfunction. The issue of GLS and its relationship to cardiac denervation has been previously assessed by Bulten et al, who also found a significant correlation between GLS and late HMR in 59 breast cancer pts who had undergone anthracycline chemotherapy.[45] However, these pts mostly had preserved LVEF (56 out of 59), and mean late HMR was 2.72 suggesting a low prevalence of cardiac denervation in this population. Our results extend this relationship to the spectrum of pts with reduced left ventricular systolic function and severely impaired cardiac autonomic function. Curiously, the magnitude of this correlation was similar between studies (− 0.23 vs − 0.282), suggesting a consistent relationship between myocardial deformation and local autonomic function. This correlation also remained at follow-up after CRT, further reinforcing the value of GLS in assessing autonomic function.

We found that the relationship between late HMR and GLS was consistent throughout our cohort; notwithstanding, GLS was more accurate in identifying severe cardiac denervation in pts with an ischemic etiology or with severely depressed LVEF, two subsets of pts which have been previously linked to less response to CRT. GLS may therefore help individualize decision making in this particular population.

The moderate correlation between GLS and late HMR[46] can be explained by the fact that ^{123}I-*m*IBG

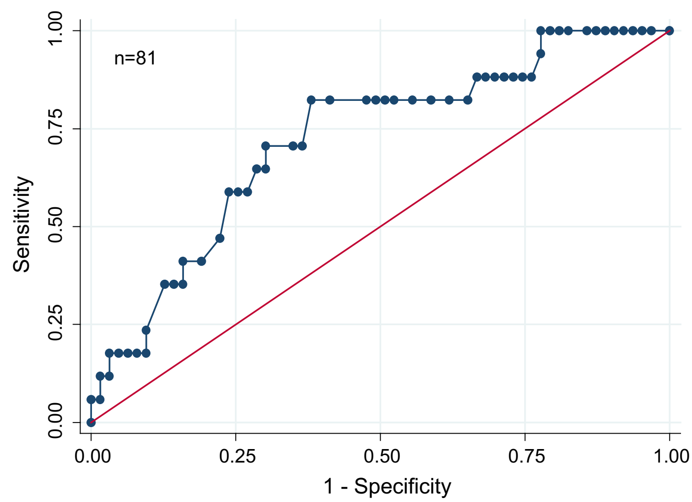

Figure 3. Receiver operating curve of global longitudinal strain for a late heart-to-mediastinum cut-off value of 1.6. Global longitudinal strain (GLS) showed a good discrimination (area under the receiver operating curve of 0.721) for a pre-specified late heart-to-mediastinum ratio cut-off value of 1.6. A GLS cut-off value of − 9% maximized the likelihood of correctly classifying a patient as having severe cardiac denervation (likelihood ratio 2.83).

cardiac uptake can be influenced by many factors, such as maintenance of β-blockers during imaging,[8] acquisition and processing conditions, such as type and brand of collimator, background correction, acquisition duration and timing, injected dose of ^{123}I-*m*IBG, energy window and ROI settings,[47,48] pt characteristics, like age and gender,[49–51] and heart disease type and stage (NYHA class and LVEF).[49,52] Even though this precludes these two variables from being interchangeable, there is a significant clinical relevance to this association, since GLS analysis is easily accessible and prevents exposure to radiation, unlike ^{123}I-*m*IBG scintigraphy. Furthermore, the ROC curve analysis supports the hypothesis that GLS can be used to discriminate pts with severe cardiac denervation and who will therefore follow a more complicated clinical course.[10]

Limitations

As this study was not powered to detect a difference in major events at follow-up, we cannot establish a relationship between late HMR or GLS and adverse events. However, as previously reported, there is ample published data on the prognostic value of different scintigraphic parameters of autonomic function, particularly late HMR.

Estimation of GLS was performed using a brand-specific algorithm for speckle tracking. Therefore, we cannot extrapolate our findings for other brands, as mean calculated GLS values differ significantly between vendors.[24]

Despite the finding that the performance of GLS in predicting cardiac denervation was better in pts with very severe left ventricular dysfunction, ischemic heart disease, and female pts and even though this subgroup analysis was predefined, this study was not formally powered to detect a significant interaction between subgroups. However, these findings may be considered as hypothesis-generating requiring further studies to be confirmed.

^{123}I-*m*IBG scintigraphy results are highly dependent on pt and disease characteristics, medication and acquisition and processing conditions, as previously explained. This might preclude the extrapolation of this information to other settings and may need further confirmation in order for these results to be generalized.

Although SPECT acquisitions were not performed, these could conceivably lead to a more accurate assessment of regional autonomic function and its relation to segmental strain analysis. However, available data show that it is difficult to reconstruct SPECT data when global ^{123}I-*m*IBG uptake is severely reduced; in addition, this technique is associated to underestimation of ^{123}I-*m*IBG uptake in the inferior and apical wall.[53]

CONCLUSION

In conclusion, in our population of pts with advanced HFrEF referred for CRT, GLS was moderately correlated with the extent of cardiac denervation as assessed by ^{123}I-*m*IBG scintigraphy and had a good discrimination for the identification of severe cardiac denervation. As such, GLS, may allow for a more readily accessible estimation of the degree of autonomic dysfunction in advanced HF pts. These findings may have future implications in the screening of CRT recipients.

NEW KNOWLEDGE GAINED

HF is a very prevalent clinical entity with a high hospitalization and mortality rate, characterized by cardiac AD. The most reliable method to assess cardiac denervation is ^{123}I-*m*IBG scintigraphy, which is able to predict mortality and cardiac events, stratify the risk of sudden cardiac death and ventricular arrhythmias, and assess response to medical and device therapy. However, it is not readily accessible and the need for radiation exposure precludes its widespread use. GLS has gained popularity in the assessment of myocardial contractility and this paper introduces its relationship to cardiac AD. It could be used to identify pts with severe cardiac denervation, as it is easy to use and widely accessible.

Future directions of research are:

(1) To validate the relationship of GLS and scintigraphic parameters for other brands of GLS.
(2) To validate the relationship of GLS and scintigraphic parameters for other acquisition and processing conditions of ^{123}I-*m*IBG scintigraphy.
(3) To investigate the association between cardiac denervation as assessed by SPECT and GLS.
(4) To detect an association between cardiac denervation as assessed by GLS and adverse events.

Disclosure

Madalena C. Cruz, Ana Abreu, Guilherme Portugal, Helena Santa-Clara, Pedro S. Cunha, Mario M. Oliveira, Vanessa Santos, Luís Oliveira, Pedro Rio, Inês Rodrigues, Luís A. Morais, Rui C. Ferreira, and Miguel. M. Carmo have no conflicts of interest to declare.

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