Original Article

Impact of obesity and acquisition protocol on ^{123}I-metaiodobenzylguanidine indexes of cardiac sympathetic innervation

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Background: This study was designed to assess the impact of obesity and acquisition protocol on ^{123}I-metaiodobenzylguanidine (MIBG) indexes of cardiac sympathetic innervation.

Methods: Forty-five patients with heart failure (HF) (38 men, age 58±15 years) underwent ^{123}I-MIBG cardiac imaging. Of these patients, 10 were obese [body mass index (BMI) ≥30 kg/m^2]. Ten-minute planar images of the thorax in anterior view were performed 15 minutes (“early” image) and 3 hours and 50 minutes (“late” image) after tracer administration in both supine- and prone-position. Early and late ^{123}I-MIBG heart-to-mediastinum (H/M) ratios and washout rate were computed.

Results: In overall study population, early and late ^{123}I-MIBG H/M ratios and washout rate were comparable between supine- and prone-position acquisitions. Obese patients had a lower early and late ^{123}I-MIBG H/M ratios both in supine ($P<0.01$) and prone ($P<0.05$) positions compared to non-obese subjects.

Conclusions: Our results indicate that in HF patients, obesity has a significant impact on ^{123}I-MIBG indexes of cardiac sympathetic innervation. Prone-position did not change early and late ^{123}I-MIBG H/M ratios and washout rate compared to supine position both in obese and non-obese HF patients.

Keywords: Metaiodobenzylguanidine cardiac imaging (MIBG cardiac imaging); obesity; prone-position acquisition; heart-to-mediastinum ratios (H/M ratios); washout rate

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Introduction

Patients with heart failure (HF) show augmented activation of the sympathetic nervous system, as reflected by an increase in plasma norepinephrine levels. In addition, neuronal uptake of norepinephrine is impaired in the failing myocardium. Both the enhanced release of norepinephrine and changes in its cardiac neuronal uptake may be responsible for the observed down-regulation of adrenoreceptors in HF (1). Myocardial innervation imaging with ^{123}I-metaiodobenzylguanidine (MIBG) scintigraphy provides a noninvasive tool for the investigation of cardiac sympathetic innervation. Increased norepinephrine turnover and pre-synaptic norepinephrine deficits can be identified by a decreased ^{123}I-MIBG activity quantified as the heart-to-mediastinum (H/M) ratio and an increased ^{123}I-MIBG washout rate from the heart (1,2). Normal cardiac ^{123}I-MIBG distribution includes a relatively low uptake in the inferior wall and extra-cardiac uptake in the liver and lungs may impact image quality and interpretation (3,4). The acquisition of images in prone position might improve the relative tracer uptake in the inferior wall, reducing diaphragmatic attenuation and limiting the liver overlap (5). Also obesity is reported to be associated with sympathetic activation (6-8). Thus, we investigated the relationship between obesity and ^{123}I-MIBG indexes of cardiac sympathetic innervation and if the acquisition protocol influences the results.

Materials and methods

Study population

Forty-five patients with HF referred to our Department for cardiac sympathetic imaging were included in the present study. All subjects underwent a complete clinical examination and blood draw for routine biochemical determinations. Demographic data, weight, height, HF medications, New York Heart Association (NYHA) class, tobacco use, hypertension, dyslipidemia, family history of coronary events, presence of diabetes mellitus, presence of co-morbidities, and ischemic versus non-ischemic HF etiology were also collected. The body mass index (BMI) was calculated as weight in kg/height in m^2. Obesity was defined as BMI value ≥30 kg/m^2 (9). Informed consent, a requirement of the protocol approved by the Institutional Clinical Research Subpanel on Human Studies at our Institute, was obtained in all patients.

^{123}I-MIBG cardiac imaging

All patients underwent ^{123}I-MIBG cardiac imaging according to the recommendations of the Cardiovascular Committee of the European Association of Nuclear Medicine and the European Council of Nuclear Cardiology (10), as previously described in detail (11). An activity of 111 MBq ^{123}I-MIBG was intravenously administered over 1 to 2 min after thyroid blockade by oral administration of 300 mg of potassium perchlorate. Ten-minute planar images of the thorax in standard anterior view (256×256 matrix) were performed 15 minutes ("early" image) and 3 hours and 50 minutes ("late" image) after tracer administration in both supine and prone positions. Imaging was performed using a dual-head camera system (Skylight, Philips) equipped with a low energy, parallel-hole, high-resolution collimator, and the camera peaked at 159 keV with a symmetrical 20% energy window. The H/M ratio was computed from supine and prone images by dividing the mean counts per pixel within the myocardium by the mean counts per pixel within the mediastinum. Using dedicated post-processing software on a dedicated workstation (Philips), the cardiac region of interest (ROI) was polygonal in shape and drawn manually over the myocardium including the LV cavity on the MIBG images. Care was taken to exclude lung and liver from the myocardial ROI. The mediastinal ROI with a square shape was placed on the upper half of the mediastinum and had a size of 7×7 pixels. The location of the mediastinal ROI was determined using as landmarks the lung apex, the upper cardiac border and the medial contours of the lungs.

Image quantification

For both supine- and prone-position acquisition protocols, ^{123}I-MIBG H/M ratios were computed for early and late imaging by dividing the mean counts per pixel within the myocardium by the mean counts per pixel within the mediastinum. The ^{123}I-MIBG washout rate was calculated for both acquisition protocols using the following formula: [(early heart counts per pixel – early mediastinum counts per pixel) – (late heart counts per pixel decay-corrected – late mediastinum counts per pixel decay corrected)]/(early heart counts per pixel – early mediastinum counts per pixel)×100. Using the mean relative uptake, the inferior to anterior uptake ratios were also calculated on early and late images for both acquisition protocols.

Statistical analysis

Continuous variables are expressed as mean ± standard deviation and categorical data as percentage. Continuous data were compared by paired or unpaired *t* test and categorical data by Fisher's exact test, as appropriate. Multiple linear regression analysis was used to evaluate clinical parameters influencing late H/M ratio. A P value <0.05 (two sided) was considered statistically significant. Statistical analysis was performed with SPSS version 19.0 (SPSS, Inc., Chicago, Illinois, USA).

Results

A total of 45 patients (35 men, age 58±15 years) were included in the study. The clinical characteristics of the patient population are shown in *Table 1*. The etiology of HF was ischemic in 42% of study population. Twenty-seven patients were in NYHA class II and 10 in NYHA class III. Mean LV ejection fraction was 41%±15% and BMI was 27±4.1 kg/m^2. The BMI was <30 kg/m^2 in 35 patients

Table 1 Clinical characteristics of the study population

Characteristic	All patients (n=45)	Non-obese (n=35)	Obese (n=10)	P value
Age (years)	58±15	58±16	58±12	0.98
Male gender, n [%]	35 [78]	26 [74]	9 [90]	0.41
Diabetes, n [%]	14 [31]	10 [29]	4 [40]	0.70
Ischemic cardiomyopathy, n [%]	19 [42]	12 [34]	7 [70]	0.07
Hypertension, n [%]	30 [67]	22 [63]	8 [80]	0.45
Dyslipidemia, n [%]	27 [60]	19 [54]	8 [80]	0.27
Smoking, n [%]	25 [55]	21 [60]	4 [40]	0.30
Familiar history of CAD, n [%]	25 [55]	18 [51]	7 [70]	0.47
New York Heart Association class				0.18
I, n [%]	8 [18]	8 [23]	0 [0]	
II, n [%]	27 [60]	21 [60]	6 [60]	
III, n [%]	10 [22]	6 [17]	4 [17]	
Left ventricular ejection fraction [%]	41±15	43±15	35±14	0.16

Data are expressed as mean ± SD or as number (%). CAD, coronary artery disease.

Table 2 ^{123}I-MIBG imaging data in overall study patients

Parameter	Supine position	Prone position	P value
Early H/M ratio	1.8±0.3	1.9±0.3	0.3
Late H/M ratio	1.7±0.4	1.7±0.3	0.8
Washout rate (%)	35±18	35±16	0.9
Early inferior/anterior ratio	0.96±0.12	1.01±0.07	<0.05
Late inferior/anterior ratio	0.99±0.15	1.01±0.08	0.2

Data are expressed as mean ± SD. MIBG, metaiodobenzylguanidine; H/M, heart-to-mediastinum.

and ≥30 kg/m^2 in 10 patients. No significant differences in clinical characteristics and in HF medications were detectable between non-obese and obese patients. At multiple linear regression analysis, among clinical variables only BMI (r=–0.03, P<0.05) and LV ejection fraction (r=0.01, P<0.05) were independently related to late H/M ratio.

^{123}I-MIBG imaging findings

^{123}I-MIBG results of the whole study population are reported in *Table 2*. As shown, early and late ^{123}I-MIBG H/M ratios, and washout rate were comparable between supine- and prone-position acquisitions. Inferior/anterior uptake ratio in the supine position was significantly lower as compared to prone position on early images (P<0.05). Conversely, inferior/anterior uptake ratio was not different between the two acquisition protocols.

Impact of obesity on indexes of myocardial innervation

Early and late ^{123}I-MIBG H/M ratios in non-obese and obese patients are depicted in *Figure 1*. In both subgroups, early and late H/M ratios were comparable between supine and prone positions. Of note, obese patients had lower H/M ratios both in supine (early 1.68±0.13 *vs.* 1.90±0.32 and late 1.46±0.23 *vs.* 1.80±0.36, both P<0.01) and prone (early 1.75±0.18 *vs.* 1.96±0.36, P<0.05 and late 1.45±0.17 *vs.* 1.81±0.35, P<0.01) positions as compared to non-obese subjects. The washout rate (*Figure 2*) was higher in obese as compared to non-obese patients in prone position only (48.7±16 *vs.* 30.8±14, P<0.01). Finally, the early inferior/anterior uptake ratio (*Figure 3*) in obese patients was lower in supine as compared to prone position (0.92±0.10 *vs.* 1.01±0.08, P<0.05). To avoid potential gender differences and influence of possible attenuation artifacts, a separate analysis was performed including only men. Obese men had

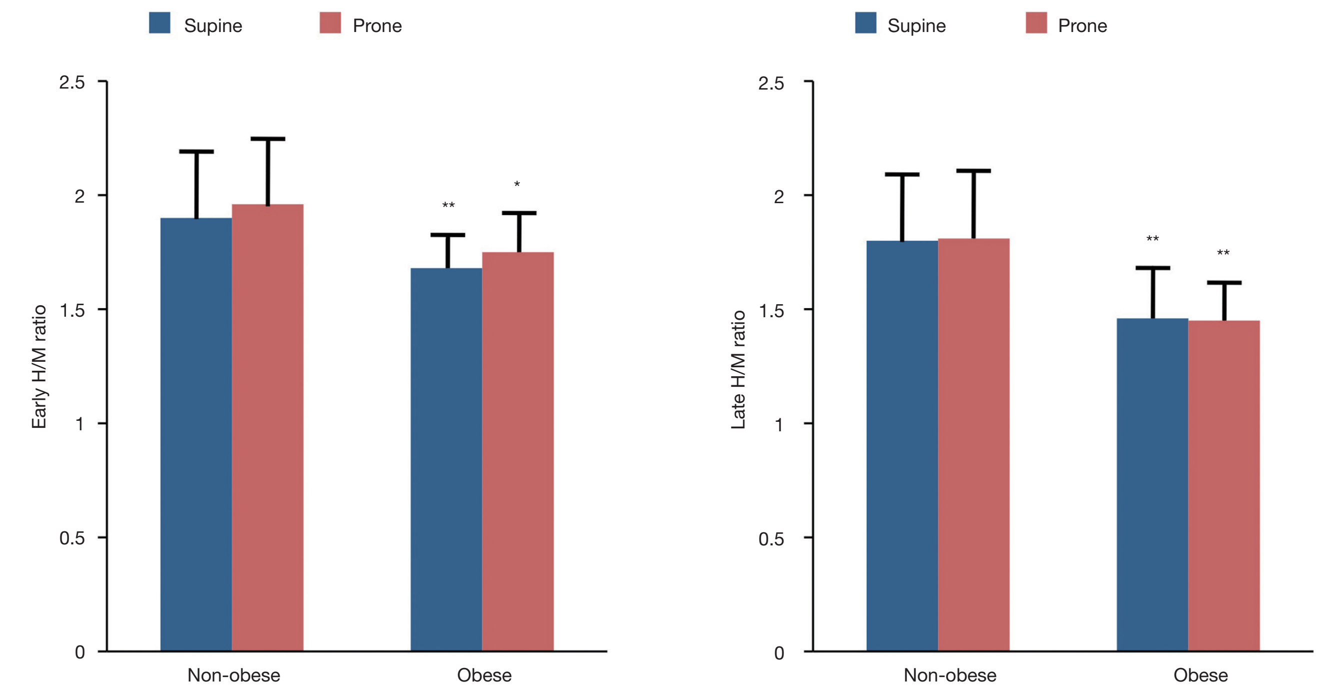

Figure 1 Mean values of early and late H/M ratios in non-obese and obese patients in supine- and prone-position acquisitions. Early and late H/M ratios were significantly reduced in obese compared to non-obese. In both subgroups, early and late H/M ratios were comparable between the two acquisition protocols. *, P<0.05; and **, P<0.01 *vs.* non-obese. H/M, heart-to-mediastinum.

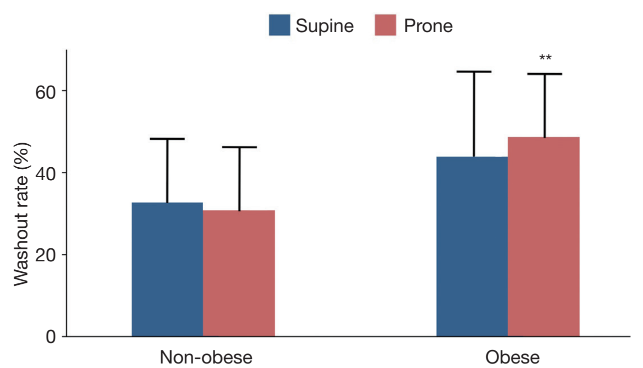

Figure 2 Mean values of washout rate in non-obese and obese patients in supine- and prone-position acquisitions. In obese, the washout rate was significantly higher compared to non-obese in prone position. In both subgroups, washout rate was comparable between the two acquisition protocols. **, P<0.01 *vs.* non-obese.

lower late H/M ratio both in supine (1.41±0.17 *vs.* 1.68±0.30, P<0.01) and prone (1.41±0.13 *vs.* 1.69±0.24, P<0.005) positions compared to non-obese. The washout rate was higher in obese men compared to non-obese in both supine (48.6±15 *vs.* 34.4±17, P<0.05) and prone position (52.3±12 *vs.* 32.8±14, P<0.001).

Discussion

Currently ^{123}I-MIBG is the most widely used tracer for assessing sympathetic nervous function in HF patients and has been also used for risk stratification. Because of the suboptimal ^{123}I-MIBG image quality with single-photon emission computed tomography (SPECT), most of studies have used as a prognostic marker global left ventricular ^{123}I-MIBG uptake H/M ratio calculated on planar supine images. It has been showed that ^{11}C-hydroxyephedrine (HED) positron emission tomography (PET) produces consistently better image quality than MIBG SPECT (4). Furthermore, late MIBG SPECT overestimates the defect area particularly in the inferior and septal regions as compared with ^{11}C-HED PET (4). New multimodality imaging systems, such as SPECT/CT, bring together anatomical and molecular information and provide a means to correct for attenuation effect (12). It has been recently demonstrated that cardiac ^{123}I-MIBG counts can be measured on the tomographic slices within the boundaries of the heart delineated by the CT component

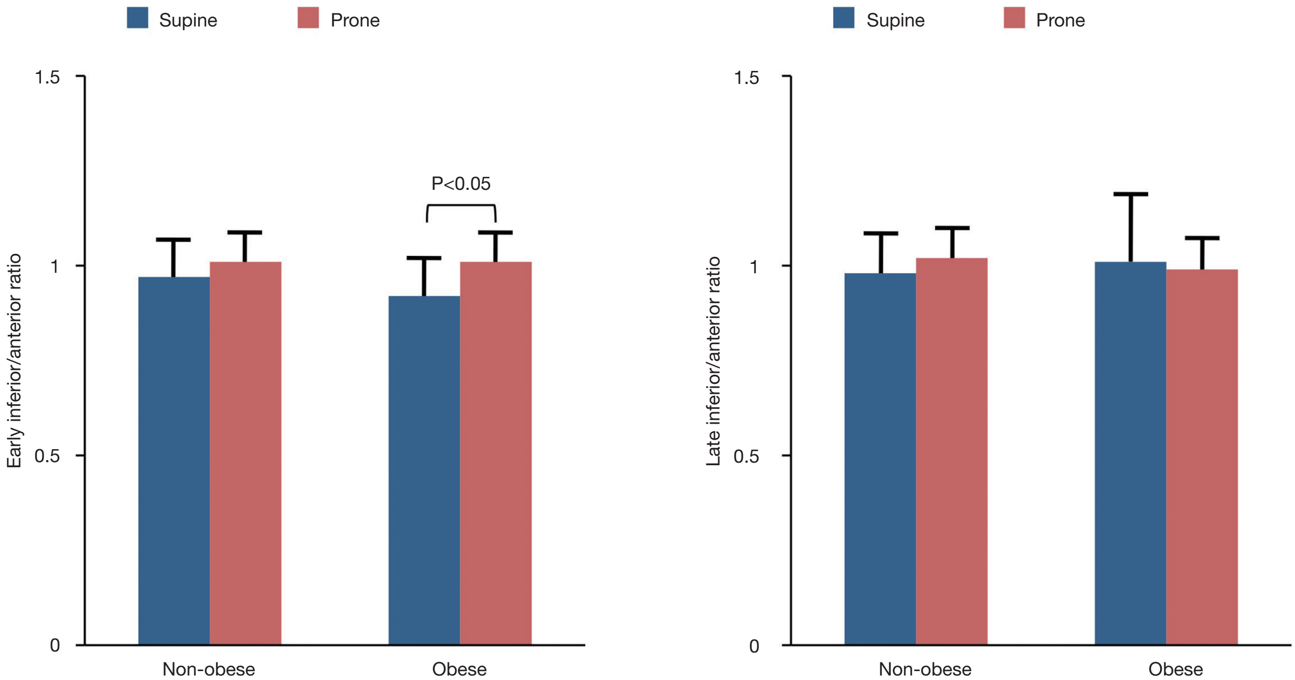

Figure 3 Mean values of early and late inferior/anterior uptake ratios in non-obese and obese patients in supine- and prone-position acquisitions. No differences were observed between non-obese and obese in both supine and prone positions. In obese, the early inferior/anterior uptake ratio was lower in supine compared to prone position (P<0.05).

even in cases in which tracer uptake is very low (13). If confirmed by further studies cardiac ^{123}I-MIBG SPECT/CT may represent an accurate tool for early diagnosis and monitoring response to treatment in patients with HF.

Several studies have indicated that ^{123}I-MIBG cardiac uptake is reduced in the inferior region also in normal subjects, mainly due to the extra-cardiac uptake by the liver and lungs (3,4,14). Thus, obesity as well as diaphragmatic attenuation, which may occur also for technical reasons, might cause a reduced uptake in the inferior region. Previous studies have demonstrated that regional sympathetic abnormalities assessed by SPECT (15,16) or PET (17) can identify myocardial regions that may be linked to lethal ventricular arrhythmias. The critical issue in the measurement of regional abnormalities on the SPECT is the image quality. Therefore, regional analysis is suitable only if image quality is acceptable. Matsunari *et al.* (4) reported that the quality of ^{11}C-HED PET images is more suitable for assessment of regional abnormalities than ^{123}I-MIBG SPECT. However, the authors showed a good correlation between late ^{123}I-MIBG H/M ratio and ^{11}C-HED retention. These findings support the use of semi-quantitative H/M ratio data to estimate cardiac sympathetic innervation. Yoshinaga *et al.* (5) more recently investigated whether prone-position acquisition improves ^{123}I-MIBG image quality in subjects with a BMI <30 kg/m^2 by comparing the results to those obtained using supine-position acquisition and high-quality ^{11}C-HED PET/CT. The authors showed that prone ^{123}I-MIBG SPECT significantly reduced heterogeneity of tracer uptake and improved inferior activity in comparison with supine imaging, providing data closer to those obtained with ^{11}C-HED PET. The improvement in inferior uptake may be related to reducing diaphragmatic attenuation and avoiding intense uptake by the liver.

The results of our study, using ^{123}I-MIBG planar scintigraphy, show that the prone-position acquisition did not significantly change H/M ratios and washout rate compared to the standard supine position. Nevertheless, the inferior to anterior uptake ratio on prone imaging increased in early images whereas in late imaging there was no difference compared to supine acquisition. In our study, 10 patients had a BMI ≥30 kg/m^2. Noteworthy, obese patients had significantly reduced early and late ^{123}I-MIBG H/M ratios both in supine and prone positions compared to non-obese subjects. These results are in agreement with those of a previous investigation demonstrating that mean H/M ratio progressively decreased with increasing BMI (18). However, also in obese subjects there were no significant differences in early and late H/M ratios and in washout rate between supine- and prone-position acquisitions. These findings suggest that the derangement of sympathetic innervation observed in obese patients with HF is not related to technical reasons. However, the relatively small number of patients of the present study makes our findings preliminary and warranting further confirmation.

Conclusions

Our results indicate that in HF patients, obesity has a significant impact on ^{123}I-MIBG indexes of cardiac sympathetic innervation. Prone-position acquisition did not change early and late ^{123}I-MIBG H/M ratios and washout rate compared to supine-position both in obese and non-obese patients. Thus, prone data acquisition may not be considered a valid alternative approach of the standard method to evaluate cardiac innervation using ^{123}I-MIBG planar imaging in obese subjects.

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None.

Footnote

Conflicts of Interest: Paper accepted for presentation during the Annual Congress of the European Association of Nuclear Medicine (EANM), Hamburg, 10-14 October 2015.

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