Published in final edited form as:

Nucl Med Commun. 2017 January ; 38(1): 44–50. doi:10.1097/MNM.0000000000000608.

123I-mIBG Scintigraphy for the Assessment of Cardiac Sympathetic Innervation and the Relationship to Cardiac Autonomic Function in Healthy Adults Using Standardized Methods

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Abstract

Background—Global ¹²³I-mIBG (MIBG) uptake is predictive of cardiovascular events and mortality in subjects with heart failure (HF). Normal variations in global and regional uptake however, are not well defined and few studies have addressed the functional relevance of MIBG uptake and distribution in healthy subjects.

Methods and Results—We undertook MIBG scintigraphy and cardiac autonomic function testing using standardized methodology in 15 healthy subjects (mean age 54.6±5.3 years, M:F 10:5) with no evidence of previous MI or ischaemic heart disease (IHD). Early heart to mediastinum ratio (HMR) was 1.67±0.13, late HMR 1.73±0.16 and washout rate (WR) 19.09±7.63% (4.20–31.30). Regional analysis revealed reduced tracer uptake at the apex, base and inferior wall in all subjects. Early and late HMR correlated negatively with R_{Fa} (r=−0.603; p=0.05 and −0.644; p=0.033) and E/I ratio (r=−0.616; p=0.043 and −0.676; p=0.022) and positively with L_{Fa}/R_{Fa} (r=0.711; p=0.014 and 0.784; p=0.004). WR correlated only with R_{Fa} (r=0.642, p=0.033).

Conclusion—Healthy adults demonstrate a heterogeneous pattern of cardiac innervation with reduced regional uptake of MIBG. Furthermore, HMR correlates with indices of cardiac

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Disclosure

Omar Asghar received an honorarium from GE. No other authors have any disclosures.

sympathetic function, suggesting that it might not only be a useful prognostic marker but may also provide insight into the functional integrity of the cardiac autonomic nervous system.

Introduction

¹²³I-meta-iodobenzylguanidine (MIBG) scintigraphy allows for the qualitative and quantitative global and regional assessment of cardiac sympathetic innervation and demonstrates cardiac denervation in a variety of pathologies ¹. Recently, MIBG has emerged as an important tool in the risk stratification of patients with heart failure (HF) ^{2,3}. The utility of the late heart to mediastinum ratio (HMR) as a prognostic indicator in HF was demonstrated in the ADMIRE-HF study in which a late HMR <1.6 was associated with an event rate of 37% over two years for HF progression, arrhythmia or death ⁴. More recently combined analyses of several studies using MIBG have shown considerably improved risk stratification for events in patients with heart failure ⁵, arrhythmic sudden cardiac death ^{6,7}, 5 year cardiac mortality ⁸ and long term prognosis ⁹. In addition to measures of global innervation, single photon emission computed tomography (SPECT) derived innervation scores are predictive of ventricular arrhythmias and may be useful in the risk stratification of subjects undergoing implantable cardiac defibrillator implantation ^{10,11}. However, in patients with Parkinson's disease and autonomic neuropathy, orthostatic symptoms and heart rate variability showed no relationship to cardiac MIBG uptake, suggesting a discordance between structure and function ¹².

However, variations in global and regional uptake in healthy individuals are not well defined and indeed have urged the need for standardizing imaging protocols ¹³. Early studies in healthy subjects were limited by variations in methodology and methods of interpretation and very few studies have addressed the functional relevance of MIBG uptake in healthy subjects. In a recent study however, an increase in cardiac presynaptic sympathetic activity was associated with reduced heart rate variability (HRV) in subjects with no evidence of myocardial ischaemia ¹⁴. The purpose of this study was to define global and regional cardiac sympathetic innervation in healthy adults using standardized methodology and to investigate the relationship with cardiac sympathetic function.

Materials and Methods

Global and regional cardiac sympathetic innervation, were quantified using MIBG scintigraphy in a cohort of healthy subjects. The study protocol was approved by the Central Manchester Research Ethics Committee. Written informed consent, according to the declaration of Helsinki, was obtained from all participants.

Patient Selection

Inclusion criteria were healthy male or female subjects aged 18–75 years. Exclusion criteria included any history of cardiac disease, diabetes, severe systemic disease (e.g. congestive cardiac failure, rheumatoid disease, systemic lupus erythematosus), chronic kidney disease, peripheral vascular disease, neuropathy and any contraindication to MIBG or CMR imaging.

Study Protocol

All study participants underwent an initial assessment including medical history; clinical examination and 12 lead ECG. Within two weeks of MIBG scintigraphy, all participants underwent CMR imaging to assess cardiac structure and function, to exclude previous MI with late Gadolinium enhancement (LGE). In addition, we performed adenosine stress CMR to exclude ischaemic heart disease. All medications known to affect the uptake of MIBG were omitted and thyroid blockade was achieved by oral administration of potassium perchlorate 170 mg on the evening prior to MIBG imaging.

Autonomic Function Testing

Spectral analysis of HRV and respiratory activity allow for real time, quantitative, independent and simultaneous measures of parasympathetic and sympathetic activity at rest and in response to physiological challenges. The ANX 3.0 autonomic monitoring system (ANSAR Medical Technologies, Inc., Philadelphia, PA) was used to perform spectral analysis of heart rate variability (HRV) during standard tests of cardiovascular reflexes¹⁵. Cardiovascular autonomic function testing was performed on the day of MIBG imaging. We assessed parameters of HRV during expiration and inspiration (E/I), Valsalva maneuver (VM), response to standing (30:15 ratio) and postural drop in systolic blood pressure. In addition, the low frequency area (LFA) to respiratory frequency area (RFa) ratio; an estimate of sympathovagal balance, was determined.

I-123 mIBG Scintigraphy

Data Acquisition—¹²³I-mIBG 185 MBq (AdreView-GE Healthcare) was administered intravenously by slow (1–2 min) injection through a peripheral venous cannula. All images were acquired using a Siemens Symbia T6 gamma camera (Siemens Healthcare) at 10 (early) and 240 minutes (late) post injection of MIBG. Planar images were acquired with a low energy high-resolution (LEHR) collimator, 159 keV $\pm$ 15% energy window, 128 $\times$ 128 image matrix, and zoom of 1.0 (pixel size 4.8 mm) for 15 minutes. SPECT images were acquired over a 180° orbit from the right anterior oblique to left posterior oblique positions with medium energy general purpose (MEGP) collimators, 159 keV $\pm$ 15% energy window, 64 $\times$ 64 image matrix, zoom of 1.45 (pixel size 6.6 mm) and 64 projections at 30 seconds per projection.

Data Analysis—Image processing was undertaken independently by a cardiology research fellow (OA) and an experienced nuclear cardiologist (PA); both blinded to clinical information. An average value of the two analyses was used except where there was a significant discrepancy (>10%) in which case images were reviewed and re-analysed. Global MIBG uptake was assessed in the early and late planar images by drawing an elliptical region of interest (ROI) over the whole heart and a 7 $\times$ 7 pixel square ROI in the upper mediastinum. The HMR was then calculated by dividing the mean myocardial count per pixel by the mean mediastinal count per pixel. Washout rate (WR), an index of sympathetic tone, was calculated from the planar data using the formula:

$$\text{Washout} = \frac{C_E - (C_L / df)}{C_E}$$

C_E = myocardial count on early image, C_L = myocardial count on late image, df = decay factor (physical decay of ^{123}I -MIBG between early and late images).

SPECT images were processed to derive short and long axis (vertical and horizontal) slices using iterative reconstruction with resolution recovery (Siemens Flash 3D), with 6 iterations, 8 subsets and an 8.4 mm Gaussian post-filter. Segmental analysis was performed using a 17 segment left ventricular model. Tracer uptake (mean count per pixel) was expressed as a percentage of maximal tracer uptake and segments were assigned a score based on this percentage; <50% = 4, 50–59% = 3, 60–74% = 2 and >75% = 1. The total segmental score was calculated. In addition, we calculated a modified score (total segmental score - apex and inferior [apical, mid and basal] segments) to correct for reduced innervation in these regions.

Statistical Analysis

SPSS Statistics for Mac version 20 (IBM corporation, New York USA) was used for all statistical analysis. All data are expressed as mean $\pm$ SD and the Shapiro-Wilk test was used to determine normality of data. Pearson correlation was used to determine associations between HMR, WR, SPECT scores and indices of autonomic function.

Results

15 subjects (10 males, 5 females) underwent assessment however one male subject was excluded on the basis of an incidental finding of atrial flutter and LV impairment (LVEF 48%). The remaining 14 participants successfully completed the imaging protocol and CMR imaging did not reveal any abnormality in cardiac structure, function or stress perfusion. The demographic and clinical data are detailed in Table 1. LV mass (LVMI $51.1 \pm 10.7 \text{ g/m}^2$) and ejection fraction (LVEF $61.0 \pm 6.4 \%$) were both within normal limits.

Autonomic Function Testing

The results of autonomic function testing are summarized in Table 2. The E/I ratio was 1.2 ± 0.1 , Valsalva ratio 1.4 ± 0.2 , 30:15 ratio 1.2 ± 0.1 and LFa/RFa ratio 2.4 ± 2.5 .

MIBG Scintigraphy

The results of MIBG scintigraphy are detailed in Table 3. A Bland Altman plot demonstrating inter-observer agreement for analysis of HMR is shown in figure 1. The early HMR was 1.67 ± 0.13 , late HMR 1.73 ± 0.16 and WR $19.1 \pm 7.6 \%$ (Figure 2). Qualitative assessment of the SPECT images revealed a consistent reduction of tracer uptake at the cardiac apex, base and inferior wall in all subjects (Figure 3). The total segmental score was 28 ± 4 and modified score 20 ± 3 . Both early and late HMR correlated negatively with RFa ($r = -0.603$; $p = 0.05$ and $r = -0.644$; $p = 0.033$) and E/I ratio ($r = -0.616$; $p = 0.041$ and $r = -0.676$; $p = 0.022$) and positively with LFa/RFa ($r = 0.711$; $p = 0.014$ and $r = 0.784$; $p = 0.004$) (Figure 4). HMR did not correlate with any other indices of autonomic function. WR correlated only

with RFa ($r=0.642$, $p=0.033$). Total segmental score ($r=0.658$; $p=0.028$) and modified score ($r=0.713$; $p=0.014$) both correlated with RFa.

Discussion

The human myocardium is predominantly innervated by sympathetic fibers in a distribution characterized by differences in nerve density between atria and ventricles, endocardium and epicardium with significant intra-ventricular regional variations^{16–18}. Originally developed as a radionuclide for imaging adrenal tumours, MIBG has emerged as a promising tool for the assessment of the cardiac sympathetic nervous system¹⁹. Early observational studies using MIBG reported homogenous tracer uptake in young healthy subjects compared to reduced uptake at the apex and inferior wall in healthy older adults^{20–22}. This heterogeneous pattern of uptake was confirmed in subsequent studies which also reported the effects of age and sex on tracer uptake^{23–25}. More recently however, the ADMIRE-HF study failed to demonstrate an association between age and MIBG uptake in older healthy controls²⁶. Studies using positron emission tomography (PET) with ¹¹C-labeled hydroxyephedrine ([¹¹C]-HED) have reported similar homogenous uptake in young healthy adults and heterogeneity in older controls^{27–29}. In our study we confirm regional heterogeneity in MIBG uptake predominantly affecting the apex, base and inferior wall in a healthy cohort with a comparable mean age to these previous studies.

Whilst HMR shows considerable promise as a prognostic indicator in a variety of clinical contexts, there is to date no universally accepted normal range. Thus HMR values for healthy adults reported in the literature have varied between studies primarily due to differences in methodology and interpretation, rendering calls for the standardization of MIBG scintigraphy^{13,30,31}. Although our imaging protocol was devised according to internationally recommended standards, we note that late HMR in our subjects was lower than that reported in ADMIRE-HF controls (1.73 ± 0.16 vs 1.77 ± 0.23). This discrepancy could be explained by a number of factors. Our study involved a much smaller group with a narrower range of age and BMI than the ADMIRE-HF controls. Furthermore, in ADMIRE-HF, there was a trend towards a reduction in late HMR with age in control subjects, albeit non-significant³². A technical factor that may also have influenced HMR values is the degree of septal penetration of the collimators used. A recent study has suggested that LEHR collimators from Siemens and Philips provide comparable HMR results³³. However, our experience of the LEHR collimators supplied by Siemens suggests that they exhibit a higher degree of septal penetration compared with LEHR collimators from GE. Hence this increased septal penetration would have reduced HMR in our subjects. Another explanation for higher HMR in ADMIRE-HF may be the range of cameras used in the study. This highlights the importance of understanding the performance of the particular manufacturer's collimators and demonstrates that normal ranges for HMR may not be transferable between manufacturers.

The low frequency component (LFa) of HRV relates to sympathetic activity, the respiratory frequency (RFa) corresponds to parasympathetic activity and the ratio of LFa/RFa is an index of sympathovagal balance. Morozumi et al reported a correlation between WR and the LF component of HRV in fifteen healthy male subjects²² however in a more recent study,

HRV did not correlate with MIBG for the detection of CAN in type 2 diabetic subjects³⁴. A major flaw of the latter study was that 60% of all reported defects in MIBG uptake involved the inferior wall (46%) and apex (14%). Subsequently, 45% of subjects with normal HRV were labeled as having an abnormal ¹²³I-MIBG study. In contrast, 92% with abnormal HRV had abnormalities in MIBG uptake. However, in a recent study of subjects without myocardial ischaemia, WR was inversely correlated with indices of HRV derived from ambulatory ECG recordings suggesting sympathetic over activity however this correlation was only significant in the very low frequency band (VLF)¹⁴.

In our study, although HMR correlated negatively with RFa and positively with LFa/RFa as expected, WR correlated positively with RFa, a finding inconsistent with those of previous studies. This unexpected finding may be explained by the small numbers in our study and the possibility of a type 1 statistical error due the outliers in the group. Nevertheless, the nature of this relationship in the context of cardiac neuropathy remains to be established and requires further study.

Despite the small study population our findings are significant given the robust MIBG methodology and detailed structural and functional cardiac phenotyping using gold standard CMR imaging. Furthermore, the highly significant correlations between MIBG parameters and autonomic function further attests to the validity of the current data in this small group of healthy subjects. Clearly, there is a need for further research to determine the functional significance of cardiac MIBG and establish it as a diagnostic tool and guide to therapeutic intervention

Conclusion

Using standardized methods of MIBG scintigraphy, we report indices of global cardiac MIBG uptake in healthy adults which are comparable to those reported in the ADMIRE-HF study. Furthermore, we confirm a heterogeneous pattern of sympathetic innervation in normal healthy adults and correlations between MIBG uptake and markers of autonomic function.

Acknowledgments

Funding

This study was funded by research grants from the NHS National Institutes for Health Research (FSF-R5-OA), NIH (R105991) and Juvenile Diabetes Research Foundation (8-2008-362).

Abbreviations

CAN	Cardiac autonomic neuropathy
HMR	Heart mediastinum ratio
LVMI	Left ventricular mass index
MIBG	¹²³ I-meta-iodobenzylguanidine
SPECT	Single photon emission computed tomography

WR	Washout rate
RFa	Respiratory frequency area
LFa	Low frequency area
E	I ratio, expiratory to inspiratory ratio

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Figure 1. Bland Altman plot demonstrating inter-observer agreement ($\beta = -0.176$) for HMR with 95% limits of agreement (dashed lines).

Nucl Med Commun. Author manuscript; available in PMC 2018 January 01.

Figure 3.
A) SPECT reconstructed images and B) *bull's eye plot* of the normal innervation pattern.
Note the reduced tracer uptake at the apex, base and inferior wall.

A **B**

C

D

Figure 4. Correlations of late HMR with RFA (A), LFa/RFa (B), E/I (C) and WR with RFA (D).

Table 1Clinical and CMR characteristics of study subjects. (Data are expressed as Mean $\pm$ SD).

Age (Years)	54.6 $\pm$ 5.4
BMI (Kg/m ²)	27.0 $\pm$ 3.1
Systolic BP (mm Hg)	118 $\pm$ 11
Diastolic BP (mm Hg)	72 $\pm$ 10
Fasting Glucose (mg/dl)	86.4 $\pm$ 9.0
HbA1c (%)	5.3 $\pm$ 1.5
Total Chol (mg/dl)	90.0 $\pm$ 13.5
LDLc (mg/dl)	52.2 $\pm$ 10.8
HDLc (mg/dl)	28.8 $\pm$ 7.2
Triglyceride (mg/dl)	29.8 $\pm$ 9.0
LVMI (g/m ²)	51.1 $\pm$ 10.7
LVEF (%)	61.0 $\pm$ 6.4

Table 2

HRV indices of autonomic function. (Data are expressed as Mean $\pm$ SD).

	Controls
E/I ratio	1.2 $\pm$ 0.1
Valsalva ratio	1.4 $\pm$ 0.2
30:15 ratio	1.2 $\pm$ 0.1
LFa/RFa	2.4 $\pm$ 2.5

Table 3

MIBG global and regional analysis. (Data are expressed as Mean $\pm$ SD).

Early HMR	1.67 $\pm$ 0.13
Late HMR	1.73 $\pm$ 0.16
Washout Rate (%)	19.1 $\pm$ 7.6
Total Segmental Score	28.4 $\pm$ 4.0
Modified Segmental Score	20.1 $\pm$ 3.2