Vascular time-activity variation in patients undergoing $^{123}$I-MIBG myocardial scintigraphy: implications for quantification of cardiac and mediastinal uptake

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Abstract
Purpose For the quantification of cardiac $^{123}$I-metaiodobenzylguanidine (MIBG) uptake, the mediastinum is commonly used as a reference region reflecting nonspecific background activity. However, variations in the quantity of vascular structures in the mediastinum and the rate of renal clearance of $^{123}$I-MIBG from the blood pool may contribute to increased interindividual variation in uptake. This study examined the relationship between changes in heart (H) and mediastinal (M) counts and the change in vascular $^{123}$I-MIBG activity, including the effect of renal function.
Methods Fifty-one subjects with ischemic heart disease underwent early (15 min) and late (4 h) anterior planar images of the chest following injection of $^{123}$I-MIBG. Vascular $^{123}$I-MIBG activity was determined from venous blood samples obtained at 2 min, 15 min, 35 min, and 4 h post-injection. From the vascular clearance curve of each subject, the mean blood counts/min per ml at the time of each acquisition and the slope of the clearance curve were determined. Renal function was expressed as the estimated creatinine clearance (e-CC) and the estimated glomerular filtration rate (e-GFR). Relations between H and M region of interest (ROI) counts/pixel, vascular activity, and renal function were then examined using linear regression.
Results Changes in ROI activity ratios between early and late planar images could not be explained by blood activity, the slope of the vascular clearance curves, or estimates of renal function. At most 3% of the variation in image counts could be explained by changes in vascular activity ($p=0.104$). The e-CC and e-GFR could at best explain approximately 1.5% of the variation in the slopes of the vascular clearance curve ($p=0.194$).
Conclusion The change in measured H and M counts between early and late planar images could not be explained by blood activity, the slope of the vascular clearance curves, or estimates of renal function. At most 3% of the variation in image counts could be explained by changes in vascular activity ($p=0.104$). The e-CC and e-GFR could at best explain approximately 1.5% of the variation in the slopes of the vascular clearance curve ($p=0.194$).

Keywords $^{123}$I-MIBG · Renal function · Quantification · Myocardial scintigraphy · Mediastinum

Introduction
The myocardial sympathetic nervous system is activated in patients with heart failure (HF) and this activation has been shown to be associated with increased mortality [1]. Cardiac sympathetic hyperactivity can be scintigraphically visualized by $^{123}$I-metaiodobenzylguanidine (MIBG), a radiolabeled analogue of noradrenaline. This noninvasive technique has been demonstrated to be a powerful prognostic marker in HF patients [2–4].
In myocardial $^{123}$I-MIBG imaging, the most commonly used quantitative parameters are the heart to mediastinum (H/M) ratio and washout (WO) determined from planar images. The H/M is a measure of specific to nonspecific uptake, while the WO is a measure of neuronal integrity. A basic assumption associated with use of the mediastinum as a reference for H/M and WO calculations is that the counts in this region represent nonspecific binding of the radioligand.

One potential confounder for assessment of nonspecific $^{123}$I-MIBG background activity is residual tracer in the blood. Since the mediastinum contains a relatively large volume of vascular structures, intravascular $^{123}$I-MIBG activity may contribute to total mediastinal activity which may influence the quantification of the H/M ratio. Since the clearance rate of $^{123}$I-MIBG from the blood is largely dependent on renal function [5, 6], and renal dysfunction is often present in HF patients, differences in the rate of vascular clearance may also contribute to increased inter-individual variation in uptake quantification [7, 8].

The objective of this study was to assess the magnitude of the influence of residual vascular $^{123}$I-MIBG activity on image quantification by examining the relationship between changes in vascular activity and changes in heart (H) and mediastinal (M) activity between early and late planar $^{123}$I-MIBG images.

**Materials and methods**

As part of a prospective multicenter trial [9], 51 subjects (48 male, 3 female; mean age 65.2) with ischemic heart disease (history of ≥ 1 myocardial infarction) underwent myocardial $^{123}$I-MIBG imaging. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by each institution's human research committee. All subjects signed informed consent before performance of any study procedure.

**Imaging procedures**

All subjects received 370 MBq (10 mCi;±10%) of $^{123}$I-MIBG (AdreView™, GE Healthcare) and underwent 10-min planar images of the anterior thorax at 15 min (early; e) and 4 h (late; l) post-injection (p.i.). The images were acquired with a 20% energy window centered at 159 keV, low-energy high-resolution (LEHR) collimation, and stored in a 128×
128 matrix. All digital image files were sent to an Imaging Core Laboratory (ICL) for evaluation and analysis.

Image analysis

An experienced nuclear medicine technologist processed all the planar images to determine the H and M count densities. The heart region of interest (ROI) was drawn manually to include both ventricles and any atrial activity that was clearly visible. A 7×7 pixel square mediastinal ROI was drawn in the upper mediastinum, using the apices of the lungs as anatomic landmarks (Fig. 1). Activity per ROI (mean counts/pixel) was corrected for decay to the time of injection and expressed as activity in the myocardium and mediastinum at 15 min and 4 h p.i. (Hc, Hb, H/Hc, Mb, M, and M/Mc). In addition, commonly used semiquantitative 123I-MIBG myocardial parameters were assessed to better describe the clinical condition of the subjects. Early (15 min p.i.) and late (4 h p.i.) H/M ratios were calculated as the ratios of the mean counts per pixel in the two ROIs. All images and ROIs were reviewed by three independent readers, and a single aggregate H/M was derived for each image, either the value accepted by at least two readers, or if this criterion was not satisfied, the average H/M for all readers [9]. In addition, myocardial WO was calculated as:

\[
\left( \frac{\text{early H/M} - \text{late H/M}}{\text{early H/M}} \right) \times 100\%
\]

Vascular activity

Blood samples (2 ml) were taken at 2 min, 15 min, 35 min, and 4 h p.i. Subsequently, 1-ml aliquots were counted in a well counter (energy peak at 159 keV with a 15% energy window). Activity (counts/min) was corrected for decay to the time of injection. For each patient a vascular clearance curve was plotted. Figure 2 shows a typical example with

![Fig. 2](image)

\[
\text{Fast slope} = \frac{(C2-C1)}{(T2-T1)} \\
\text{Slow slope} = \frac{(C4-C3)}{(T4-T3)}
\]

Fig. 2 In this typical example of a blood activity clearance curve, there is a clear distinction between a more accelerated phase and a slower phase. The slopes of both the faster (Sf) and slower (Ss) phases were calculated as illustrated in the figure

![Fig. 3](image)

Fig. 3 Scatter plot showing the blood activity in relation to time for all subjects

### Table 1

Demographic and cardiac medical history information for the 51 subjects included in the study

| Baseline characteristics |        |
|--------------------------|--------|
| Male/female              | 48/3 (94/6%) |
| Age (years)              | 65.3±9.1 (42–84) |
| NYHA (I/II/III)          | 4/28/11 (8/55/22%) |
| ACC/AHA HF class (B/C)   | 15/36 (29/71%) |
| LVEF                     | 33±8 (15–48) |
| Medication               |        |
| Beta-blockers            | 45 (88%) |
| ACE inhibitor/AT-II receptor blockers | 46 (90%) |
| Aldactone                | 16 (32%) |
| Amiodarone               | 10 (20%) |
| Calcium channel blocker  | 12 (24%) |

| Estimates of renal function |        |
|-----------------------------|--------|
| Creatinine (μmol/l)         | 113.4±42.4 (59–296) |
| e-CC (ml/min)               | 74.8±29.2 (19.9–156.9) |
| e-GFR (ml/min per 1.73m²)   | 66.2±21.4 (19.1–125.6) |

| Semiquantitative 123I-MIBG parameters |        |
|---------------------------------------|--------|
| Early H/M                             | 1.51±0.25 (0.60–1.99) |
| Late H/M                              | 1.44±0.18 (1.05–1.96) |
| Myocardial WO (%)                     | 8.2±6.8 (5.3–10.8) |

Data are expressed as mean ± SD and range or as absolute numbers and percentage

NYHA New York Heart Association functional classification, LVEF left ventricular ejection fraction, ACC/AHA HF class American College of Cardiology and American Heart Association classification of HF, e-CC estimated creatinine clearance calculated using the Cockcroft-Gault equation, e-GFR estimated glomerular filtration rate calculated using the abbreviated Modification of Diet in Renal Disease (MDRD) equation
two distinct phases, an accelerated clearance followed by a slower clearance. The slopes of the two phases of the clearance curves were determined according to biexponential curve fitting \(S_f\) and \(S_s\), expressed as cpm/ml per min.

Based upon the vascular clearance curve, the mean activity (cpm/ml) was calculated for the time intervals during which the two planar images were acquired (15–25 min and 3 h 50 min–4 h p.i.: \(V_e\) and \(V_l\)). The ratio of \(V_e\) and \(V_l\) and the ratio between the slopes of the accelerated phase \(S_f\) and the slower phase \(S_s\) of the blood clearance were then calculated.

### Determination of renal function

Serum concentrations of creatinine were determined from blood samples obtained as part of screening evaluations performed within 7 days prior to \(^{123}\text{I}-\text{MIBG}\) imaging. Analyses were performed at a central laboratory, with reference ranges of 75–111 \(\mu\text{mol/l}\) for men and 53–106 \(\mu\text{mol/l}\) for women.

Renal function was estimated using two methods. Estimated creatinine clearance (e-CC) was calculated (in ml/min) using the Cockcroft-Gault equation [10]:

\[
e-\text{CC} = \frac{[140 - \text{[age (years)]}] \times \text{[weight (kg)]}}{[\text{serum creatinine (\(\mu\text{mol/L}\))}]}
\times (1.04 \text{ for females and } 1.23 \text{ for males})
\]

Estimated glomerular filtration rate (e-GFR) was calculated using the abbreviated Modification of Diet in Renal Disease (MDRD) equation [11]:

\[
e-\text{GFR} = 32788 \times [\text{serum creatinine (\(\mu\text{mol/L}\))}]^{-1.154} \\
\times [\text{age (years)]}^{-0.203} \times [0.742 \text{ for females}] \\
\times [1.212 \text{ for blacks}]
\]

### Statistical analysis

Linear regression was used to examine the relationships between the vascular activity ratio \((V_l/V_e)\), the slope of the vascular clearance curve \((S_f/S_s)\), and the scintigraphically determined activity in the myocardium and mediastinum at 15 min and 4 h p.i. \(H_e, H_l, M_e, M_l, H_l/He, M_l/Me\). The overall goodness-of-fit was expressed as the adjusted \(R^2\). The \(F\) test was used to assess whether the analysis explained a significant proportion of the variability. A \(p\) < 0.05 was considered to indicate a statistically significant difference. A significant adjusted \(R^2\) would indicate that variation in the scintigraphically determined parameters could be explained by a percentage (adjusted \(R^2\)) of change in vascular activity. All statistical analyses were performed with SPSS (SPSS for Windows, version 17.0.2, SPSS Inc., Chicago, IL, USA).

### Results

Demographic and cardiac medical history information for the 51 subjects included in the study is summarized in Table 1. The majority of patients was male, had New York Heart Association (NYHA) class II HF, and had left ventricular ejection fraction (LVEF) < 40%. Eight patients had no history of HF. The majority of subjects were on a combination of beta-adrenergic receptor blockers and angiotensin-converting enzyme (ACE) inhibitors.
inhibitors or angiotensin II (AT-II) receptor blockers (Table 1).

Estimates of renal function showed a substantial variation (Table 1). In 26 (51%) patients creatinine levels were above the normal limit (25 men and 1 woman). Calculated e-CC was < 60 ml/min in 19 (38%) patients and the calculated e-GFR was < 60 ml/min per 1.73 m² in 24 (47%) patients.

There was a considerable range in the initial (i.e., fast) part of the 123I-MIBG vascular clearance curves (Fig. 3). Despite this individual variation, the mean Sf was more than 60 times steeper compared to the mean Ss (Table 2). Mean intravascular activity (cpm/ml) decreased approximately 65% between 15 min and 4 h p.i. (Table 3). The mean scintigraphically determined myocardial and mediastinal activity (counts/min) decreased approximately 37 and 33%, respectively, between 15 min and 4 h p.i. (Table 3).

Variation in any of the scintigraphic parameters (Me, Ml, Mf/Me, He, Hl, and Hl/He) could not be explained by intravascular activity (Table 4). At most the counts in the blood at 15 min (Vt) could explain approximately 3% of the variation in the medistinal counts at 15 min (Ml) (p = 0.120). Variation of the scintigraphic parameters could also not be explained by the slope of the clearance curves (Table 5). The slope of the clearance curves could at best explain up to 3% of the variation in the medistinal counts (Me vs Sf and Ml vs Ss, p = 0.105 and p = 0.100, respectively).

The variability in the change of intravascular activity (Sn and Sf/Sf) could not be explained by either estimate of renal function (e-CC or e-GFR) (Table 6). The e-CC could at best explain approximately 1.5% of the variation in the fast slope of the vascular clearance curve (e-CC vs Sf, p = 0.194).

Discussion

Most in vivo scintigraphic quantification of regional neurotransporter activity or receptor density involves comparison of uptake in a target ROI to that in a reference region of nonspecific uptake/binding. For assessment of sympathetic myocardial activity with 123I-MIBG scintigraphy, use of the mediastinum as a reference region is based on the assumption that there is a negligible amount of specific uptake of 123I-MIBG in this region. In addition, presence of 123I-MIBG in the blood pool is also assumed to be insignificant. The present results demonstrate that changes in blood pool/vascular 123I-MIBG activity do not significantly correlate with changes in heart and mediastinum activity between early and late planar images. This is

### Table 4: Variability of scintigraphic parameters in relation to intravascular activity (linear regression)

|               | Constant | SE c | Coefficient b | SE b | Adjusted $R^2$ | p value |
|---------------|----------|------|---------------|------|----------------|---------|
| Me vs Vt     | 564.2    | 64.8 | 0.001         | 0.001| 0.028          | 0.120   |
| Ml vs Vl     | 430.2    | 45.8 | 0.001         | 0.001| 0.001          | 0.905   |
| Mf/Me vs Vf/Vc | 0.67 | 0.05 | 0.014         | 0.122| 0.006          | 0.912   |
| He vs Vc     | 878.4    | 97.3 | 0.001         | 0.001| 0.014          | 0.191   |
| Hl vs Vl     | 602.8    | 63.2 | 0.001         | 0.002| 0.001          | 0.822   |
| Hl/He vs Vf/Vc | 0.59 | 0.04 | 0.126         | 0.109| 0.01           | 0.253   |

SE standard error, Me: scintigraphically determined mediastinal counts 15 min p.i. (early), Ml: scintigraphically determined mediastinal counts 4 h p.i. (late), He: scintigraphically determined myocardial counts 15 min p.i. (early), Hl: scintigraphically determined myocardial counts 4 h p.i. (late), Vt: intravascular radioactivity 15 min p.i. (early), Vl: intravascular radioactivity 4 h p.i. (late)

### Table 5: Variability of scintigraphic parameters in relation to the slopes of the blood activity clearance curve (linear regression)

|               | Constant | SE c | Coefficient b | SE b | Adjusted $R^2$ | p value |
|---------------|----------|------|---------------|------|----------------|---------|
| Me vs Sf     | 532.9    | 83.3 | −738.779      | 447.576| 0.033          | 0.105   |
| Ml vs Ss     | 542.0    | 69.4 | 33.361        | 19.957| 0.032          | 0.100   |
| Mf/Me vs Sf/Sf | 0.670 | 0.022 | 4.44 × 10⁻⁵  | 0.022| 0.001          | 0.875   |
| He vs Sf     | −0.127   | 0.031| −3.99 × 10⁻⁷ | −0.192| 0.018          | 0.172   |
| Hl vs Ss     | 0.004    | 0.000| 8.98 × 10⁻⁷  | 0.000| 0.016          | 0.177   |
| Hl/He vs Sf/Sf | 0.631 | 0.020 | −2.21 × 10⁻⁷ | 0.000| 0.001          | 0.999   |

SE standard error, Me: scintigraphically determined mediastinal counts 15 min p.i. (early), Ml: scintigraphically determined mediastinal counts 4 h p.i. (late), He: scintigraphically determined myocardial counts 15 min p.i. (early), Hl: scintigraphically determined myocardial counts 4 h p.i. (late), Sf: slope of the accelerated (fast: f) part of the blood activity clearance curve, Ss: slope of the slower (s) part of blood activity clearance curve.
consistent with rapid clearance of $^{123}$I-MIBG from the blood and uptake into organs (such as the heart) by means of the norepinephrine transporter.

As intravascular activity appears to play no role in the variation of the counts measured in the mediastinum, those counts likely reflect a combination of mediastinal tissue activity and scatter from $^{123}$I-MIBG in adjacent organs (e.g., liver, lungs) [13]. This shows that for routine quantification, the mediastinum is acceptable as a reference region. However, these findings do not confirm that the mediastinum represents a background region with only nonspecific uptake/binding. To test this hypothesis would require a study where the specific uptake of $^{123}$I-MIBG via the presynaptic norepinephrine transporter (i.e., uptake 1) was blocked and compared to a similar study without blocking. To our knowledge this type of study has not been performed in humans.

In subjects with normal renal function, intravenously administered $^{123}$I-MIBG is almost exclusively excreted via the kidneys within 24 h after injection, with approximately 35% of administered $^{123}$I-MIBG already excreted by 6 h [5, 6]. There are complex interactions between sympathetic regulation of renal function and cardiac function. For example, increased sympathetic activity reduces the filtration fraction [14, 15]. In addition, renal dysfunction is often present in HF patients, which may further increase the interindividual variation of blood pool clearance [7, 8].

Moreover, as a reduced GFR is associated with a reduced blood clearance of $^{123}$I-MIBG, the excretion of $^{123}$I-MIBG is not only dependent on filtration but also by tubular secretion [16]. In the present study, although approximately 40% of the patients had decreased renal function, differences in the rate of renal excretion did not contribute to variability in the mediastinal and myocardial $^{123}$I-MIBG uptake. Therefore, within the typical time frame of $^{123}$I-MIBG cardiac imaging (up to 4 h after injection), $^{123}$I-MIBG mediastinal and myocardial activity determinations appear independent of the rate of blood clearance via the kidneys.

Radioactivity as measured in the blood samples may be in part explained by $^{123}$I not bound to MIBG and this may have influenced our results. However, according to specifications of the manufacturer the radiochemical purity of the $^{123}$I-MIBG used prior to injection is always more than 97% and in clinical practice the fraction of free $^{123}$I does not exceed 2%. Secondly, after intravenous administration, $^{123}$I-MIBG in humans is very stable and not subject to in vivo deiodination [17]. In addition, the clearance rate of both $^{123}$I-MIBG and free $^{123}$I from the blood pool is rapid and is almost exclusively dependent on renal excretion. Therefore, the impact of free $^{123}$I on the present results should be negligible.

In conclusion, in patients with ischemic heart disease, due to rapid clearance of $^{123}$I-MIBG from the blood, the heart and mediastinal count densities measured on planar $^{123}$I-MIBG images at 15 min and 4 h are not affected by residual vascular activity. In addition, this observation holds for the broad range of renal function commonly encountered in heart disease patients. Therefore, no correction for blood pool activity or renal function is needed for the calculation of myocardial WO. However, the clinical appropriateness of using mediastinal activity as a background correction in such calculations, which depend on the assumption that there is no specific uptake/binding in this region, remains to be demonstrated.

Conflicts of interest  Arnold F. Jacobson is employed by GE Healthcare. None of the other authors have a conflict of interest to disclose. Grant support: none of the authors has been supported by a grant.

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| Table 6 | Variability of estimates of renal function in relation to the slopes of the blood activity clearance curve (linear regression) |
|---------|----------------------------------------------------------------------------------------------------------------------------------|
|         | Constant | SE c | Coefficient b | SE b | Adjusted $R^2$ | p value |
| e-CC vs Sf | 62.9 | 8.4 | −59.3 | 45.1 | 0.014 | 0.194 |
| e-CC vs Ss | 63.6 | 10.3 | −3,470.1 | 2,953.7 | 0.007 | 0.245 |
| e-CC vs Sf/Ss | 69.9 | 6.5 | 0.052 | 0.084 | −0.012 | 0.536 |
| e-GFR vs Sf | 63.5 | 6.3 | −11.0 | 33.8 | −0.017 | 0.746 |
| e-GFR vs Ss | 63.2 | 7.6 | −947.9 | 2,158.8 | −0.015 | 0.666 |
| e-GFR vs Sf/Ss | 65.4 | 4.8 | −0.002 | 0.62 | −0.019 | 0.970 |

SE standard error, e-CC estimated creatinine clearance based on Cockcroft-Gault equation, e-GFR estimated glomerular filtration rate according to the abbreviated Modification of Diet in Renal Disease (MDRD) equation, $S_f$ slope of the accelerated (fast: f) part of the blood activity clearance curve, $S_s$ slope of the slower (s) part of blood activity clearance curve.
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