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Quantitation of myocardial iodine-123 MIBG uptake in SPET studies: a new approach using the left ventricular cavity and a blood sample as a reference

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Abstract. In patients with chronic heart failure increased sympathetic activity is related to unfavourable prognosis. Since myocardial iodine-123 metaiodobenzylguanidine ([^{123}I]MIBG) uptake is related to myocardial noradrenaline content, i.e. cardiac sympathetic activity, measurement of myocardial [^{123}I]MIBG uptake may be of clinical use in determining prognosis or the effect of pharmacological intervention in these patients. The aim of the present study was to evaluate a new method to quantitate myocardial [^{123}I]MIBG uptake with respect to reproducibility and accuracy. Eighteen [^{123}I]MIBG planar and single-photon emission tomographic (SPET) studies of patients with chronic heart failure were evaluated. Myocardial uptake was calculated from the myocardial (MYO) to left ventricular cavity (C) count density ratio and the ^{123}I activity in a blood sample. This was performed employing planar LAO images, a single-slice SPET method using the midventricular myocardial short-axis slice, and finally a multi-slice SPET method analysing semi-automatically drawn volumes of interest (VOIs). The accuracy of the multi-slice SPET method was verified using a cardiac phantom. The planar method was found to be reproducible [intra- and interobserver coefficients of variation (IACV and IRCV) were 0.025 and 0.012 respectively] but the mean MYO/C count density ratio was only 1.31±0.16 as a consequence of overprojection. For the single-slice SPET method IACV was 0.2 and IRCV was 0.13, representing poor reproducibility. For the multi-slice SPET method IACV was 0.051, IRCV was 0.047 and the mean MYO/C count density ratio was 5.4±2.42. Accuracy was 81% at a true MYO/C count density ratio of 6 in the phantom. It is concluded that the multi-slice SPET method using the left ventricular cavity VOI and a blood sample as a reference is a reproducible and accurate method for assessing myocardial [^{123}I]MIBG uptake.

Key words: Iodine-123 metaiodobenzylguanidine – Myocardial quantitation method – Single-photon emission tomography – Heart failure

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Introduction

Metaiodobenzylguanidine (MIBG) is a compound which has the same affinity for neuronal uptake and release mechanisms of the sympathetic nerve endings as noradrenaline (NA) [1]. In contrast to NA, MIBG is not metabolized by either monoamine oxidase or cathechol-*o*-methyltransferase [2]. Besides its classical use for the detection of neuro-endocrine tumours, iodine-123 MIBG can also be used to assess the integrity and function of cardiac presynaptic sympathetic nerve endings [3, 4]. This non-invasive approach is of interest since neuronal changes have been recognized in various cardiac diseases [5–9]. In chronic heart failure decreased myocardial [^{123}I]MIBG activity has been related to poor prognosis [10].

Since the beneficial effect of pharmacological intervention on prognosis may in part be due to a reduction of cardiac sympathetic activity, a suitable method to evaluate cardiac sympathetic acticity in a non-invasive manner as an alternative to endomyocardial biopsy may be of clinical value in these patients.

To quantitate, some authors express [^{123}I]MIBG uptake only relative to the highest uptake in the myocardium [11, 12], whereas others use reference organs such as lung [6], liver [11] and mediastinum [6, 13]. The use of other organs as an internal reference is not reliable, as

the inter-individual variation is large. Schofer et al. reported count densities for the lung, liver and mediastinum of 68±17, 140±41 and 52±11 (10^{-5} · counts · pixel^{-1} · s^{-1} · MBq^{-1}) respectively in patients with idiopathic dilated cardiomyopathy [13]. Henderson et al. observed 211±98 counts/voxel for the liver and 102±33 counts/voxel for lungs in patients with dilated cardiomyopathy after correction for dose [5]. This large inter-individual variation may in part be due to the software codes for attenuation correction. This is a recognized problem for intrathoracic organs. Moreover, planar scintigraphy is not suitable for quantitation since the superimposed counts from other anatomical structures (overprojection) cause low ratios between myocardium and reference organs.

Early experimentation in our institution raised doubts with regard to the reproducibility and accuracy of planar and single-photon emission tomographic (SPET) analysis involving reference organs when used for cardiac receptor imaging. Quantitative data on reproducibility were not available in the literature. The aim of the present study was to evaluate the reproducibility and accuracy of a new method for the quantitation of myocardial uptake of [^{123}I]MIBG, using a blood sample to calibrate the left ventricular cavity activity, thereby limiting the effect of changes in uptake in the reference organ on the calculated myocardial uptake. Furthermore, this method was compared with conventional techniques.

Materials and methods

Patient selection. Consecutive patients with stable chronic heart failure for at least 2 months (class II–IV according to the criteria of the New York Heart Association) and unchanged medication for at least 2 weeks participated in the study. Patients with diabetes mellitus or neuropathy and patients using medication interfering with NA kinetics were excluded. Written informed consent was obtained.

Investigational drug. MIBG (Cygne, Eindhoven, The Netherlands) was labelled with ^{123}I (radiochemical purity>97% and specific activity>0.2 TBq/mmol at calibration time), synthesized via proton irradiation of highly enriched xenon-124. Labelling was performed by a copper-catalysed exchange reaction between aqueous ^{123}I and MIBG, as previously described [14]. The interval between the final synthesis reaction and injection was less than 21 h.

Acquisition protocol. All patients received a single oral dose of 100 mg potassium iodide to block thyroid uptake 1 h prior to the injection of 185 MBq [^{123}I]MIBG. After 4 h of bedrest, when an equilibrium in myocardial [^{123}I]MIBG concentration had been reached and non-neuronal uptake was less than 10%, SPET images were obtained (Siemens MultiSpect-3, medium-energy collimators) using a 20% energy window centered on the 159 keV photopeak of ^{123}I. Data collection was performed in 20 frames per camera head, for 60 s per frame, over 360°, in a 64×64 pixel matrix, using the camera auto-contour facility and a zoom factor of 1.23. The frames were corrected for camera non-uniformity using the built-in software and data from periodic multi-head calibration and separate high-count intrinsic and extrinsic flood studies as acquired according to the recommendations of the manufacturer.

The ^{123}I activity in blood samples, drawn at the time of acquisition, was obtained using a gamma counter (Auto-gamma 5000, Packard Instruments, Company, Downers Grove, Ill., USA).

Reconstruction. After translation of the data to the Interfile format version 3.1 [15], the studies were reconstructed using the SPETS package (Hermes computer system, Nuclear Diagnostics, Sweden) and a Wiener prereconstruction filter. Images were zoomed to 200% to obtain transverse, short-axis and long-axis views of the heart and surrounding tissues in a 64×64 matrix. No correction for attenuation was performed. Slice thickness was one pixel.

Planar scintigraphy method with various reference organs. Planar LAO and anterior images were obtained from the SPET acquisition data (typically 300000 counts per frame). Regions of interest (ROIs) for the mediastinum (M), right lung (L), left ventricular cavity (C) and the entire myocardium (MYO) were manually drawn using the LAO images. For the mediastinal uptake the anterior images were used. Ratios of MYO/M, MYO/L and MYO/C were calculated. All views were quantitated 3 times by two experienced observers independently and blindly.

Single-slice SPET method with various reference organs. ROIs for M and L were drawn in a representative transverse slice. ROIs for C and MYO were drawn in the mid-venticular long-axis slice and the mid-ventricular short-axis slice, respectively.

The C ROI was defined as the part of the ventricular cavity with the lowest average count density. This was visualized by manipulating colour table tresholds. The C ROI was then drawn manually. Various sizes were evaluated for the C ROI. The smallest C ROI size was used in which a minimum of 100 counts was measured. Ratios of MYO/M, MYO/L and MYO/C were calculated. All regions were quantitated 3 times by two experienced observers independently and blindly.

Multi-slice SPET method with blood pool reference. The short-axis and long-axis slices were used to manually define the centre line through the ventricular cavity. Volumes of interest (VOIs)

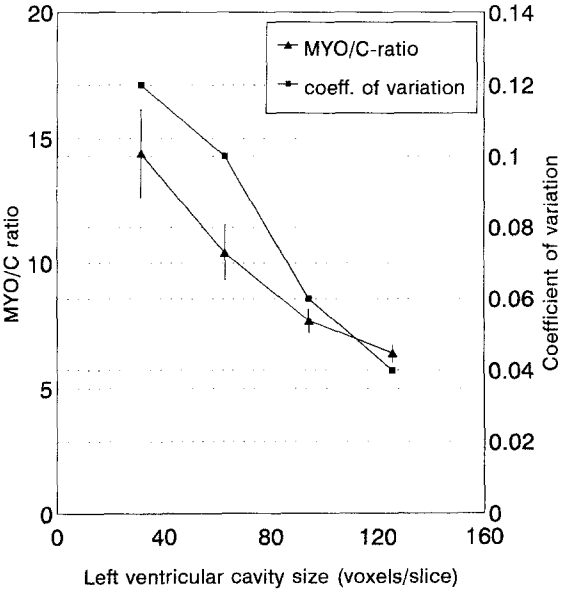

Fig. 1. Myocardial-left ventricular cavity count density ratio (MYO/C and its reproducibility (coefficient of variation) versus C area for cardiac [^{123}I]MIBG SPET. The highest MYO/C ratio with acceptable reproducibility was found at a C area of approximately 80 voxels/slice

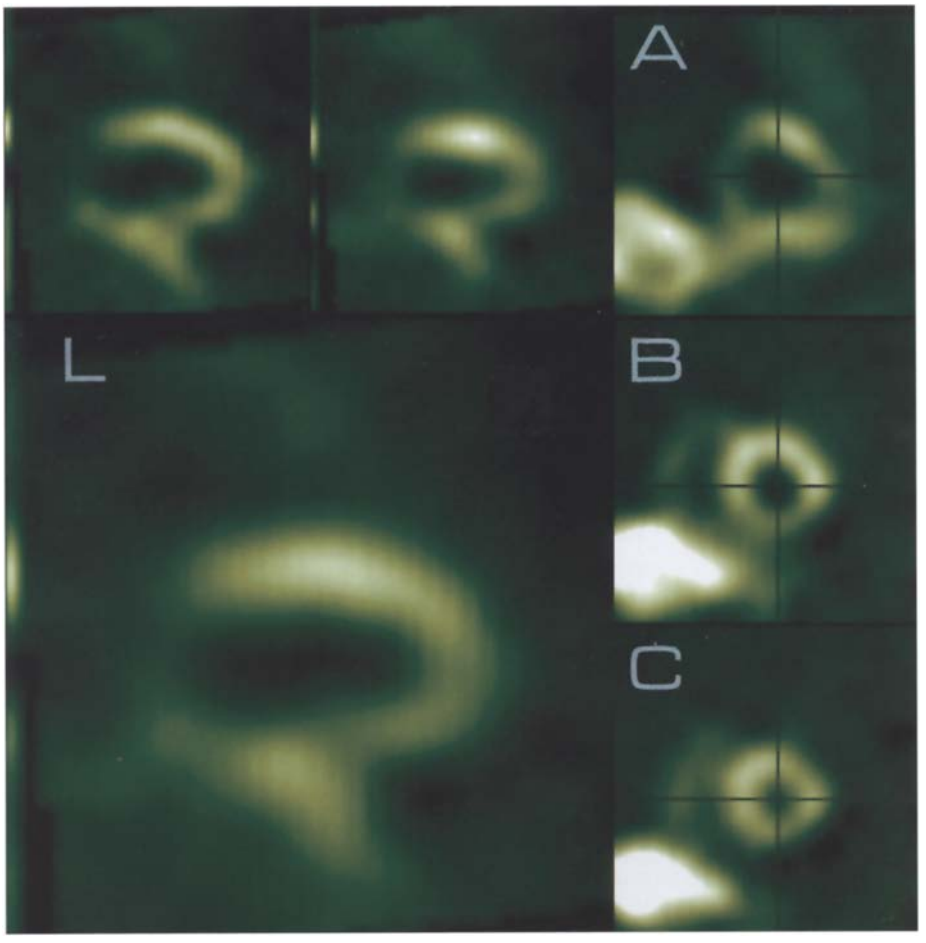

Fig. 2. Cardiac [^{123}I]MIBG SPET study of a patient with chronic heart failure. In the centered long-axis view (*L*) the basal, midventricular and apical short-axis slices are chosen (*A, B* and *C* respectively)

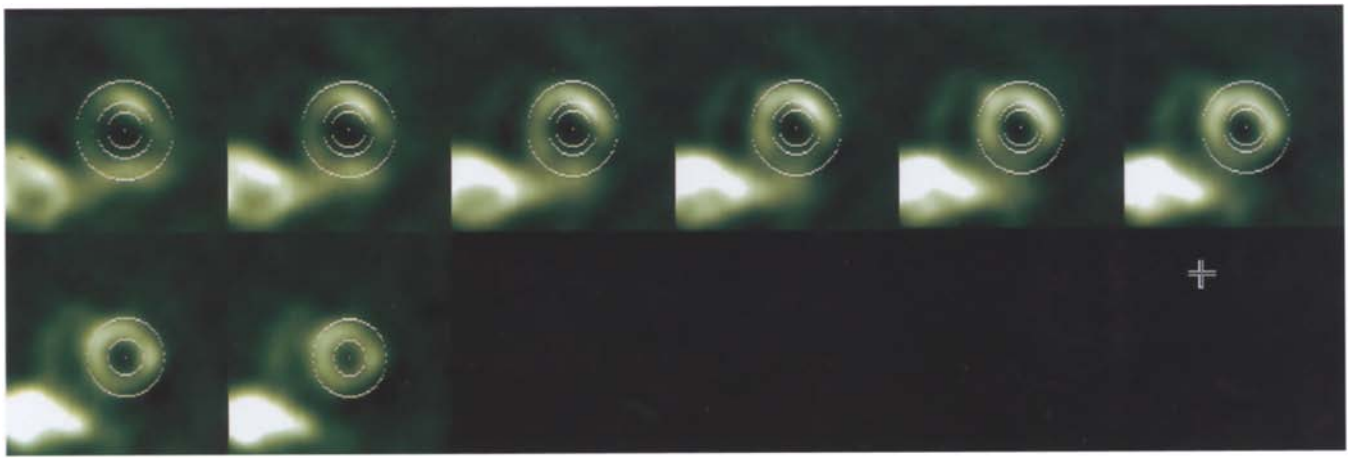

Fig. 3. Cardiac [^{123}I]MIBG SPET study of a patient with chronic heart failure. In short-axis slices ROIs are drawn to mark the myocardium (area between the outer and the middle ellipse) and ventricular cavity (inner ellipse). The ventricular cavity is assessed in short-axis slices between the defined basal and the midventricular slice

were obtained by drawing elliptical ROIs in short-axis slices and summing the corresponding data. These ROIs were all centered along the centre line. Only for the C VOI was a fixed volume of 80 voxels per short-axis slice used to minimize intra- and interobserver variability and maximize accuracy (Fig. 1). In each short-axis slice the ROI used to generate the MYO VOI was defined as the area between two adjustable concentric ellipses. The distance between the inner and outer ellipses was kept at three pixels in each short-axis slice. This resulted in a fixed wall thickness of the MYO VOI. Per slice, the main axes of the ellipsoidal band were manually adjusted to best cover the myocardium. The above algorithm was implemented in the CASPAN software package (see addendum) (Figs. 2, 3). MYO/C ratios were calculated. ^{123}I activity was measured in a blood sample, drawn at the time of acquisition (when an equilibrium in myocardial and blood concentration of [^{123}I]MIBG had been reached). ^{123}I activity in the blood sample (BS) was used to calibrate C. Myocardial [^{123}I]MIBG activity was calculated according to the equation:

$$\text{Myocardial}[^{123}]\text{MIBG activity} = \frac{\text{MYO}}{\text{C}} \cdot \text{BS(Bq / ml)}.$$

All studies were assessed 5 times by two experienced observers independently and blindly.

Validation of SPET quantitation. In the Elliptical Lung-Spine Body Phantom with Cardiac Insert (Data Spectrum Corporation, Hillsborough, N.C., USA) different compartments were filled with ^{123}I, to obtain MYO/C and MYO/background ratios comparable to those found in in vitro animal studies using [^{123}I]MIBG (MYO/C=6; MYO/background=2). The volumes of the myocardial and the ventricular cavity compartments were 117 and 64 ml, respectively.

The accuracy of the quantitation was defined as the ratio between the observed and the true MYO/C ratio.

Statistical analysis. The ratio between myocardial count density and count density in the reference region was used as the primary result from each study for each method. An analysis of variance (ANOVA) was performed. All results were expressed as mean±(sample) standard deviation.

Results

Among the 16 patients enrolled in the study, cardiomyopathy was due to ischaemic heart disease in 12 and to hypertension in one, and was idiopathic in three. Two patients participated a second time, after a major change had been made in their cardiac medication. Patients' baseline characteristics are given in Table 1.

Planar scintigraphy method

Both inter- and intra-observer coefficients of variation were low for MYO/C count density ratios (Table 2). The ratio in count densities between myocardium and any other reference organ never exceeded 3.0 (Table 3). After normalization of the count density to the administered activity and body mass, the count densities in C, M, and L varied from 13 to 150, 10 to 70 and 18 to 90 ($10^{-4} \cdot$ counts $\cdot$ pixel$^{-1} \cdot$ MBq$^{-1} \cdot$ kg^{-1}) respectively (Table 4).

Single-slice SPET method

Despite substantial optimization efforts, the single-slice SPET method showed poor reproducibility when C was used as a reference region (Table 2). The long-axis view gave better reproducibility and less region size dependency than the short-axis view for the definition of the ventricular cavity count density. This was mostly due to poor count statistics of C. The MYO/C count density ratios varied from 4.5 to 400. The inter- and intra-observer coefficients of variation for MYO/M and MYO/L count density ratios were much better than for MYO/C count density ratio, but after correction for dose and body weight, the specific M and L count densities ranged from 1 to 150 and 30 to 300 ($10^{-4} \cdot$ counts $\cdot$ voxel$^{-1} \cdot$ MBq$^{-1} \cdot$ kg^{-1}) respectively (Table 4), despite good count statistics.

Table 1. Patient characteristics

Number of patients (M/F)	16 (14/2)
Number of [^{123}I]MIBG studies	18
Age[a]	61 (±6.6)
Aetiology of heart failure:	
Ischaemic heart disease	12
Idiopathic	3
Hypertension	1
Functional class (NYHA):	
I	0
II	12
III	2
IV	2
Ejection fraction (%)[a]	25 (±10.4)

[a] Mean±SD

Table 2. Reproducibility of MYO/C count density ratio for each method

	Planar method	Single-slice SPET method	Multi-slice SPET method
Intra-observer CV	0.025	0.20	0.051
Inter-observer CV	0.012	0.13	0.047

CV, Coefficient of variation

Table 3. Count density ratios for each method

Ratio	Planar method	Single-slice SPET method	Multi-slice SPET method
MYO/C	1.31 (±0.16)	69 (±11.4)	5.44 (±2.42)
MYO/M	1.80 (±0.68)	42.4 (±40.9)	–
MYO/L	1.20 (±0.47)	1.12(±0.54)	–

Values are means±SD
C, Left ventricular cavity; L, lung; M, mediastinum; MYO, myocardium

Table 4. Absolute count densities corrected for dose and body weight, for each method and reference region

Region	Planar method	Single-slice SPET method	Multi-slice SPET method
C	0.006 (±0.004)	0.0015 (±0.002)	0.002 (±0.002)
MYO	0.009 (±0.005)	0.02 (±0.016)	0.009 (±0.006)
M	0.004 (±0.0018)	0.0007 (±0.0005)	–
L	0.006 (±0.002)	0.017 (±0.008)	–

Counts $\cdot$ pixel$^{-1} \cdot$ MBq$^{-1} \cdot$ kg^{-1}; values are means±SD
C, Left ventricular cavity; M, mediastinum; MYO, myocardium; L, lung

Multi-slice SPET method

The inter- and intra-observer coefficients of variation for the MYO/C count density ratios were 0.047 and 0.051 respectively (Table 2). The coefficient of variation for C

count density was typically 0.032. The count density ratios ranged from 2.08 to 10.81 (Table 3). After correction for dose and body weight, MYO and C count density ranged from 10 to 200 and from 4 to 20 ($10^{-4} \cdot voxel^{-1} \cdot MBq^{-1} \cdot kg^{-1}$) respectively (Table 4). The average ^{123}I activity, measured in a venous blood sample at the time of acquisition, corrected for dose and body weight, was 0.04 (±0.01) ($Bq \cdot ml^{-1} \cdot MBq^{-1} \cdot kg^{-1}$).

Phantom studies

Multi-slice SPET analysis for ^{123}I was performed using the Elliptical Lung-Spine Body Phantom with Cardiac Insert. The accuracy of the quantitation method was 81% for a MYO/C ratio of 6 with a myocardium/background ratio of 2.

Discussion

[^{123}I]MIBG scintigraphy is a non-invasive technique to assess cardiac sympathetic neuronal function and activity. In this study we evaluated various quantitation methods for cardiac [^{123}I]MIBG uptake.

The planar scintigraphy method showed good reproducibility but all observed ratios ranged from 1 to 2, probably due to overprojection, which makes it unsuitable for quantitation purposes. Also the interpatient variation in count density ratios was relatively small compared to the inter- and intra-observer coefficient of variation, resulting in a limited discriminative power. The count densities of the mediastinum and the lung showed a high patient-to-patient variability despite correction for dose and body weight and were therefore considered unsuitable as internal references.

The single-slice SPET method had large inter- and intra-observer coefficients of variation because of poor statistics of the left ventricular cavity count density. Increasing the size of the cavity region will reduce such noise but will decrease MYO/C, i.e. no acceptable reproducibility could be obtained in combination with acceptable accuracy. Similar to the planar method, large patient-to-patient variations in uptake for the other reference organs were encountered. Because none of the reference regions gave satisfactory results, the single-slice SPET method is not suitable for quantitative analysis.

The multi-slice SPET method showed good reproducibility combined with an accurate MYO/C ratio in the phantom study. The statistics for the left ventricular cavity were improved by using a volume of interest. Also the inter- and intra-observer coefficients of variation were quite small compared to the interindividual variation in count densities, which is a requirement for obtaining good discriminatory power. Furthermore, the ^{123}I activity in a venous blood sample corrected for dose and body weight showed a low interpatient variation.

The influence of the attenuation effects on the measured activity will be limited since the cavity area is contained within the myocardial area. This implies that the [^{123}I]MIBG activity in a venous blood sample can be used to calibrate the cavity count density and myocardial [^{123}I]MIBG activity can be calculated.

Elliptically shaped volumes of interest centered along the long axis were used because preliminary experiments showed a major improvement in reproducibility over manually drawn regions per slice, especially in the case of large myocardial regions with a decreased MIBG uptake.

The MYO/C count density ratios found for ^{123}I in the phantom were 81% of the actual ratios, reflecting adequate accuracy of this method. However, the heart phantom is small compared to the dilated and hypertrophic hearts normally encountered in clinical MIBG studies. A small heart is a worst case geometry for the quantitation, resulting in an underestimation of the MYO/C count density ratio.

To optimize reproducibility of the multi-slice SPET method a fixed cavity size of 80 voxels/slice was used, providing an acceptable MYO/C ratio. For the same reason a fixed distance of three pixels between the inner and outer boundaries of the MYO was used. The negative effects of moderate spatial resolution, respiration and cardiac motion (smoothing and blurring) were limited by quantitating the centre part of ventricular cavity and of the myocardial wall in a highly uniform and standardized manner. The distance between the C VOI and the inner boundary of the MYO VOI was kept as large as possible, to minimize the contribution of myocardial activity to the counts in the C VOI.

A possible limitation of the study is that the multi-slice SPET method was not validated. Using an endomyocardial biopsy to determine the actual myocardial [^{123}I]MIBG activity in vivo is not sufficient since regional variation in myocardial MIBG uptake has been demonstrated [16]. Moreover, no data are available on the reproducibility and accuracy of in vivo biopsy techniques. However, phantom studies showed an acceptable accuracy of this method in an unfavourable geometry.

In general, when using the multi-slice SPET method for myocardial receptor imaging, the issues of in vitro radiolysis and in vivo metabolism of the labelled compound must be resolved. It has been demonstrated by others that both radiolysis and metabolism of [^{123}I]MIBG are limited and hardly affect quantitation [2].

It must be stressed that the applicability of our multi-slice SPET quantitation method is limited to the whole myocardium. This method is probably less reliable when applied to small regions, as counts may be misregistered. Although this is a three-dimensional phenomenon, for the heart geometry the effects in two of the three dimensions are averaged out.

In conclusion, the results of this study indicate that the multi-slice SPET method as described, using the left ventricular cavity as a reference region in combination with a blood sample as a reference, is a reproducible and

accurate technique for the assessment of myocardial [^{123}I]MIBG uptake in vivo. Further evaluation of this method for cardiac quantitation, especially regarding segmental uptake, is needed.

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Addendum

The CASPAN tool (version 1.1) is a freeware package, programmed in IDL (version 3.5 Research Systems Inc., Boulder, Colo.) by the first and second authors. It is a post-processing package for use of files in the Interfile format. The code is portable and should run on most Unix, Macintosh and MS-windows based computers. Version 1.1 of CASPAN includes code for the measurement of absolute cardiac uptake and display in a bullseye format, normalized for defined size, as well as code to export intermediate results in CSV format for use in most commercial spreadsheet and statistical packages. A copy of the annotated code can be obtained from the first or second author for the cost of media and handling.

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