

Proposal for standardization of ^{123}I -metaiodobenzylguanidine (MIBG) cardiac sympathetic imaging by the EANM Cardiovascular Committee and the European Council of Nuclear Cardiology

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Abstract This proposal for standardization of ^{123}I -metaiodobenzylguanidine (iobenguane, MIBG) cardiac sympathetic imaging includes recommendations for patient information and preparation, radiopharmaceutical, injected activities and dosimetry, image acquisition, quality control, reconstruction methods, attenuation, scatter and collimator response compensation, data analysis and interpretation,

reports, and image display. The recommendations are based on evidence coming from original or scientific studies whenever possible and as far as possible reflect the current state-of-the-art in cardiac MIBG imaging. The recommendations are designed to assist in the practice of performing, interpreting and reporting cardiac sympathetic imaging. The proposed standardization does not include clinical indications,

Disclaimer This proposal summarizes the views of the Cardiovascular Committee of the EANM and the European Council of Nuclear Cardiology, and reflects recommendations for which the EANM and the ESC cannot be held responsible. The recommendations should be taken in the context of good practice of nuclear medicine and do not substitute for national and international legal or regulatory provisions.

On behalf of the Cardiovascular Committee of the EANM and the European Council of Nuclear Cardiology.

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benefits or drawbacks of cardiac sympathetic imaging, and does not address cost benefits or cost effectiveness; however, clinical settings of potential utility are mentioned. Standardization of MIBG cardiac sympathetic imaging should contribute to increasing its clinical applicability and integration into current nuclear cardiology practice.

Keywords MIBG imaging · Cardiac sympathetic imaging · Guidelines

Introduction

This proposal for standardization of MIBG cardiac sympathetic imaging was developed under the auspices of the Cardiovascular Committee of the European Association of Nuclear Medicine and the European Council of Nuclear Cardiology (joint group of the European Association of Nuclear Medicine and of the European Society of Cardiology). This proposal for standardization is intended to present information specifically adapted to European practice, it is based on evidence from available original scientific studies, and as far as possible it reflects the state-of-the-art in cardiac sympathetic imaging with MIBG.

The aim of this article is to document state-of-the-art applications and procedures supported by experts in the field and to help dissemination across the European nuclear cardiology community. The proposal for standardization is designed to assist physicians and other health-care professionals perform, interpret and report MIBG cardiac sympathetic imaging. The proposed standardization does not discuss clinical indications, benefits or drawbacks of cardiac sympathetic imaging, and does not cover cost benefit or cost effectiveness; however, some clinically useful settings are mentioned. The authors comprised scientists from different countries, all with subspeciality expertise in nuclear cardiology.

Patient information and preparation

Written information should be provided to patients or their relatives in relation to scheduling, duration, purpose and a brief description of the test. Additionally, oral information should be provided on the day of the procedure. On the other hand, information regarding clinical data, active medications and previous relevant cardiovascular examinations should be obtained from the patient. According to local regulations, it is also necessary to obtain a signed informed consent form. The radioactive nature of the procedure should be explained with mention of the injection of a nonallergenic radioactive isotope that is eliminated from the body quickly through natural decay and excretion. Radiation risks for the patient and accompanying

persons may be discussed according to local rules and patient demand.

Before injection of MIBG, specific information must be obtained in women of child-bearing age concerning pregnancy, lactation and the possibility of pregnancy. If pregnancy is suspected or confirmed, a clinical decision is necessary to consider the benefits against the possible harm of carrying out any radioactive procedure. It is unknown whether MIBG is excreted into human milk, but it is known that ^{123}I is excreted into human milk. Based on the physical half-life of ^{123}I (13.2 h), breastfeeding should be discontinued for 48 h after MIBG administration in order to minimize the risk to nursing infants [1].

Patient preparation

The technologist, nurse or physician should explain to the patient the details of the scintigraphic study.

Usually, MIBG is administered after blockade of thyroid uptake of free ^{123}I , but it is possible that this can be omitted considering that ^{123}I is a gamma emitter (principal radiation emission of 159 keV, 83% of abundance) with a short half-life. Thyroid blockade can be achieved by oral administration of either potassium perchlorate (500 mg for adults, body weight-adjusted for children) or, if the patient is not allergic to iodine, potassium iodide solution or Lugol's solution (equivalent to 130 mg iodide for adults, body weight-adjusted for children) at least 30 min before injection of MIBG. For paediatric patients, newborns should receive 16 mg potassium iodide, children from 1 month to 3 years of age should receive 32 mg, and children from 3 to 13 years of age 65 mg.

From initial data obtained in patients with neuroendocrine tumours, several drugs are known, or may be expected, to interfere with organ MIBG uptake. However, many studies have demonstrated that cardiac MIBG imaging can be performed in patients with optimum medical therapy including beta-blockers, angiotensin-converting enzyme inhibitors and/or angiotensin receptor blockers [2–4]. Therefore, there is no need to withdraw such medication prior to cardiac MIBG imaging. Table 1 includes some of the most important medications that may influence MIBG organ uptake. In addition, it is also important that patients stop eating food containing vanillin and catecholamine-like compounds (e.g. chocolate and blue cheese) since some of these may interfere with the uptake of MIBG (depletion of granules) [5, 6]. Patients are encouraged to void frequently to facilitate excretion of the radiopharmaceutical.

Radiopharmaceutical

MIBG is an aralkylguanidine noradrenaline analogue resulting from the combination of the benzyl group of

Table 1 Most important medications that may affect organ uptake of MIBG

Drug		Mechanism of interference (known or expected)	Discontinuation prior to MIBG scan (days)
Opioids		Uptake inhibition	7–14
Cocaine		Uptake inhibition	7–14
Tramadol		Uptake inhibition	7–14
Tricyclic antidepressants	Amitriptyline and derivatives, imipramine and derivatives, amoxapine, doxepine, others	Uptake inhibition	7–21
Sympathomimetics ^a	Phenylpropanolamine, ephedrine, pseudoephedrine, phenylephrine, amphetamine, dopamine, isoproterenol, salbutamol, terbutaline, phenoterol, xylometazoline	Depletion of granules	7–14
Antihypertensive/ cardiovascular agents	Labetalol	Inhibition uptake and depletion	21
	Reserpine	Depletion and transport inhibition	14
	Bretylium, guanethidine	Depletion and transport inhibition	14
	Calcium channel blockers (nifedipine, nicardipine, amlodipine)	Increased uptake and retention	14
Antipsychotics	Phenothiazines ^b (chlorpromazine, promethazine, fluphenazine, others)	Uptake inhibition	21–28
	Thioxanthenes (maprotiline, trazolone)	Uptake inhibition	21–28
	Butyrophenones (droperidol, haloperidol)	Uptake inhibition	21–28
	Loxapine	Uptake inhibition	7–21

^a Components of bronchodilators, decongestants and diet aids.

^b Frequent components of antiemetic and antiallergic agents.

Modified from reference [1].

bretylium and the guanidine group of guanethidine. Iodination of MIBG with ¹²³I enables successful imaging of neuroectodermally derived cells [7]. MIBG is internalized by neuroendocrine cells through the energy-dependent uptake-1 system, and is stored, unmetabolized, in the neurosecretory granules, resulting in a specific concentration in contrast to cells of other tissues.

MIBG for imaging disorders of sympathetic innervation of the heart is labelled with ¹²³I. In addition, MIBG can be used to study tumours of neuroendocrine origin, particularly those of the sympathoadrenal system (phaeochromocytomas, paragangliomas and neuroblastomas), although other neuroendocrine tumours (carcinoids, medullary thyroid carcinoma, Merkel cell tumours of the skin) and metastases of these tumours can also potentially be visualized.

Preparation

MIBG is normally radioiodinated by isotope exchange and distributed to laboratories where no additional preparation is required. The preparation should have a high specific activity. Extensive quality control (QC) is normally performed on the preparation by the producer before shipping. Laboratories receiving MIBG should assay the radioactive concentration by measurement in a calibrated ionization chamber. Radiochemical purity may be confirmed using thin-layer chromatography. The preparation may be diluted with sterile

physiological saline if required. The radiopharmaceutical should be used within the expiry time set by the supplier.

The activity of radiopharmaceutical to be administered should be determined in accordance with the European Atomic Energy Community Treaty, and in particular article 31, which has been adopted by the Council of the European Union (Directive 97/43/EURATOM) [8].

Administration

MIBG should be administered by slow (over 1 to 2 min) secure peripheral intravenous injection flushed with saline, in accordance with local radiation protection practices. If paravenous injection is suspected, imaging may be tried, and if sufficient activity uptake has been obtained, the examination can be performed; otherwise, the examination should be repeated whenever possible.

Contraindications

MIBG is contraindicated in patients with known hypersensitivity to MIBG or MIBG sulphate.

Side effects

Very rarely (<1%) adverse effects of MIBG (dizziness, rash, pruritus, flushing and injection site haemorrhage) can occur

when slow injection is used. Rapid or central venous injections are contraindicated since they may induce these effects [9]. The benzyl alcohol constituent of MIBG may cause serious adverse reactions in premature or low birth-weight infants, and exposure to excessive amounts has been associated with a fatal “gasping syndrome”, hypotension, metabolic acidosis and increased incidence of kernicterus. The safety and effectiveness of MIBG have not been established in neonates below the age of 1 month [9].

A skin eruption after an intravenous injection of ^{131}I -MIBG suggestive of an adverse allergic reaction has been reported [10], which could draw attention to a potential similar adverse allergic reaction to ^{123}I -MIBG. Therefore, prior to administration, patients should be questioned for a history of reactions to iodine, an iodine-containing contrast agent or other products containing iodine. If the patient is known or strongly suspected to have hypersensitivity to iodine, an iodine-containing contrast agent or other products containing iodine, the decision to administer MIBG should be based upon an assessment of the expected benefits compared to the potential risks of hypersensitivity.

Physiological distribution

The uptake of MIBG in different organs depends on catecholamine excretion and/or adrenergic innervation. Most MIBG is excreted unaltered by glomerular filtration; <1% of the injected dose is eliminated via the faeces. A rapid initial clearance of circulating MIBG is observed, followed by a slow clearance as MIBG is released from other compartments. In patients with normal renal function, approximately 50% of the administered radioactivity appears in the urine by 24 h, and 70–90% of the residual activity is recovered within 48 h. MIBG is not cleared by dialysis. MIBG is generally taken up mainly by the liver; lower uptake has been reported in the spleen, lungs, salivary glands, thyroid, skeletal muscles and myocardium. Normal adrenal glands do not usually show activity, but faint uptake may be visible 48 h after injection in up to 15% of patients. MIBG may accumulate to a variable degree in the nasal mucosa, lungs, gallbladder, colon, uterus, bladder and urinary tract. Free ^{123}I in the bloodstream may lead to some uptake in the digestive system and also in the thyroid (if not properly blocked). Bone uptake is not seen after MIBG administration [1, 5, 7].

Administered activity, dosimetry and radiation exposure

It is not possible to make precise recommendations regarding injected activities in this proposal for standardization since solid evidence documenting superior results with certain activities is not available. The injected activity

is always a compromise between higher activities to obtain better image quality and lower activities to keep radiation doses as small as possible, taking into account the image acquisition and instrumentation used and the anthropometric characteristics of the patient.

Around 111–370 MBq of MIBG is administered in an adult patient of normal weight for a study on a multiple-head camera. The activities to be administered in paediatric patients should be in agreement with the views of the Paediatric and Dosimetry Committees of the EANM [11], with a minimum recommended activity of 80 MBq [11, 12]. The dosage recommendations should be taken in the context of “good practice” of nuclear medicine and do not substitute for national and international legal or regulatory provisions. Nuclear medicine physicians should respect the diagnostic reference levels and the rules dictated by local legislation. The injection of greater activities needs to be justified.

Radiation dosimetry

The absorbed radiation doses to various organs in healthy subjects of various ages following administration of MIBG are given in Table 2. The data are quoted from ICRP 80 [13]. The organs with the highest absorbed dose per unit activity administered (mGy/MBq) are the liver, bladder, gallbladder, spleen, heart, and adrenals. It is advisable to encourage frequent voiding for the first 48 h after MIBG administration to minimize radiation dose to the bladder.

In patients with severe renal impairment the absorbed radiation dose may be increased and the quality of images decreased due to the delayed elimination of the radiopharmaceutical. MIBG may have a limited role in the diagnostic evaluation of patients with severe renal impairment; moreover, the safety and efficacy of MIBG have not been established in these patients.

Radiation exposure

In general, radiation exposure to the hospital staff and to relatives of patients is limited, and no special precautions are needed.

Image acquisition

Instrumentation

A single (or multiple) head gamma camera is necessary to acquire planar and SPECT images. Dual- or triple-head systems represent the state of the art for SPECT imaging since they reduce the acquisition time for the same amount

Table 2 Absorbed doses per unit of activity of ^{123}I -MIBG administered (mGy/MBq)

Organ	5-year-old child	15-year-old child	Adult
Adrenals	0.045	0.022	0.017
Bladder	0.084	0.061	0.048
Bone surfaces	0.034	0.014	0.011
Brain	0.016	0.0060	0.0047
Breast	0.017	0.0068	0.0053
Gallbladder	0.054	0.025	0.021
Stomach	0.030	0.011	0.0084
Small intestine	0.030	0.011	0.0084
Colon	0.029	0.011	0.0086
Heart	0.055	0.024	0.018
Kidneys	0.036	0.017	0.014
Liver	0.18	0.087	0.067
Lungs	0.049	0.023	0.016
Muscles	0.020	0.0084	0.0066
Oesophagus	0.021	0.0088	0.0068
Ovaries	0.025	0.011	0.0082
Pancreas	0.042	0.017	0.013
Red marrow	0.018	0.0079	0.0064
Skin	0.013	0.0051	0.0042
Spleen	0.066	0.028	0.020
Testes	0.018	0.0075	0.0057
Thymus	0.021	0.0088	0.0068
Thyroid	0.019	0.0073	0.0056
Uterus	0.029	0.013	0.010
Remaining organs	0.020	0.0085	0.0067
Effective dose (mSv/MBq)	0.037	0.017	0.013

Modified from reference [1]

of administered dose, thus reducing the likelihood of patient motion during the acquisition.

Although issues related to extensive availability of low-energy, high-resolution (LEHR) parallel-hole collimators determine their common use for ^{123}I studies, medium-energy (ME) collimators have been shown to provide superior semiquantitative accuracy in these types of studies [14–16]. This is because, in addition to the prime emission of 159-keV photons, ^{123}I emits high-energy photons of more than 400 keV (approximately 2.87%, main contributor 529 keV, 1.28%), which lead to penetration of the LEHR collimator septa and cause scatter detected in the 159-keV energy window. ME collimators minimize the effects of septal penetration [14–16].

The energy window is usually symmetrically centred to 20% of the 159-keV ^{123}I photopeak.

Acquisition modality

Planar images of the thorax are acquired 15 min (early image) and 4 h (late image) after injection, with the patient lying in the same supine position (female patients without wearing bra). Optionally, a SPECT study using a pixel size

of 6.4 ± 0.4 mm can be performed after early and late planar imaging, with the patient's left arm elevated above the head. Zoom should be performed as necessary for cameras with a large field of view.

Planar images are acquired for 10 min in the anterior view and stored in a 128×128 or 256×256 matrix. In addition to the type of collimation used, the time delay after injection of MIBG to the start of the acquisition and acquisition duration may explain variations in MIBG uptake semiquantification [17].

For SPECT studies using single- and dual-detector systems, a rotation of 180° is used, starting at 45° right anterior oblique projection and proceeding anticlockwise to the 45° left posterior oblique projection. Dual detectors should be in a 90° or "L" configuration. For triple-head systems, 360° rotation is used. Acquisitions at 180° generally give higher contrast resolution but more geometric distortions than the 360° rotation. Images are stored in a 64×64 matrix.

Comparable to myocardial perfusion SPECT imaging [18], 64 projections over 180° or 128 projections over 360° are usually recommended. The time per projection is a compromise between improved count statistics and increasing the

likelihood of patient movement. The overall acquisition time should be ≤ 25 min. The acquisition time or injected dose can be reduced with the combination of new iterative reconstruction methods with dedicated detectors and collimators optimized specifically for myocardial perfusion imaging [19, 20]. Compensation for attenuation and scatter (cf. Sect. "Attenuation, scatter and collimator response compensation") will slightly prolong the study time. Studies with gated SPECT have not been reported in the literature.

Quality control

QC includes assessment and calibration of gamma camera performance in planar and SPECT modes, as well as revision of the acquired and processed data [21, 22]. Checking of gamma camera performance should follow the manufacturer's specifications and should be measured according to the recommendations of the National Electrical Manufacturers Association [23]. The schedule and frequency of QC tests should accord with national guidelines and requirements.

The acquired cardiac sympathetic data must be reviewed immediately after acquisition and before the patient leaves the department to be able to correct any detected problem or repeat the acquisition. The review should be made with the rotating cinematic mode of data projection and a sinogram at the level of the myocardium, and should include the following:

- Complete data within the set of projection views (no blank/corrupted views).
- Expected count content of the study.
- Problems related to detectors (e.g. drift in energy window, unexpected detector artefacts).
- Smooth transition of images between projections and detector heads (for multiple-head acquisition).
- Attenuation artefacts.
- Patient motion.
- Unusual activity (e.g. injection site, arms at the side of the body).
- Truncation of cardiac activity or severe truncation of body activity.
- Consistent positioning and rotation orbit.

For QC regarding attenuation and scatter compensation, cf. Sect. "Attenuation, scatter and collimator response compensation"; for reconstruction and processing, cf. Sect. "SPECT reconstruction methods"; and for display, cf. Sect. "Reports, image display".

Different motion correction software packages are currently available to correct for vertical translational motion of the heart during acquisition. Some methods use external point sources [24], while others use fitting to an idealized sinogram [25]. If manual methods are chosen, consistent

landmarks should be used. Only those movements of two or more pixels in the projections are able to produce significant artefacts and are recommended to be corrected [25].

SPECT reconstruction methods

SPECT cardiac sympathetic images result from a complex process of reconstruction algorithms. A high quality of the acquired raw data is of paramount importance regardless of potential corrections that can be applied during the reconstruction process.

Two different reconstruction methods are currently available: the analytical or filtered back-projection (FBP) method and the statistical or iterative reconstruction method. FBP commonly uses a ramp filter in conjunction with a low-pass filter (e.g. Hanning or Butterworth) to reduce the high spatial frequency components of the image thus decreasing the noise (at the expense of a reduction in spatial resolution) of the image. Usually, the cut-off frequency and power factors of the low-pass filter may follow the recommendations of the vendors if standard activity amounts of radiopharmaceuticals and imaging techniques are used, although preferably they should be determined empirically by each department. The chosen filter should produce images of similar quality over a reasonable range of count levels. Filter characteristics should not be varied routinely, and if a study is expected to have low count rates, it is preferable to adjust the acquisition time. Care must be taken when filter parameters from one manufacturer's system are compared with those from another system since the mathematical definition of the filter may vary between systems.

Iterative reconstruction [26] works by creating the final image by successive approximations or estimates, and it does not require a filtering step such as the ramp filter in FBP. If the acquired data are noisy, a low-pass 2-D filter can be applied to the projection data or a 3-D post-filter can be applied to the tomographic images. The most commonly used iterative methods are the maximum likelihood expectation maximization (MLEM) and the ordered subsets expectation maximization (OSEM), the latter reducing the processing time [27]. The number of iterations should guarantee a sufficient quality of the images and depends on the method used and the image noise. Usually, 10 to 15 iterations are recommended for MLEM [28] and two for OSEM.

Reorientation of the reconstructed transaxial data into the three standard image planes should be consistent to avoid artefacts, which may be mistaken for sympathetic innervation defects. Automated methods of reorientation are available [29, 30], and have been shown to be at least as accurate as trained operators, and probably achieve greater reproducibility in SPECT myocardial perfusion studies.

However, these methods may fail in patients with large tracer uptake defects and cardiac orientation abnormalities. If manual reorientation is chosen, the operators should use reproducible landmarks for definition of the long axes. Common landmarks include the apex and points on the valve plane.

Attenuation, scatter and collimator response compensation

Currently most commercial camera systems offer a combination of software and hardware to perform attenuation, scatter and collimator response compensation. However differences from one vendor to another force to consult for each system characteristics before utilization. In addition, because of the rather fast development in the technology and the significantly different requirements of the systems available, it is not feasible at present to establish a standardization of these compensations. However, combined application of both the attenuation and the scatter compensation to the emission data is necessary since these data usually contain a significant percentage of scattered events. Failure to incorporate the effects of scatter into the attenuation map may result in over-compensation of the data and introduction of artefacts. There are several algorithms for scatter compensation with still no evidence in favour of any one of them: (1) utilization of one or more additional energy windows to model the scatter component [31, 32]; (2) reduction of the primary energy window to minimize scatter; and (3) modelling of the scatter based on the emission data [33]. The last of these algorithms is potentially the most attractive option, as unlike the others it does not incorporate additional noise into the data [33]. However, data on the effect of scatter correction methods in MIBG studies on semiquantitative cardiac analysis are limited [14, 16].

The purpose of depth-dependent resolution recovery algorithms is to improve the uniformity of resolution over the myocardium since parameters such as type of collimation, type of orbit and acquisition arc affect spatial resolution and result in different resolution of the images with rotation. The accuracy and validity of these algorithms has not been well studied, but they probably improve SPECT imaging, especially when they are incorporated in combination.

Noncompensated and compensated data should be viewed side by side to determine changes in image quality resulting from the compensation applied [34]. Furthermore, careful QC of the attenuation map (e.g. uniformity of attenuation coefficients, truncation, and definition of lung boundaries) and its registration with the emission are essential.

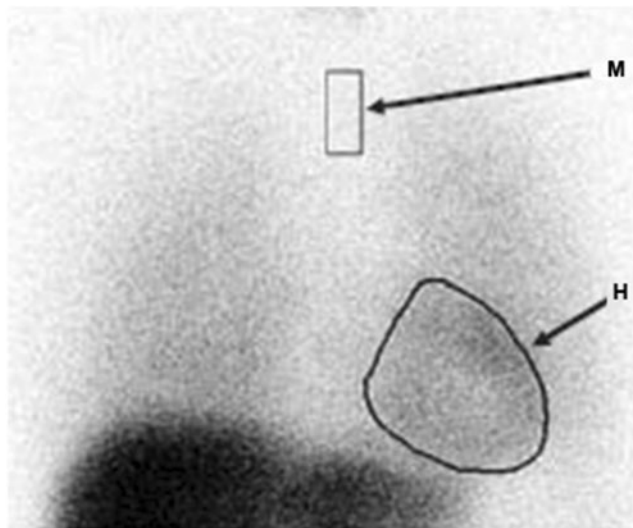
Data analysis and interpretation

For adequate interpretation of cardiac sympathetic images, a systematic visual review of planar and SPECT raw data and reconstructed images on a computer screen is recommended. The system for reviewing comprises several reviewing levels of increasing complexity:

- Simple analysis of raw data for assessment of QC, LV size and degree of lung uptake of the tracer.
- Planar H/M ratio semiquantification (Fig. 1).
- SPECT slices (without and, if available, with attenuation/scatter/collimator response compensation).
- Polar maps.
- Integration with clinical data.

MIBG uptake is semiquantified by calculating a heart-to-mediastinum (H/R) ratio [35, 36], after drawing ROIs over the heart (including or not including the cavity) and the upper mediastinum (avoiding the thyroid gland) in the planar anterior view. Average counts per pixel in the myocardium are divided by average counts per pixel in the mediastinum [37]. The myocardial washout rate (WR) from initial to late images is also calculated, and expressed as a percentage, as the rate of decrease in myocardial counts over time between early and late imaging (normalized to mediastinal activity) (Fig. 1). The late H/M ratio reflects the relative distribution of sympathetic nerve terminals, offering global information about neuronal function resulting from uptake, storage and release [38]. The WR reflects the neuronal integrity or sympathetic tone, mainly representing uptake-1 [38]. More studies are needed to establish the differences between early H/M ratio, late H/M ratio and WR. Intraobserver and interobserver variability in these calculations are <5% [37]. Normal values for late H/M ratio and WR vary in relation to age (inversely for the late H/M ratio, directly for the WR) [36, 39] and image acquisition (LEHR vs. ME collimation and acquisition time). A time decay correction is required when comparing different image acquisition times (Fig. 1). Improved standardization of cardiac MIBG imaging protocols would contribute to increased clinical applicability of this procedure [3, 17].

For SPECT image interpretation, tomographic slices should be assessed scaled to the planar appearance. All three image planes should be inspected: short axis, horizontal long axis and vertical long axis. Late and early images should be identically aligned in such a way that the tomograms are carefully displayed with anatomically corresponding late and early slices under each other, from apex to base. Preferably, a format that allows simultaneous inspection of the three image planes is used. A continuous colour scale should be used, preferably the same as that employed for myocardial perfusion imaging (Fig. 2). If attenuation/scatter/collimator response compensation has



$$H/M = \frac{\{H\}}{\{M\}}$$

$$WR = \frac{\{H\}_e - (\{H\}_i \times 1.21^*)}{\{H\}_e} \times 100$$

$$WR_{BKG \text{ corrected}} = \frac{(\{H\}_e - \{M\}_e) - ((\{H\}_i - \{M\}_i) \times 1.21^*)}{(\{H\}_e - \{M\}_e)} \times 100$$

{ } = mean counts per pixel

* = ^{123}I decay correction for 3 h and 45 min ($1 \div 0.8213$)

Fig. 1 Semiquantification of MIBG uptake on the planar anterior view of the thorax. Heart-to-mediastinum ratio (H/R) and myocardial washout rate (WR) are calculated after drawing a ROI over the heart (H) and the upper mediastinum (M) in the early (e) and late (l) images (BKG background)

been applied, both images with and images without compensation should be evaluated (cf. Sect. "Attenuation, scatter and collimator response compensation") and cf. Sect. "Reports, image display").

Polar maps (bull's eye) display facilitates assessment of the presence, extent and location of sympathetic abnormalities. LV size, however, is not represented in the polar map. In addition, the polar map does not disclose possible artefacts such as extracardiac hot spots or attenuation problems. Polar maps should be derived from an identical delineation and orientation of the early and late tomograms. Otherwise, the corresponding parts of the polar maps will not relate to identical parts of the myocardium and false-positive differences in sympathetic activity may be seen in the polar maps. Some programs include manual steps such as identification of apex and base in the short axis slices, resulting in considerable interoperator variability. Completely automated programs have the advantage of low interoperator variability, but there can be considerable differences between different automated programs, which should be taken into account, especially if more than one program is used at the same site.

Three-dimensional display of the LV may also facilitate assessment of the presence, extent and location of sympathetic abnormalities, and would allow assessment of LV size and configuration. In addition it may be helpful for correlation of sympathetic activity data with other examinations such as myocardial perfusion, echocardiography and coronary angiography, in particular in the communication with clinical cardiologists. Careful interpretation should be performed, with knowledge of normal variants and potential artefacts. Normal cardiac MIBG distribution includes a relatively low uptake in the inferior wall [40], which is more pronounced in the elderly. In addition, there may be substantial MIBG uptake in the liver, which overlaps the inferior LV wall (Fig. 2). Moreover, scattering from the lung field to the lateral LV wall may also occur.

An area of decreased uptake of the radiopharmaceutical should be described with respect to localization, severity and extent. One approach consists of dividing the myocar-

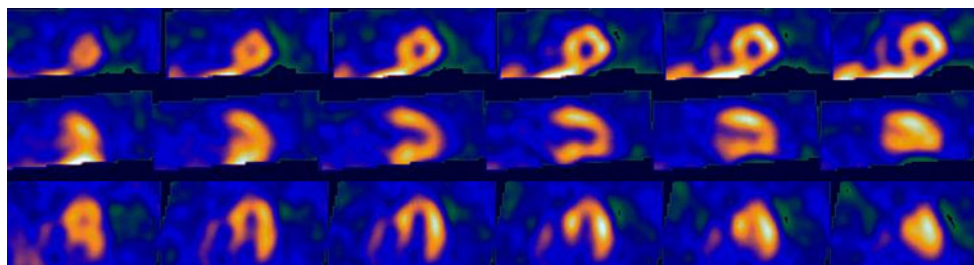


Fig. 2 Normal MIBG cardiac sympathetic SPECT study. Images were obtained 4 h after tracer injection. There is homogeneous distribution of the radiotracer throughout the left ventricular walls. *Top row*: short-axis slices (extending from the apex to the base). *Middle row*: vertical

long-axis slices (extending from the septum to the lateral wall). *Bottom row*: horizontal long-axis slices (extending from the inferior wall to the anterior wall)

dium into a standardized 17-segment model using the associated nomenclature, parallel to myocardial perfusion SPECT [41]. It is essential to bear in mind that since SPECT imaging only provides information about relative innervation heterogeneity, tracer uptake in the different segments is assigned to a relative scale where the best innervation region is set to maximum and has the brightest colour. Therefore, SPECT segments should be mentally rescaled according to the level of tracer uptake of the late planar image and corresponding H/M ratio. Accordingly, a five-point scale ranging from 0 (normal uptake) to 4 (uptake absent) can be used to score each segment. The total score of the LV is referred to as the summed score, which has been shown to be of prognostic value [42]. The extent of tracer uptake abnormality can be qualified as small, intermediate or large in terms of the number of segments affected or the percentage of LV involvement (e.g. <11%, 11–19% and >20%, respectively).

Variables such as patient age, acquisition and processing protocols, as well as the compensation algorithms applied, can potentially influence cardiac sympathetic images. Therefore there is a need to develop programs that highlight regions with “significantly” reduced tracer uptake and quantify the extent and severity of sympathetic activity defects, based on suitable databases comprising different reference populations and similar acquisition/processed parameters for the examined patient. Simultaneous assessment of myocardial sympathetic and perfusion imaging allows evaluation of the presence of match/mismatch, and may have additional value in particular in patients with arrhythmogenic risk [4].

Reports, image display

Reports should be concise and easily understandable by referring physicians.

The patient’s personal details (name, age, date of birth and gender) should be included at the start of the report. Any hospital/clinic identification number and the source of the referral should also be included. The clinical indication (s) for the study should be stated, including relevant clinical history. The information provided in this section supports the justification for the study and provides a focus for the final conclusion.

The appearance of images should be described succinctly, including a statement on quality if suboptimal. Sympathetic activity defects should be classified in terms of location relative to myocardial walls, extent and severity. Other abnormalities that should be mentioned are LV dilatation, increased lung uptake of tracer, or significant noncardiopulmonary tracer uptake. The findings should be integrated with the clinical data to reach a final interpretation. A comparison with any previous study should be included.

If the study is considered normal, this should be stated, specifically bearing in mind that homogeneous cardiac sympathetic activity confers a benign prognosis [43]. If the study is abnormal, the report should comment on the presence (if any) of focal or diffuse sympathetic abnormalities and significant artefact. If there is an abnormality, its location (in terms of segments affected), extent (in terms of numbers of segments affected) and severity (in terms of summed score) should be noted.

Hard copies of the anterior planar early and late images should accompany the report. Optionally, all three SPECT projections in the standard orientation should be represented with careful alignment of the early and late slices. If multiple slices are presented then short axis slices should be displayed with the apical slices to the far left and progression of slices toward the base in a left to right mode, vertical long axis slices should be displayed left to right from the septal slices through the midventricular slices to the lateral slices and with the apex on the right, and horizontal long axis slices should proceed left to right from the inferior to the anterior/superior surface with the apex on the top (Fig. 2) [44].

Early and late images should be presented in a format that allows ready comparison of corresponding tomograms. Polar map displays can additionally be appended. It is recommended that images be displayed using a continuous colour scale, which should be shown on all image reproductions. Each set of tomograms should be displayed with the top of the colour scale at the maximum within the myocardium for each set. Care should be taken if the maximum lies outside the myocardium or in different myocardial locations between late and early studies; these are cases where manual adjustment or masking of extracardiac activity may be required. The bottom end of the colour scale should be set to zero and background subtraction should be avoided.

Clinical settings

Reduced cardiac MIBG uptake has been observed in patients with chronic heart failure, and among these patients, those with the lowest uptake tend to have the poorest prognosis [35, 38, 43, 45–49]. Some studies have also revealed that abnormalities of cardiac MIBG uptake may be predictive of increased risk of ventricular arrhythmia and sudden cardiac death [42, 50–53]. Efforts need to be made to standardize the procedure to help obtain extensive data and appropriate evidence to support routine clinical application. Accordingly, indications for MIBG cardiac imaging have been included in the guidelines for the clinical use of cardiac nuclear medicine published by the Japanese Circulation Society [54]. In these guidelines,

MIBG cardiac imaging has received class I classification for the evaluation of severity and prognosis of heart failure, but at evidence level C, since most studies had been conducted in a small number of patients at a single institution. A number of studies have recently been published with larger numbers of patients in Europe and the US, including prospective and multicentre accrual, and have provided additional evidence on the utility of cardiac sympathetic imaging in heart failure. The ADMIRE-HF study has recently provided validation of the independent prognostic value of cardiac MIBG imaging in the assessment of patients with heart failure [43].

References

- Bombardieri E, Aktolun C, Baum RP, Bishof-Delaloye A, Buscombe J, Chatal JF, et al. 131I/123I-Metaiodobenzylguanidine (MIBG) scintigraphy procedure guidelines for tumour imaging. https://www.eanm.org/scientific_info/guidelines/gl_onco_mibg.pdf. Accessed 24 May 2010.
- Yamashina S, Yamazaki J. Neuronal imaging using SPECT. *Eur J Nucl Med Mol Imaging* 2007;34:S62–73.
- Agostini D, Carrió I, Verberne HJ. How to use myocardial 123I-MIBG scintigraphy in chronic heart failure. *Eur J Nucl Med Mol Imaging* 2009;36:555–9.
- Carrió I, Cowie MR, Yamazaki J, Udelson J, Camici PG. Cardiac sympathetic imaging with MIBG in heart failure. *Am Coll Cardiol Img* 2010;3:92–100.
- Solanki KK, Bomanji J, Moyes J, Mather SJ, Trainer PJ, Britton KE. A pharmacological guide to medicines which interfere with the biodistribution of radiolabelled meta-iodobenzylguanidine (MIBG). *Nucl Med Commun* 1992;13:513–21.
- Wafelman AR, Hoefnagel CA, Maes RA, Beijnen JH. Radioiodinated metaiodobenzylguanidine: a review of its biodistribution and pharmacokinetics, drug interaction, cytotoxicity and dosimetry. *Eur J Nucl Med* 1994;21:545–59.
- Shapiro B, Gross MD. Radiochemistry, biochemistry, and kinetics of 131I-metaiodobenzylguanidine (MIBG) and 123I-MIBG: clinical implications of the use of 123I-MIBG. *Med Pediatr Oncol* 1987;15:170–7.
- European Commission. Council Directive 97/43/Euratom of 30 June 1997 on health protection of individuals against the dangers of ionizing radiation in relation to medical exposure, and repealing Directive 84/466/Euratom. *Official Journal of the European Union L* 1997;180:22–7.
- GE Healthcare. AdreView: Iobenguane I 123 injection. Revised September 2008. URL: <http://md.gehealthcare.com/shared/pdfs/pi/adreview.pdf>. Accessed 24 May 2010.
- Ishibashi N, Abe K, Furuhashi S, Fukushima S, Yoshinobu T, Takahashi M, et al. Adverse allergic reaction to 131I MIBG. *Ann Nucl Med* 2009;23:697–9.
- Jacobs F, Thierens H, Piepsz A, Bacher K, Van de Wiele C, Ham H, et al. Optimized tracer-dependent dosage cards to obtain weight independent effective doses. *Eur J Nucl Med Mol Imaging* 2005;32:581–8.
- Olivier P, Colarinha P, Fettich J, Fischer S, Frökier J, Giammarile F, et al. Guidelines for radioiodinated MIBG scintigraphy in children. *Eur J Nucl Med Mol Imaging* 2003;30:B45–50.
- ICRP. Radiation dose to patients from radiopharmaceuticals. ICRP Publication 80. *Ann ICRP* 1998;28(3).
- Verberne HJ, Feenstra C, de Jong WM, Somsen GA, Van Eck-Smit BL, Busemann Sokole E. Influence of collimator choice and simulated clinical conditions on 123I-MIBG heart/mediastinum ratios: a phantom study. *Eur J Nucl Med Mol Imaging* 2005;32:1100–7.
- Dobbeleir AA, Hambye AS, Franken PR. Influence of high energy photons on the spectrum of iodine-123 with low- and medium-energy collimators: consequences for imaging with 123I labelled compounds in clinical practice. *Eur J Nucl Med* 1999;26:655–8.
- Inoue Y, Suzuki A, Shirouzu I, Machida T, Yoshizawa Y, Akita F, et al. Effect of collimator choice on quantitative assessment of cardiac iodine 123 MIBG uptake. *J Nucl Cardiol* 2003;10:623–32.
- Verberne HJ, Habraken JB, van Eck-Smit BL, Agostini D, Jacobson AF. Variations in 123I-metaiodobenzylguanidine (MIBG) late heart mediastinal ratios in chronic heart failure: a need for standardisation and validation. *Eur J Nucl Med Mol Imaging* 2008;35:547–53.
- Hesse B, Tägil K, Cuocolo A, Anagnostopoulos C, Bardies M, Bax J, et al. EANM/ESC procedural guidelines for myocardial perfusion imaging in nuclear cardiology. *Eur J Nucl Med Mol Imaging* 2005;32:855–97.
- Slomka PJ, Patton JA, Berman DS, Germano G. Advances in technical aspects of myocardial perfusion SPECT imaging. *J Nucl Cardiol* 2009;16:255–76.
- Esteves FP, Raggi P, Folks RD, Keidar Z, Askew JW, Rispler S, et al. Novel solid-state-detector dedicated cardiac camera for fast myocardial perfusion imaging: multicenter comparison with standard dual detector cameras. *J Nucl Cardiol* 2009;16:927–34.
- IAEA. Quality control of nuclear medicine instruments 1991. TECDOC-602. International Atomic Energy Agency, Vienna
- Society of Nuclear Medicine. Procedure guideline for general imaging, version 2.0. Reston, VA: Society of Nuclear Medicine, 2004.
- NEMA. Standards publication NU 1-2001: Performance measurements of scintillation cameras. Rosslyn, VA: National Electrical Manufacturers Association, 2001.
- Germano G, Chua T, Kavanagh PB, Kiat H, Berman DS. Detection and correction of patient motion in dynamic and static myocardial SPECT using a multi-detector camera. *J Nucl Med* 1993;34:1349–55.
- Matsumoto N, Berman DS, Kavanagh PB, Gerlach J, Hayes SW, Lewin HC, et al. Quantitative assessment of motion artifacts and validation of a new motion-correction program for myocardial perfusion SPECT. *J Nucl Med* 2001;42:687–94.
- Hutton BF, Hudson HM, Beekman FJ. A clinical perspective of accelerated statistical reconstruction. *Eur J Nucl Med* 1997;24:797–808.
- Hudson HM, Larkin RS. Accelerated image reconstruction using ordered subsets of projection data. *IEEE Trans Nucl Sci* 1994;41:601–9.
- Llacer J, Velkerov E. Feasible images and practical stopping rules for iterative algorithms in emission tomography. *IEEE Trans Med Imaging* 1989;8:186–93.
- Germano G, Kavanagh PB, Chen J, Waechter P, Su HT, Kiat H, et al. Operator-less processing of myocardial perfusion SPECT studies. *J Nucl Med* 1995;36:2127–32.
- Slomka PJ, Hurwitz GA, Stephenson J, Craddock T. Automated alignment and sizing of myocardial stress and rest scans to three-dimensional normal templates using an image registration algorithm. *J Nucl Med* 1995;36:1115–22.
- Kobayashi H, Momose M, Kanaya S, Kondo C, Kusakabe K, Mitsuhashi N. Scatter correction by two-window method standardizes cardiac I-123 MIBG uptake in various gamma camera systems. *Ann Nucl Med* 2003;17:309–13.

32. Nakajima K, Matsubara K, Ishikawa T, Motomura N, Maeda R, Akhter N, et al. Correction of iodine-123-labeled metaiodobenzylguanidine uptake with multi-window methods for standardization of the heart-to-mediastinum ratio. *J Nucl Cardiol* 2007;14:843–51.
33. Zaidi H, Koral KF. Scatter modelling and compensation in emission tomography. *Eur J Nucl Med Mol Imaging* 2004;31:761–82.
34. Wackers FJT. Attenuation compensation of cardiac SPECT: a critical look at a confusing world (editorial). *J Nucl Cardiol* 2002;9:438–40.
35. Merlet P, Valette H, Dubois-Rande JL, Moyses D, Duboc D, Dove P, et al. Prognostic value of cardiac metaiodobenzylguanidine imaging in patients with heart failure. *J Nucl Med* 1992;33:471–7.
36. Estorch M, Carrió I, Berna L, Lopez-Pousa J, Torres G. Myocardial iodine-labeled metaiodobenzylguanidine uptake relates to age. *J Nucl Cardiol* 1995;2:126–32.
37. Somsen GA, Verberne HJ, Fleury E, Righetti A. Normal values and within-subject variability of cardiac I-123 MIBG scintigraphy in healthy individuals: implications for clinical studies. *J Nucl Cardiol* 2004;11:126–33.
38. Wakabayashi T, Nakata T, Hashimoto A, Yuda S, Tsuchihashi K, Travin MI, et al. Assessment of underlying etiology and cardiac sympathetic innervation to identify patients at high risk of cardiac events. *J Nucl Med* 2001;42:1757–67.
39. Chen W, Botvinick EH, Alavi A, Zhang Y, Yang S, Perini R, et al. Age-related decrease in cardiopulmonary adrenergic neuronal function in children as assessed by I-123 metaiodobenzylguanidine imaging. *J Nucl Cardiol* 2008;15:73–9.
40. Gill JS, Hunter GJ, Gane G, Camm AJ. Heterogeneity of the human myocardial sympathetic innervation: in vivo demonstration by iodine 123-labeled metaiodobenzylguanidine scintigraphy. *Am Heart J* 1993;126:390–8.
41. Cerqueira MD, Weissman NJ, Dilsizian V, Jacobs AK, Kaul S, Laskey WK, et al. Standardized myocardial segmentation and nomenclature for tomographic imaging of the heart. A statement for healthcare professionals from the Cardiac Imaging Committee of the Council on Clinical Cardiology of the American Heart Association. *Circulation* 2002;105:539–42.
42. Bax JJ, Kraft OR, Buxton AE, Fjeld JG, Parizek P, Agostini D, et al. 123I-mIBG Scintigraphy to predict inducibility of ventricular arrhythmias on cardiac electrophysiology testing: a prospective multicenter pilot study. *Circ Cardiovasc Imaging* 2008;1:131–40.
43. Jacobson AF, Senior R, Cerqueira MD, Wong ND, Thomas GS, Lopez VA, et al. Myocardial iodine-123 meta-iodobenzylguanidine imaging and cardiac events in heart failure. Results of the prospective ADMIRE-HF (AdreView Myocardial Imaging for Risk Evaluation in Heart Failure) study. *J Am Coll Cardiol* 2010;55:2212–21.
44. American Heart Association, American College of Cardiology, and Society of Nuclear Medicine. Standardization of cardiac tomographic imaging. From the Committee on Advanced Cardiac Imaging and Technology, Council on Clinical Cardiology, American Heart Association; Cardiovascular Imaging Committee, American College of Cardiology; and Board of Directors, Cardiovascular Council, Society of Nuclear Medicine. *Circulation* 1992;86:338–9.
45. Merlet P, Benvenuti C, Moyses D, Pouillart F, Dubois-Rande JL, Duval AM, et al. Prognostic value of MIBG imaging in idiopathic dilated cardiomyopathy. *J Nucl Med* 1999;40:917–23.
46. Cohen-Solal A, Esanu Y, Logeart D, Pessione F, Dubois C, Dreyfus G, et al. Cardiac metaiodobenzylguanidine uptake in patients with moderate chronic heart failure: relationship with peak oxygen uptake and prognosis. *J Am Coll Cardiol* 1999;33:759–66.
47. Yamada T, Shimonagata T, Fukunami M, Kumagai K, Ogita H, Hirata A, et al. Comparison of the prognostic value of cardiac iodine-123 metaiodobenzylguanidine imaging and heart rate variability in patients with chronic heart failure: a prospective study. *J Am Coll Cardiol* 2003;41:231–8.
48. Verberne HJ, Brewster LM, Somsen GA, van Eck-Smit BL. Prognostic value of myocardial 123I-metaiodobenzylguanidine (MIBG) parameters in patients with heart failure: a systematic review. *Eur Heart J* 2008;9:1147–59.
49. Agostini D, Verberne HJ, Burchert W, Knuuti J, Povinec P, Sambucetti G, et al. I-123-mIBG myocardial imaging for assessment of risk for a major cardiac event in heart failure patients: insights from a retrospective European multicenter study. *Eur J Nucl Med Mol Imaging* 2008;35:535–46.
50. Arora R, Ferrick KJ, Nakata T, Kaplan RC, Rozengarten M, Latif F, et al. I-123 MIBG imaging and heart rate variability analysis to predict the need for an implantable cardioverter defibrillator. *J Nucl Cardiol* 2003;10:121–31.
51. Paul M, Schafers M, Kies P, Acil T, Schafers K, Breithardt G, et al. Impact of sympathetic innervation on recurrent life-threatening arrhythmias in the follow-up of patients with idiopathic ventricular fibrillation. *Eur J Nucl Med Mol Imaging* 2006;33:866–70.
52. Nagahara D, Nakata T, Hashimoto A, Wakabayashi T, Kyuma M, Noda R, et al. Predicting the need for an implantable cardioverter defibrillator using cardiac metaiodobenzylguanidine activity together with plasma natriuretic peptide concentration or left ventricular function. *J Nucl Med* 2008;49:225–33.
53. Tamaki S, Yamada T, Okuyama Y, Morita T, Sanada S, Tsukamoto Y, et al. Cardiac iodine-123 metaiodobenzylguanidine imaging predicts sudden cardiac death independently of left ventricular ejection fraction in patients with chronic heart failure and left ventricular systolic dysfunction: results from a comparative study with signal-averaged electrocardiogram, heart rate variability, and QT dispersion. *J Am Coll Cardiol* 2009;53:426–35.
54. Tamaki N, Kusakabe K, Kubo A, Kumazaki T, Shimamoto K, Senda S, et al. Guidelines for clinical use of cardiac nuclear medicine (JSC2005). *Circ J* 2005;69 Suppl 4:1125–202.