

# <sup>123</sup>I-mIBG Cardiac Sympathetic Innervation Scintigraphy

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**Preamble:** The information in this section on <sup>123</sup>I-metaiodobenzylguanidine (*m*IBG) cardiac sympathetic imaging is largely based on the Proposal for standardization of <sup>123</sup>I-metaiodobenzylguanidine (*m*IBG) cardiac sympathetic imaging by the EANM Cardiovascular Committee and the European Council of Nuclear Cardiology.

## 1. Introduction

In heart failure, abnormal activity of the sympathetic nervous system has been shown to be of pathophysiological importance. Increased neuronal release of norepinephrine (NE) in response to a deterioration of cardiac function is accompanied by decreased presynaptic NE reuptake due to down regulation of the cardiac NE transporter. If prolonged, this leads to a reactive desensitization of the myocardial beta-adrenergic receptors in the synaptic cleft, further exacerbating ventricular dysfunction.

*m*IBG is a radio-labelled NE-analogue that allows for the visualization and quantification of myocardial sympathetic innervation. *m*IBG shares the same uptake, storage and release mechanisms as NE but is not metabolized.

Reduced cardiac *m*IBG uptake has been observed in patients with chronic heart failure (CHF), and those with the lowest uptake tend to have the poorest prognosis. The two available meta-analyses on the prognostic role of *m*IBG in CHF showed that CHF subjects with abnormal myocardial *m*IBG parameters had a significantly worse prognosis compared to those with relatively preserved myocardial *m*IBG parameters (i.e. late H/M and *m*IBG myocardial washout). The ADMIRE-HF trial demonstrated for the first time in a large prospective study that the late H/M ratio, especially in conjunction with left ventricular ejection fraction (LVEF) and B-type natriuretic peptide (BNP), is a strong independent predictor of prognosis in HF patients.

## 2. Methodology

This guideline is based on available scientific literature on the subject, the previous guideline (Aanbevelingen Nucleaire Geneeskunde 2007), international guidelines from EANM and/or SNMMI if available and applicable to the Dutch situation.

## 3. Indications

*m*IBG can be used for the evaluation of severity and prognosis of heart failure. In addition some studies have shown that myocardial *m*IBG uptake may be predictive of increased risk of ventricular arrhythmia and sudden cardiac death. However these later findings need to be confirmed in ongoing trials.

## 4. Relation to other diagnostic procedures

The recent publication by Nakata et al. confirmed, by pooled analyses of independent cohort studies from Japan, the long-term prognostic value of cardiac *m*IBG uptake in patients with chronic heart failure independently of other markers, such as NYHA

functional class, BNP, and LVEF. However, the lack of consensus on how to extrapolate the available *m*IBG data into clinical practice is reflected in the absence of *m*IBG in the majority of current guidelines regarding heart failure except in Japan. The Japanese Circulation Society guidelines for nuclear cardiology list the use of *m*IBG for the evaluation of severity and prognosis of heart failure as class I recommendation (general agreement of effectiveness and usefulness) based on level B evidence (verified by two or more multicentre randomized intervention trials on fewer than 400 patients, well-designed comparative studies, or large-scale cohort studies). As the amount of high-quality data continues to accumulate, it is likely that *m*IBG imaging will eventually be incorporated into the European and the USA HF guidelines. However the prerequisite for this is that future studies must be of high quality and with sufficient numbers of patients to allow for adequate and statistically reliable analyses.

**5. Medical information necessary for planning**

Prior to administration, patients should be asked about 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 *m*IBG should be based upon an assessment of the expected benefits compared to the potential risks of hypersensitivity.

*m*IBG is contraindicated in patients with known hypersensitivity to *m*IBG or *m*IBG sulphate.

**6. Radiopharmaceutical**

- Tracer: <sup>123</sup>I-metaiodobenzylguanidine
- Nuclide: Iodine-123
- Activity: 185 MBq
- Administration: *m*IBG should be administered slowly (over 1 to 2 min) via a secure peripheral intravenous cannula/injection flushed with saline

**7. Radiation safety/side effects**

Before injection of *m*IBG, 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 compared to the possible harm of carrying out any procedure involving radioactivity. Breast feeding should be interrupted for at least 3 weeks according to ICRP 106.

The organs with the highest absorbed dose per unit of activity administered (mSv/MBq) are the liver, bladder, gallbladder, spleen, heart, and adrenals. It is advisable to encourage frequent voiding for the first 48 h after *m*IBG administration in order to minimize the radiation dose to the bladder. Radiation exposure is estimated to be 0,013 mSv/MBq, resulting in an effective dose of approximately 1,9 mSv. In general, radiation exposure to hospital staff and to patient relatives is limited, and no special precautions are needed.

Very rarely (<1%) adverse effects of *m*IBG (dizziness, rash, pruritus, flushing and injection site haemorrhage) occur when a slow injection is given. Rapid or central venous injections are contraindicated since they may induce these effects. The benzyl alcohol constituent of

*m*IBG 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 *m*IBG have not been established in neonates below the age of 1 month. Rashes suggestive of an adverse allergic reaction after intravenous injection of <sup>131</sup>I-*m*IBG have been reported, these could draw attention to a potentially similar adverse allergic reaction to <sup>123</sup>I-*m*IBG.

### **8. Patient preparation/essentials for procedure**

The details of the scintigraphic study should be explained to the patient either by a technologist, nurse or physician. Usually, *m*IBG is administered after blockage of thyroid uptake of free <sup>123</sup>I. Thyroid blockage 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 *m*IBG. Neonates 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.

Several drugs are known, or may be expected, to interfere with *m*IBG uptake. However, many studies have demonstrated that cardiac *m*IBG imaging can be performed in patients with optimum medical therapy including beta-blockers, angiotensin-converting enzyme inhibitors and/or angiotensin receptor blockers. Therefore, there is no need to withdraw such medication prior to cardiac *m*IBG imaging.

To minimize effects of variation in sympathetic tone, patients are asked to rest for at least 30 min before the injection of *m*IBG. A peripheral intravenous cannula should be placed just prior to this 30 min resting period.

### **9. Acquisition and processing**

A single (or multiple) head gamma camera is necessary to acquire planar and SPECT images. Although the extensive availability of low-energy, high-resolution (LEHR) parallel-hole collimators determine their common use for <sup>123</sup>I studies, medium-energy (ME) collimators have been shown to provide superior semi-quantitative accuracy. This is because, in addition to the primary emission of 159-keV photons, <sup>123</sup>I emits high-energy photons of more than 400 keV (approximately 2,87%, main contributor 529 keV, 1,28%), which penetrate the LEHR collimator septa and cause scatter detected in the 159-keV energy window. ME collimators minimize the effects of septal penetration.

The energy window is usually symmetrically centred to 20% of the 159-keV <sup>123</sup>I photopeak.

Anterior 10 min 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 a bra). Images are stored in a 128×128 or 256×256 matrix.

Optionally, a SPECT study (pixel size of 6,4±0,4 mm) can be performed after early and late planar imaging, with the patient's arms elevated above the head. A zoom should be used as necessary for cameras with a large field of view. 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. Comparable to myocardial perfusion SPECT imaging, 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.

*m*IBG uptake is semi-quantified by calculating a heart-to-mediastinum (H/M) ratio. ROIs are drawn over the heart (including the cavity) and the upper mediastinum (avoiding the thyroid gland) in the planar anterior view. Average counts per pixel (CPP) in the myocardium are divided by average counts per pixel in the mediastinum. 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). The most commonly used semi-quantitative measurements of myocardial *m*IBG uptake are the early and late H/M and WR derived from the planar *m*IBG images:

$$H/M = \frac{\text{heart CPP}_{\text{averaged}}}{\text{mediastinum CPP}_{\text{averaged}}}$$

$$WR = \frac{H/M_{\text{early}} - H/M_{\text{late}}}{H/M_{\text{early}}} * 100$$

$$WR = \frac{H_{\text{early}} - H_{\text{late}} * 1,21}{H_{\text{early}}} * 100$$

$$WR = \frac{(H_{\text{early}} - M_{\text{early}}) - (H_{\text{late}} - M_{\text{late}}) * 1,21}{H_{\text{early}} - M_{\text{early}}} * 100$$

## 10. Interpretation

The early H/M reflects the integrity of sympathetic nerve terminals. The late H/M offers information about neuronal function resulting from uptake, storage and release. It has been suggested that WR reflects neuronal integrity of sympathetic tone/drive mainly representing uptake-1. Intra-observer and inter-observer variability in these calculations are <5%. 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) and image acquisition (LEHR vs. ME collimation and acquisition time).

## 11. Report

Reports should be concise and easily understandable to referring physicians. The patient's personal details (name, age, date of birth and sex) 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 non-cardiopulmonary tracer uptake. The findings should be integrated with the clinical data to reach a final interpretation. A comparison to any previous studies 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. If the study is abnormal, the report should comment on the presence (if any) of focal or diffuse sympathetic abnormalities and significant artefacts. 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 mid-ventricular 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. 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 extra-cardiac activity may be required. The bottom end of the colour scale should be set to zero and background subtraction should be avoided.

## 12. Literature

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