Review

Metaiodobenzylguanidine scintigraphy of cardiac sympathetic innervation

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Abstract

Metaiodobenzylguanidine (MIBG), a noradrenaline analogue, labelled with radioactive iodine I-123 is used for assessing pre-synaptic activity of the myocardial adrenergic system. The paper describes the mechanism of myocardial I-123-MIBG uptake and the relevant examination methods. It also refers to the necessity of standardising acquisition methods and assessment criteria in order to improve comparability of results, especially numerical results, originating from various countries and centres. Although first introduced as a cardiological diagnostic procedure 30 years ago, I-123-MIBG myocardial scintigraphy continues to be mostly applied as a research method, even though its diagnostic and/or prognostic importance, especially in the case of heart failure, has been widely reported. The recently published results of two extensive retrospective works and a major prospective, multi-centre international ADMIRE-HF study confirmed that I-123-MIBG scintigraphy has a high independent prognostic value in evaluating patients with heart failure. Abnormal myocardial I-123-MIBG uptake can also be indicative of higher risk of ventricular arrhythmias and sudden cardiac death in patients with heart failure. I-123-MIBG myocardial scintigraphy also seems to have considerable potential for the detection and differentiation of neurodegenerative diseases.

Key words: cardiac sympathetic innervation, scintigraphy, iodine-123 metaiodobenzylguanidine, MIBG

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Introduction

The autonomic nervous system consists of the adrenergic (sympathetic) system with stimulating action — and noradrenaline as the main transmitter, and the cholinergic (parasympathetic) system with inhibiting action — and acetylcholine as the main transmitter. The imaging of the cardiac cholinergic system is very limited due to the low density of parasympathetic nerves in the ventricular muscles and the lack of appropriate analogues of acetylcholine, which undergoes rapid decomposition in the pre-synaptic nerve terminals, suitable for radioisotope examinations. However, the adrenergic fibres are abundant in the heart — they run in the epicardium along the coronary arteries and penetrate the myocardium similarly as the smaller coronary vessels; they are present in the ventricles (in particular at the base thereof) and to a significant extent are more concentrated in the atria.

Metaiodobenzylguanidine (MIBG) is a chemical analogue of noradrenaline — its uptake and storage mechanisms in the adrenergic nerve terminals are similar to those of noradrenaline, while it hardly undergoes metabolism and remains unchanged for a longer period of time in the nerve terminals — therefore, when labelled with radioactive iodine, it is considered a pharmaceutical suitable for the assessment of the presynaptic portion of the cardiac adrenergic innervation [1–6].

As the radiation energy (159 keV) of radioactive iodine I-123 is comparable to that of technetium Tc-99m (thus it is possible to use low-energy collimators and acquire relatively high-resolution scintigraphic images) and it has comparatively short half-life (13.3 h), it currently seems to be the best one of the available iodine radioisotopes for MIBG labelling.

The I-123-MIBG radiotracer, used for assessing the presynaptic part of the adrenergic system, is the most extensively researched and practically the only radiotracer available in the classical scintigraphy of the cardiac autonomic nervous system. This radiotracer was first used for the assessment of a human heart by Kline et al. in 1981 [1].

Other imaging agents include noradrenaline analogues labelled with positron radiotracers for PET scintigraphy (hydroxyephedrine, epinephrine and phenylephrine labelled with C-11 [7] and a completely new LMI1195 radiotracer for labelling with F-18 which has a longer half-life [8]).

The research is also underway into the labelling of post-synaptic receptors which transmit signals from the adrenergic system to

the myocardial tissue, regulating the chronotropic, inotropic and dromotropic effects within the myocardium. There are reports of clinical applications of the CGP12177 positron radiotracer labelled with C-11 – non-selective hydrophilic compound binding to beta-receptors – to demonstrate their myocardial density in diagnosing [9] and prognosing [10] based on PET scintigraphy.

Description of MIBG uptake, examination methods and interpretation of results

Mechanism of the myocardial MIBG uptake

Following intravenous administration, MIBG diffuses from the vascular to the intracellular space, and from there it is actively transported, similarly as noradrenaline, to the adrenergic terminals or a small fraction of MIBG diffuses (to neurons, muscle cells, the vascular space).

The first mechanism (so-called uptake-1, energy-dependent) is the prevailing mechanism. From the synaptic cleft, MIBG undergoes active uptake at the nerve terminal which is facilitated by the specific noradrenaline monoamine transporter (NET) protein and most of the radiotracer, by means of another active transport process facilitated by the specific vesicular monoamine transporter (VMAT) protein, is stored in noradrenaline-storing vesicles in the neuron's terminal. Uptake-1 becomes saturated. Nerve stimulation induces the secretion of noradrenaline and MIBG: vesicles combine with the neuron's membrane and secrete their content to the synaptic space by exocytosis. Metaiodobenzylguanidine is re-transported to the nerve terminal by the uptake-1 mechanism or diffuses (into the vascular space and conceivably to neurons, and also to myocytes in animals). Unlike the noradrenaline fraction which is not stored in the vesicles, but metabolised in the cytosol of the nerve terminal [by monoamine oxidase (MAO)], MIBG is not catabolised — therefore the extravesicular concentration of MIBG is larger than that of noradrenaline. Metaiodobenzylguanidine can diffuse from the cytosol of the nerve terminal into the intracellular space.

The mechanism eliminating noradrenaline into the extraneural tissue (sometimes called uptake-2) is probably based on passive diffusion. Uptake-2 has no saturation point. It was shown using animal models that the extraneural uptake-2 of MIBG can reach a significant level. However, it is not the same in humans — no MIBG uptake is observed in the transplanted (and initially fully de-innervated) heart until at least 4 months after the transplantation. In contrast to noradrenaline, MIBG in the cardiomyocyte cytosol is not catabolised by catechol-O-methyltransferase (COMT).

The compound exhibits low affinity to post-synaptic adrenergic receptors, and for that reason — as opposed to noradrenaline — has a highly insignificant pharmacological effect.

It was demonstrated that the level of myocardial MIBG uptake is correlated with the myocardial noradrenaline level [13] and it is explicitly dependent on the presence of non-damaged sympathetic nerve fibres [14–17].

MIBG pharmacokinetics and pharmacodynamics

The dynamics of myocardial MIBG accumulation can be described as follows:
— after intravenous administration, myocardial MIBG uptake follows immediately and achieves a stable level after 2–3 mi-

nutes [60], after 60 minutes it reaches about 1% of the administered dosage [1];
— intravesicular myocardial accumulation of I-123-MIBG is relatively constant starting from the 5th minute after administration, while extravesicular myocardial accumulation decreases to a significant extent between the 5th minute and 6th hour after the administration; the intravesicular percentage of the total myocardial accumulation achieves a constant (and maximal) value equal to 50% within 4 hours after the administration; hence it is considered that images acquired about 4 hours after the injection of the tracer would best reflect the neuronal MIBG uptake in the heart [19].

MIBG pharmacokinetics and pharmacodynamics in the human body is as follows:
— I-123-MIBG blood level decreases quite rapidly: about 10% of the injected dosage remains in blood after 5 minutes from the administration, about 5% after 15 minutes, and about 2% after 1 hour [1];
— the highest MIBG fraction is accumulated in the liver (about 0.33 of the administered dosage), the greatest uptake is observed in the lungs (about 0.03), the heart (0.008), the spleen (about 0.006) and in the salivary glands (about 0.004);
— tracer uptake in the liver is always greater compared to the heart: the ratio of the myocardial-to-hepatic uptake is about 0.7 after 15 minutes and remains at 0.3–0.6 during the next 24 hours [1, 11, 20];
— tracer uptake in the lungs is always smaller compared to the myocardium: the ratio of the myocardial-to-pulmonary uptake is about 1.2 after 15 minutes, 1.4 after 2 hours and 2.9 after 24 hours [1, 11];
— I-123-MIBG is excreted from the body through the kidneys — 85–90% as an unchanged compound (scarcely any amount of the tracer is metabolised in living organisms) and about 10% as a de-iodinated compound; 55% of MIBG is excreted within 24 hours after the injection and 90% after 4 days.

Impact of medication on MIBG accumulation and preparation of patients for examination

A number of drugs are known or can be assumed to have an impact on the MIBG uptake and/or storage [21–23, 24]. Patients should be taken off such medication (if possible) for a sufficiently long period of time before the examination. If it is impossible to discontinue medication, at least its possible impact on the acquired images of the adrenergic system should be taken into consideration.

There are several mechanisms which affect — separately or jointly after the administration of specific drugs — the MIBG storage process (approved names of the drugs which have been demonstrated to influence the MIBG uptake in specific organs are given in brackets):
— inhibited active uptake (cocaine, tricyclic antidepressants, labetalol);
— inhibited active transport to vesicles (reserpine);
— competition for vesicular transport (guanethidine);
— secretion of the vesicular content (sympathomimetic drugs, labetalol, reserpine);
— other non-explained mechanisms.

Table 1. Recommended acquisition parameters for cardiac I-123-MIBG studies [25]

Parameter	Value/Description
Energy window:	20% symmetrically around 159 keV
Collimators:	Low energy high resolution (LEHR) or medium energy (ME)
Planar imaging:	
— projection:	Anterior
— matrix:	128 × 128 or 256 × 256
— starting time *p.i.*:	10 min and 4 h
— length of each acquisition:	10 min
SPECT imaging:	
— detectors:	Single or dual heads (in a 90° or "L" configuration)
— rotation:	180° (starting at 45° right anterior oblique projection and proceeding anticlockwise to the 45° left posterior oblique projection)
— number of projections:	64
— time/projection:	20/25 s
— overall acquisition time:	≤ 25 min

It is also recommended that patients should refrain from consuming foods containing vanilla and catecholamine-like ingredients (e.g. chocolate, blue cheese) as some of them might interfere with the MIBG uptake.

MIBG is usually administered after the uptake of free iodine-123 by the thyroid is blocked. The thyroid can be blocked by administering potassium or sodium perchlorate (400–500 mg) or Lugol's iodine (equivalent of 130 mg of potassium iodide) at least 30 minutes before the MIBG injection [24, 25].

Patients should drink plenty of liquids and frequently urinate for the first 48 hours after the administration of MIBG to accelerate the excretion of the radiopharmaceutical from their bodies and reduce the exposure of the bladder and the whole body to radiation.

MIBG examinations of the myocardial adrenergic system

Acquisition parameters recommended for cardiac I-123-MIBG studies are shown in Table 1.

Normal-weight adult patients are administered a dosage of 111-370 MBq (3–10 mCi) of the radiopharmaceutical [25].

The effective dosage received by an adult patient after the administration of I-123-MIBG is 0.013 mSv/MBq (i.e. a standard patient administered 370 MBq of the radiopharmaceutical receives a dosage of 4.81 mSv).

MIBG should be administered intravenously very slowly (for at least 1–2 minutes according to [25], and for at least 5 minutes according to [24]).

During the acquisition of scintigraphic images a 15- or 20-percent energy window is used, positioned symmetrically around the iodine-123 photopeak (159 keV).

Planar images of the chest are registered (anterior projection, 128 × 128 matrix, acquisition time — 10 minutes); early images are registered 15 minutes, and late images 4 hours after the administration of the radiopharmaceutical. As the planar technique is known to have limitations (overlapping images of extra-cardiac structures and myocardium as well as no possibility of segmental analysis), additional SPECT images (64 × 64 matrix) can be registered immediately after the registration of planar images.

Medium-energy collimators are preferred in the case of iodine-123 as in addition to the primary emission of photons at 159 keV, iodine-123 emits also about 3% of photons at > 400 keV which leads to the penetration of the septa in low-energy high-resolution (LEHR) collimators and causes a high contribution of scattered radiation to the energy window around 159 keV. Medium-energy collimators enable better diagnostic accuracy of I-123 examinations compared to low-energy collimators. However, so far nearly every report relating to the quantitative assessment of the myocardial I-123-MIBG uptake in patients with heart failure (including all 96 centres registered in the most extensive prospective international study — ADMIRE-HF [26], 5/6 centres included in the retrospective multi-centre European study [27] and probably 17/18 works underlying a meta-analysis of the best studies [28]) was based on the acquisition of images with low-energy collimators. The numerical data gathered in these studies cannot be used for interpreting results obtained with medium-energy collimators.

Assessment of the global myocardial MIBG uptake based on the planar examination

The methods underlying the assessment of MIBG myocardial planar examinations are based on a semi-quantitative measurement of the global radiotracer uptake in the heart after 15 minutes and/or 4 hours from its administration and/or the washout rate of the tracer from the heart between the 15th minute and 4th hour from its administration.

The global uptake of I-123-MIBG is most often expressed as the H/M ratio, i.e. the ratio of the average number of counts within the heart to the average number of counts within the mediastinum (i.e. the background) after the examined area of the heart and the upper part of the sternum are mapped onto the scintigraphic planar image in anterior projection [25] (Figure 1). The H/M ratio after 15 minutes (H/M_{15m}) most probably reflects the continuity of pre-synaptic nerve terminals and the functioning of uptake-1. The H/M ratio after 4 hours (H/M_{4h}) enables integrating information about the neuronal function, starting from the MIBG uptake, through storage, up to the ejection from the storing vesicles in the nerve terminals. It was demonstrated that the H/M ratio after
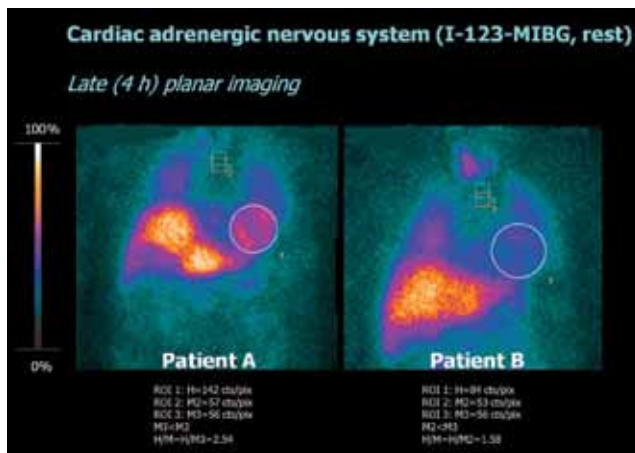
Figure 1. Planar anterior I-123-MIBG images obtained 4 hours after radiopharmaceutical injection in two patients with ischaemic heart failure. The counts per pixel within a circular ROI 1 (H) correspond to the global radioactivity accumulated in the heart. The counts per pixel within the square ROI 2 or ROI 3 (M, from the region with lower value) correspond to the non-specific radioactivity accumulated in the upper mediastinum. The heart-to-mediastinum ratio (H/M) is used as a measure of myocardial uptake of MIBG. **A.** Patient with high MIBG myocardial uptake (H/M$_{4h}$ = 2.54). **B.** Patient with lower MIBG uptake (H/M$_{4h}$ = 1.58) and a higher risk of major cardiac events

Figure 2. Comparison of the images of regional adrenergic innervation (at rest) and perfusion (at rest and under stress) of the left ventricular myocardium in SPECT studies. From each study, the summary uptake of the radiotracer ('bull's-eye' map) is presented. I-123-MIBG uptake deficit evaluated at rest is much bigger than Tc-99m-MIBI uptake deficit at rest; rest image of the innervation is more corresponding to perfusion image in stress conditions

4 hours is correlated with the total myocardial MIBG uptake referred to as % of the uptake of the administered dosage (r = 0.72, p < 0.0001) [29]. Furthermore the H/M ratio is correlated with the myocardial noradrenaline level (r = 0.63) [13]. Thus, the H/M ratio is a measure of the global myocardial MIBG uptake and can be used as a practical rate of uptake [29–31].

The washout rate (WR) of MIBG from the heart is most often expressed as a percentage difference between the average number of counts within the heart after 15 minutes and 4 hours and the average number of counts within the heart after 15 minutes. However, there is a wide variety of calculation methods — with or without standardisation of H-to-M counts, with or without background correction by subtracting M counts from H counts, with or without correction for radioisotope decay in time [25, 32, 33]. The washout rate of MIBG from the heart indicates the excitation level of the adrenergic system (greater activity of the myocardial adrenergic system is related to the high WR value and low MIBG uptake in late images). Nonetheless, there are doubts about the interpretation of the washout rate — most probably it represents several mechanisms (at least vesicular exocytosis and extravesicular diffusion in the nerve terminals). Greater WR values were described in a number of cardiological diseases — but the mechanisms responsible for the phenomenon have not been fully explained.

Most often the H/M ratio, in particular after 4 hours from the MIBG administration, is considered to be the most important factor in the global assessment of the myocardial adrenergic system — also on account of the larger number of studies in which this parameter was tested. However, it has not been unambiguously determined whether any single parameter — H/M or WR — or their combination should be taken into consideration in the prognostic process.
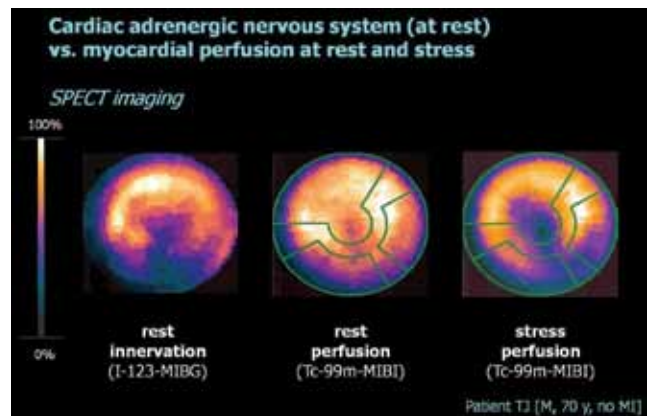
SPECT-based assessment of the regional myocardial MIBG uptake

The papers known from the literature on the SPECT-based examination of "normal" myocardial I-123-MIBG uptake, performed within several hours after the administration of radiotracer, were related to the relative assessment of the radiotracer distribution in specific regions of the left-ventricular muscle and the determination of the correlation between the distribution and the patient's sex and/or age [34–38]. Normal I-123-MIBG uptake in the left-ventricular muscle is non-uniform and depends on the patient's age and probably sex. It also seems that the normal relative uptake in specific regions is comparable to the relative uptake of perfusion tracers in the muscle: the greatest number of counts is observed above the anterolateral wall, the lowest number above the lower wall (especially in men). Reduced number of counts can be present in the apex. The nerves of the cardiac adrenergic system are more sensitive to ischaemia than cardiomyocytes. Therefore, the defects observed in MIBG rest images are bigger (more extensive and more intense) than the rest perfusion defects and more often are similar to stress-induced ischaemic perfusion defects (Figure 2).

It should be noted that if the primary objective of the MIBG uptake assessment is not to diagnose the myocardial adrenergic innervation in a given population (compared to normal results), but the evaluation of any expected regional changes in the innervation in relation to the initial condition of a given patient or of any differences in the regional innervation between well-defined groups of patients, then it is not critically necessary to have maps of normal uptake levels.

The quality of I-123-MIBG SPECT can be much lower than the quality of SPECT-based myocardial perfusion with technetium tracers. As many as 16% of the I-123-MIBG SPECT examinations carried out by our team [39] were non-diagnostic studies due to the very low uptake level within the myocardium and/or very high radioactivity in non-myocardial structures (liver, bowels, lungs), the images of which were not separated from myocardial images. Also Gill et al. [34] reported that the artefacts on the inferior left ventricu-

lar wall — due to the very high MIBG uptake in the liver or spleen in SPECT images registered within 3 hours after the administration of the tracer — were so frequent that the authors decided to discontinue the assessment of radiotracer distribution in this wall.

Necessity of standardisation of MIBG examinations

During their retrospective assessment of the studies relating to the myocardial adrenergic system, Agostini, Verberne and Jacobson determined large differences in the acquisition methods applied in Europe, which could affect the resulting parameters of the global MIBG uptake [27]. Their efforts to standardise the technical aspects of the procedure (and thus to increase the prospect that it is accepted as a clinical tool for patients with heart failure) [32, 33] resulted in a proposal for standardisation of I-123-MIBG imaging of the myocardial adrenergic system, announced by the Cardiovascular Committee of the European Association of Nuclear Medicine and the European Council of Nuclear Cardiology [25]. It should contribute to reducing differences between results, including numerical results, originating from various countries and centres [40].

Clinical applications of I-123-MIBG myocardial examinations

Although first introduced as a cardiac diagnostic procedure in the early 1980s, I-123-MIBG myocardial scintigraphic methods continue to be mostly applied in scientific research (Table 2). Their advantage over the existing diagnostic methods has not been sufficiently documented (lack of multi-centre randomised studies with large groups of patients), even though there are numerous reports of the diagnostic and/or prognostic importance of this examination, especially in the case of heart failure. The testing results of MIBG-based examinations have been described for a variety of other heart diseases, including: primary arrhythmias [41–43], myocardial ischaemia with infarction [14–17] or without [44–48], in the assessment of the development of the innervation system after heart transplant [11, 12, 49], in the assessment of cardiotoxicity of anticancer chemotherapy [50–52]. There are also numerous reports showing that the I-123-MIBG imaging enables effective monitoring of the effects of conventional pharmacological therapies; images of MIBG uptake are improved after therapy with beta-blockers and often associated with reduced volume of the ventricles, better LVEF and reduced symptoms of heart failure; carvedilol has been most extensively researched in this respect (the recent randomised multi-centre double-blind placebo-controlled study was the French study described by Cohen-Solal in 2005 [53]); also other approved drugs which do not directly affect the myocardial adrenergic functions, such as ACE inhibitors, ARB blockers, spironolactone or amiodarone, have also been shown to improve MIBG uptake. MIBG-based myocardial examinations have also been applied in cardiomyopathies [13, 54–58], myocarditis [59], and also in diabetic neuropathy [60–63, MIBG examinations will perhaps enable identifying high-risk patients — Nagamachi observed patients with type 2 diabetes, with no cardiological symptoms, for an average period of 7 years; $H/M_{4h} < 1.7$ was an independent predictor of general mortality rate] and in neurological diseases (mainly in Parkinson's disease). Furthermore I-123-MIBG was used in studies of the impact of transmyocardial laser revascularisation (TMLR) on live tissue, which

Table 2. Clinical applications of I-123-MIBG myocardial examinations

Heart diseases
Heart failure
Primary arrhythmias
Coronary artery disease with infarction
Myocardial ischaemia without infarction
Assessment of the development of the innervation system after heart transplantation
Assessment of cardiotoxicity of anticancer chemotherapy
Monitoring of the effects of pharmacological therapies
Cardiomyopathies
Myocarditis
Diabetic neuropathy
Churg-Strauss syndrome
Neurological diseases
Diseases with Lewy bodies:
— Parkinson's disease (PD)
— Dementia with Lewy bodies (DLB)
Parkinson's syndromes
Other types of dementia [mainly Alzheimer's disease (AD)]

showed that a damage of the myocardial adrenergic system can be responsible for the significant clinical improvement generally observed at an early stage after TMLR, however, in the light of reinnervation, it is not responsible for the improvement covering a period of several years [64–67].

Most recently MIBG imaging was applied for the assessment of cardiac involvement and prediction of cardiac events in patients with Churg-Strauss syndrome (a rare variety of systemic vasculitis, often involving myocardial vessels) [68].

Below are discussed results of the studies relating to some selected clinical situations which have been described in a number of publications and new original works published over the past 2 years, which shows the continuous/increasing interest in I-123-MIBG myocardial examinations.

I-123-MIBG examinations in heart failure

The clinical applications of I-123-MIBG in cardiology have been most extensively examined in patients with heart failure.

Heart failure (HF) is a condition with clinical symptoms of impaired heart performance — patients experience shortness of breath at rest or during exertion and/or fatigue, have symptoms of fluid retention, such as stasis in the pulmonary circulation or oedema around ankles, and the objective data suggest irregularities in the heart structure and functions at rest. The incidence of HF in Europe varies from 2 to 3%, but it increases rapidly around the age of 75 (10–20% in the age group of 70–80 years). Coronary artery disease is still the most frequent cause of myocardial disease and it is estimated to be a causative factor in about 70% of HF patients. The general prognosis in HF is poor; on average 50% of HF patients die within 4 years of the diagnosis [69].

The adrenergic nervous system plays one of the major roles in HF pathophysiology. The primary changes in HF are characte-

rised by the increased activity of the adrenergic system (however, the precise cause of sympathetic activation in HF is not known). Initially, the increased sympathetic activation (greater conductivity in the sympathetic nerves) is a compensating mechanism: increased noradrenaline (NE) secretion from the neuron terminal of the myocardial adrenergic system causes a greater amount of NE in the synaptic cleft and increases the myocardial contractility and heart rate. A small fraction of NE passes from the cleft to the blood circulation and thus increases the NE level in blood plasma, and the remaining NE is transported by NET back to the nerve terminal; increased NE secretion is usually associated with reduced NE reuptake to the nerve terminal due to the reduced sensitivity of the NET transporter. In patients with chronic HF the greater activity of the myocardial adrenergic system has adverse effects — increased NE concentration in the synaptic cleft decreases the sensitivity of post-synaptic adrenergic beta-1 receptors on the cardiomyocyte membrane, reduces the activation conductivity and contributes to the impairment of heart functions. These changes in the activity of the myocardial adrenergic system are also relevant to the generation of ventricular arrhythmias and sudden cardiac death in HF patients.

As the reduced NE reuptake contributes to the low MIBG concentration in neurons (reduced H/M ratio) and the increased NE secretion causes greater MIBG washout (greater WR value), an assessment of the activity of the adrenergic system based on MIBG as well as H/M and WR imaging parameters is used for obtaining prognostic information in the case of HF patients.

The study of Merlet et al., published in 1992, was the first report showing that the myocardial MIBG uptake is a strong predictive factor for cardiac events in the case of patients with chronic HF [31]. Low H/M value was determined to be the best independent predictor of the death rate, better than low EF value: after 20 months the survival rate was 10% in the case of patients with H/M < 1.22, and 30% in the case of patients with EF < 20%.

It has been shown in a number of single-centre studies that the myocardial MIBG uptake has a prognostic value for HF patients. Recently Agostini et al. have carried out a retrospective review and an important prospective quantitative re-analysis of the studies conducted over the past 10 years in 6 European centres with a view to verifying these observations based on the rigorous methodology of clinical studies [27]. Their study focused on the analysis of the H/M ratio after four hours (H/M_{4h}), and more specifically, on account of considerable non-uniformity of the methods applied in each centre, after 2–7 hours from the administration of a radiotracer — in HF patients, Class II–IV according to the NYHA classification. (Early scans were only available for 28% of the patients, and SPECT results for 7% of the patients.) 290 patients with EF < 50% (including 42% of the patients with ischaemic heart failure) were evaluated in the study. Major cardiac events (MCEs) defined as: cardiac death (infarction, HF progression, SCD), transplantation, potentially life-threatening arrhythmia, were observed over a period of 24 months. The images acquired during blind studies were subject to standardised assessment. In the MCE group, the average H/M_{4h} ratio was 1.51 ± 0.3, and in the non-MCE group — 1.97 ± 0.54 (p < 0.0001). The optimised cut-off threshold for the H/M_{4h} ratio was defined as 1.75; 2-year survival rate for non-MCE patients was 62% with lower values, and 95% with values ≥ 1.75. Additionally, the non-MCE survival rate

was 52% for the high-risk H/M_{4h} value ≤ 1.45, and 98% for the low-risk H/M_{4h} value ≥ 2.18. It was shown that the H/M_{4h} parameter was the strongest independent predictor of the risk of MCE occurrence; the EF parameter ranked second, a weaker predictor. The assessment of interactions between EF and H/M_{4h} values showed that the prognostic value of the H/M_{4h} parameter was evident in the population of patients with intensified dysfunction of the left ventricle (EF ≤ 35%).

The application of the methodology used in clinical studies based on a retrospective analysis of MIBG uptake images confirmed the previously reported prognostic value of this method for HF patients, including a possibility of determining the numerical threshold indicating low risk of cardiac death, necessary transplantation or serious ventricular arrhythmias [27].

At the same time as Agostini et al. conducted their analysis, another study was published — a meta-analysis of 18 studies with a total of 1755 patients with heart failure (including 31% with ischaemic HF) — carried out by Verberne et al. [28]. The objective of the systematic review was to provide a critical assessment of the existing facts relating to the prognostic value of semi-quantitative myocardial I-123-MIBG uptake parameters (H/M_{15m}, H/M_{4h}, WR) for HF patients. The occurrence of cardiac death and cardiac events (cardiac death, stroke, transplantation, hospitalisation due to HF progression) was assessed. It was shown that patients with reduced H/M_{4h} ratio or greater WR value have a considerably worse prognosis.

Recently there were published the results of the first large (961 patients with EF ≤ 35% and assigned to Class II-III according to the NYHA classification) multi-centre international prospective study conducted by Jacobson et al. (ADMIRE-HF Study [26]) which included 96 centres from North America and Europe. The study focused on the analysis of the H/M_{4h} parameter. Control observations covered a period of 2 years. The endpoint was determined as the occurrence of a cardiac event defined as a progression of NYHA class or occurrence of potentially life-threatening arrhythmia or cardiac death. It was compared to H/M_{4h} values in relation to the adopted lower limit (H/M_{4h} = 1.6) or taking the H/M_{4h} ratio as a continuous variable. The study confirmed that symptomatic patients with heart failure have worse prognosis with reduced myocardial I-123-MIBG uptake. The percentage of cardiac events within the observation period of 2 years was 15% at H/M_{4h} ≥ 1.6 and was significantly greater at H/M_{4h} < 1.6 (37%). The ADMIRE-HF study confirmed the independent prognostic value of I-123-MIBG scintigraphy for the assessment of patients with heart failure.

The main cause of death in the case of HF patients is cardiac death due to ventricular disorders of heart rate. In the case of some patients the final arrhythmia is a natural result of the end-stage irreversible heart pump dysfunction; while in the case of some patients functioning quite well, sudden cardiac death (SCD) occurs. It was suggested in numerous studies that the disorders of MIBG uptake can be used as predictors of the higher risk of serious ventricular arrhythmias and SCD [43,70–73]. On the other hand, a high level of myocardial MIBG uptake, measured by the H/M ratio, has a high value as a negative predictor, especially for potentially life-threatening arrhythmias. Thus, the results of extended MIBG studies can be used in the future for optimising therapy for HF patients, in particular when considering very expensive therapies involving specialist devices, such as implantable cardioverter

defibrillator (ICD), cardiac resynchronisation therapy (CRT), left ventricular assist device (LVAD) [73, 74].

I-123-MIBG studies can also be used for monitoring the efficacy of these therapies. The recently published study of Drakos et al. [75], in which patients at the end-stage of HF and provided with LVAD were described, showed that the clinical, functional and haemodynamic improvement observed after 3 months was associated with better MIBG uptake and washout parameters in scintigraphic imaging. Another recently published study showed that the reduced H/M ratio was associated with weak response to the applied cardiac resynchronisation therapy [76].

I-123-MIBG myocardial imaging in neurological pathological conditions

Since 1994 there have been published papers describing the application of MIBG myocardial scintigraphy as a diagnostic and potentially prognostic tool in neurological pathological conditions, mainly Parkinson's disease.

A distinctive objective of neuroimaging techniques is to enable differentiating between neurodegenerative diseases, in particular diseases with Lewy bodies — including Parkinson's disease (PD) or dementia with Lewy bodies (DLB) — and Parkinson's syndromes or other types of dementia [including Alzheimer's disease (AD)] on account of the significant differences in their treatment. The accuracy of clinical diagnostic criteria for these diseases is limited; the similarity between specific clinical symptoms can delay diagnosis and application of treatment.

In 1994 Hakusui et al. [77] described a total lack of myocardial MIBG accumulation in patients with Parkinson's disease. Five years later Satoh et al. [78] demonstrated not so much non-existence of uptake as substantially reduced uptake, based on the H/M ratio, in patients with Parkinson's disease compared to healthy subjects – which was confirmed in the subsequent studies.

Recently Muxi et al. have shown that the significantly reduced H/M_{4h} ratio is a scintigraphic parameter which best differentiates between PD patients and healthy people and that the optimised threshold value of 1.43 detects PD with sensitivity at 93% and specificity at 100% [40].

Sawada et al. have assessed the diagnostic accuracy of I-123-MIBG scintigrams in detecting Parkinson's disease in a large group (400 patients) suspected of this disease [79]. In 267 patients the disease was diagnosed based on diagnostic criteria and confirmed based on magnetic resonance results. The myocardial MIBG accumulation was significantly reduced in PD patients (H/M_{20m} was 1.66 vs. 2.39 in non-PD patients, and the H/M_{4h} ratio was 1.44 vs. 2.42). With an optimised cut-off threshold at 1.68 for H/M_{4h}, the sensitivity of PD detection was 84% and specificity 90%. However, in a subgroup of patients diagnosed with the disease not more than 3 years earlier, the sensitivity of PD detection was 73% and specificity 88% with an optimised cut-off threshold at 1.8 for H/M_{4h}. The authors determined that the diagnostic accuracy of MIBG myocardial scintigraphy is limited in the case of patients with early-stage PD due to the insufficient sensitivity.

Similarly, the study of Ishibashi et al., in which PD was diagnosed based on clinical criteria and PET dopamine tests, and compared to Parkinson's syndromes (non-PD), showed that

MIBG scintigraphy has a limited diagnostic value for patients with early-stage PD. In a general group of PD patients, with an optimised cut-off threshold for H/M_{4h} at 1.60, the sensitivity was determined at 71% and specificity at 93% for the disease detection, but in a subgroup of patients with early-stage disease, the sensitivity was only 54% [80].

The reduced MIBG uptake and the corresponding degeneration of the myocardial sympathetic innervation was observed in early stages of DLB and PD by Suzuki et al., and the functions of the adrenergic system, measured with the H/M ratio, was significantly reduced in DLB patients compared to PD patients [81].

In the differentiation between DLB and Alzheimer's disease it was shown that the H/M ratio is significantly lower in DLB patients [82, 83]. In the studies of Yoshita et al. the optimised threshold value at 1.68 for H/M_{4h} enabled 100% sensitivity and specificity of the differentiation process; it was also shown that the WR value at 23.6% enables differentiating between DLB (with greater washout rate) and Alzheimer's disease with sensitivity at 84% and specificity at 83% [83].

Estorch et al. investigated the possibility of early MIBG-based diagnostic differentiation between DLB and other neurodegenerative diseases characterised by cognitive disorders [84]. The results of MIBG-based examinations at an early stage of the disease were verified based on the final clinical diagnosis made 4 years later, after the disease developed. The H/M ratio was significantly reduced in patients diagnosed with DLB in relation to patients with other neurodegenerative diseases. The H/M_{4h} ratio at 1.36 enabled differentiating between DLB and other diseases with sensitivity at 94% and specificity at 96%, while the WR value was significantly higher in DLB patients only compared to patients with Alzheimer's disease (34% vs. 22%).

Conclusions

Although first introduced as a cardiac diagnostic procedure 30 years ago, I-123-MIBG myocardial scintigraphic methods continue to be mostly applied in scientific research. Their advantage over the existing diagnostic methods has not been sufficiently documented (lack of multi-centre randomised studies with large groups of patients), even though there are numerous reports of the diagnostic and/or prognostic importance of this examination, especially in the case of heart failure. The testing results of MIBG-based examinations have been described for a variety of heart diseases, including: primary arrhythmia, myocardial ischaemia, cardiomyopathies, myocarditis, diabetic neuropathy, in relation to the assessment of the development of the innervation system after heart transplant, assessment of cardiotoxicity of anticancer chemotherapy, monitoring of the therapy effects, and in neurological diseases (mainly Parkinson's disease).

The paper discusses in more detail the testing results in some clinical situations which have been described in a number of publications and new original papers over the past 2 years, demonstrating the continuous/growing interest in I-123-MIBG myocardial examinations.

The results of two extensive retrospective works and a major prospective, multi-centre international ADMIRE-HF study, published in the recent years, confirmed that I-123-MIBG scintigraphy

has a high independent prognostic value for the assessment of patients suffering from heart failure: patients with the lowest MIBG uptake are patients with the worst prognosis. Improper myocardial I-123-MIBG uptake can be indicative of the increased risk of ventricular arrhythmia and SCD in patients with heart failure.

I-123-MIBG myocardial scintigraphy seems also to have a considerable potential for detection and differentiation of neurodegenerative diseases. In the case of diseases with Lewy bodies, such as Parkinson's disease and dementia with Lewy bodies, the functions of the adrenergic system are to a significant extent worse compared to the healthy population and patients with Parkinson's syndromes or other types of dementia. Furthermore, the functions of the cardiac adrenergic system are significantly worse in patients suffering from dementia with Lewy bodies compared to patients with Parkinson's disease, Alzheimer's disease or other neurodegenerative diseases characterised by cognitive disorders. However, the sensitivity of MIBG-based myocardial scintigraphy in detecting early stage of Parkinson's disease seems to be limited.

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