

# Is MIBG really of no use in the diagnosis of heart failure?

Czy zastosowanie MIBG jest rzeczywiście nieprzydatne w diagnostyce niewydolności serca?

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It is estimated that in 70% of heart failure (HF) patients, the underlying cause of HF is coronary heart disease, in particular a recent myocardial infarction.

In Europe, HF affects approximately 15 million people, including 0.7 million in Poland. The prevalence is closely related to age and it significantly increases after the age of 60 years. In order to correctly diagnose and treat HF, it is necessary to determine its underlying causes, based on a detailed medical history, plasma B-type natriuretic peptide (BNP) levels, electrocardiogram (ECG), chest X-ray, and echocardiography findings. In patients with uncertain diagnosis nuclear medicine imaging studies may be useful, such as assessment of cardiac adrenergic innervation by <sup>123</sup>I-iodine metaiodobenzylguanidine (<sup>123</sup>I-MIBG) scintigraphy. The method has been known since 1981, and in Poland it has been employed sporadically since the late 1990s [1].

MIBG scintigraphy is a non-invasive procedure and it is used in the clinical setting to assess the autonomic innervation of the heart and its activity. MIBG, a guanidine derivative and noradrenaline analogue, is accumulated and subsequently released by the presynaptic adrenergic nerve fibres. Unlike noradrenaline, however, it undergoes almost no metabolism. MIBG uptake by the heart muscle and the washout time vary and may depend on, for example, the subject's age. The parameters assessed during the procedure include the global uptake of MIBG heart to mediastinum ratio (HMR) and the global washout (WO) rate, and they are of considerable prognostic value in HF.

Scintigraphy consists of two phases: an early phase (planar imaging) 10–20 min after administration of the radiotracer and a delayed phase (planar imaging and SPECT) after 3.5–4 h. For objective assessment of the findings, HMR is used, which compares radioactivity for the heart to that for the upper mediastinum from planar images. The normal value is not less than 1.6 (the mean value in healthy subjects reduced by

two standard deviations). The difference between the delayed and early ratios should not exceed 10%.

Although <sup>123</sup>I-MIBG scintigraphy has been the subject of many studies, the clinical value of the method is still questioned. In 2013, the Polish Agency for Health Technology Assessment and Tariff System (AOTMiT) gave a negative opinion of the method. Was it the right decision?

The aim of this letter is to suggest the need for reappraisal of the decision in the light of the evidence from the literature review.

Stefanelli et al. [2] found that <sup>123</sup>I-MIBG scintigraphy helped to assess, predict, and monitor the effects of therapeutic interventions in HF patients. It helps to assess the risk of mortality due to cardiovascular disease and potentially life-threatening ventricular arrhythmias. It allows identification of interdependencies between plasma BNP, left ventricular ejection fraction (LVEF), and HMR. The parameters measured in the study, including the myocardial washout rate of <sup>123</sup>I-MIBG ( $\Delta$ WO), can predict a sudden lethal event in patients with mild to moderate HF, and the results are not related to the LVEF. The same predictive potential based on  $\Delta$ WO was confirmed in patients with stable HF. The studies by Bax et al. [3] and Stefanelli et al. [2] observed that <sup>123</sup>I-MIBG uptake abnormalities are associated with lethal arrhythmias and may predict the need for an implantable cardioverter defibrillator (ICD) in patients with HF.

Arora et al. [4], in their study of 17 patients with previous ICD, found that all patients with an HMR lower than 1.54-min and 5-min low frequency below 443 ms<sup>2</sup> had an ICD discharge (4/4), whereas an ICD discharge did not occur in patient with an uptake ratio greater than 1.54-min and 5-min low frequency above 443 ms<sup>2</sup> (0/3,  $p = 0.03$ ). The authors concluded that cardiac autonomic assessment using a combination of myocardial scintigraphic and neurophysiologic techniques may identify patients at increased risk for

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potentially fatal arrhythmias, who would most benefit from an ICD implantation [4].

Nagahara et al. [5] found that altered cardiac autonomic innervation assessed by myocardial  $^{123}\text{I}$ -MIBG uptake was closely related to fatal cardiac events, including ICD shock for malignant tachyarrhythmias and sudden cardiac death. Cardiac  $^{123}\text{I}$ -MIBG uptake together with plasma BNP levels can precisely identify patients at greater risk for lethal arrhythmias, who would benefit from an ICD. Additionally, assessment by  $^{123}\text{I}$ -MIBG scintigraphy could effectively guide more appropriate use of ICD implantation and help predict and prevent lethal cardiac episodes in future. An HMR < 1.95 with a plasma BNP level < 187 pg/mL or an LVEF > 50% was a strong predictor of ICD shock: positive predictive values, 82% (HMR + BNP) and 58% (HMR + LVEF); negative predictive values, 73% (HMR + BNP) and 77% (HMR + LVEF); sensitivities, 45% (HMR + BNP) and 67% (HMR + LVEF); and specificities, 94% (HMR + BNP) and 70% (HMR + LVEF).

Koutelou et al. [6] observed that the frequency of fast ventricular arrhythmic episodes (FVAE) was positively related to the WO in  $^{123}\text{I}$ -MIBG scintigraphy, although the WO is an independent predictor of FVAE. FVAE demonstrated an inverse relation to baroreflex sensitivity (BRS,  $p < 0.0001$ ), root mean square of the successive differences (rMSSD,  $p = 0.001$ ), and proportion of NN50 divided by total number of NNs (pNN50,  $p = 0.0034$ ), while it was positively related to low frequency range (LF,  $p < 0.0001$ ) and  $^{123}\text{I}$ -MIBG % WO ( $p = 0.001$ ). BRS, LF, rMSSD, and  $^{123}\text{I}$ -MIBG washout were also independent predictors of FVAE.  $^{123}\text{I}$ -MIBG WO was related to only one heart rate variability (HRV) marker standard deviation of NN intervals (SDNN-I,  $p < 0.0001$ ), while no correlation was observed with BRS. In patients with implanted ICDs and well-compensated HF, autonomic markers derived from BRS, HRV, and MIBG studies are related to FVAE. These markers have limited inter-dependency and may be used to predict the risk for sudden cardiac death in this subgroup of patients. A significant relation was observed between  $^{123}\text{I}$ -MIBG % WO and SDNN-I ( $\beta$  coefficient  $-0.647$ ,  $p = 0.001$ ).

Higuchi et al. [7], who observed patients undergoing biventricular resynchronisation therapy, found marked improvement of cardiac symptoms, exercise capacity, and sympathetic function of the heart based on the delayed HMR in MIBG imaging.  $^{123}\text{I}$ -MIBG uptake is useful for the evaluation of the severity of HF, and, in addition, HMR and total defect score of the delayed  $^{123}\text{I}$ -MIBG images correlate with the LVEF.  $^{123}\text{I}$ -MIBG can also be employed to predict and to evaluate the efficacy of treatment. Cardiac  $^{123}\text{I}$ -MIBG activity has the most powerful independent long-term prognostic value in both ischaemic and idiopathic cardiomyopathy, indicating a common pathophysiologic effect and prognostic impact of impaired cardiac sympathetic innervation in the two conditions.

Tanaka et al. [8] demonstrated that in patients with dys-synchrony but HMR  $\geq 1.6$  frequently improved function of left ventricular is observed. Using a delayed HMR of 1.20 to identify reduced  $^{123}\text{I}$ -MIBG uptake, they found that only delayed HMR and ejection fraction were independent predictors of mortality, with delayed HMR being the best predictor of event-free survival. Reduced and delayed HMR was found to be the most powerful predictor of cardiac mortality.

Although a delayed HMR  $\leq 1.74$ , age > 60 years, a history of myocardial infarction, and New York Heart Association (NYHA) class III or IV were identified as strong predictors of poor clinical outcomes,  $^{123}\text{I}$ -MIBG imaging was the most powerful independent long-term prognostic indicator for ischaemic or idiopathic cardiomyopathy patients. Furthermore, Wakabayashi et al. [9] reported that a delayed HMR was the most powerful independent predictor of cardiac mortality in both ischaemic and idiopathic cardiomyopathy, superior to an early HMR and WO rate, with an identical threshold for both groups for identifying patients at risk of cardiac death and ejection fraction < 50%. According to the authors, preserved cardiac sympathetic activity identifies a very low-risk HF population, with delayed HMR  $\geq 1.60$  associated with 1%/year incidence of cardiac death. In contrast, among patients with delayed HMR < 1.20, the annual rate of cardiac mortality (9.6%) was 10-fold greater.  $^{123}\text{I}$ -MIBG scintigraphy may be employed in the management of patients undergoing cardiac resynchronisation therapy (CRT), and the HMR may be a valuable additional predictor of response to CRT, with potential clinical value.

Zipes et al. [10], comparing  $^{123}\text{I}$ -MIBG scintigraphy to other imaging methods, concluded that  $^{123}\text{I}$ -MIBG scintigraphy is the only imaging study that can assess the sympathetic innervation of the heart. It also allows identification at the primary prevention stage of patients who could benefit from ICD.

Miranda et al. [11] observed that  $^{123}\text{I}$ -MIBG scintigraphy findings correlated with severe systolic dysfunction symptoms in HF (patients naive to  $\beta$ -blockers) better than with LVEF. This finding may significantly contribute to a better understanding of HF, improved diagnostic accuracy, and new approaches to predicting the risk of HF development.

Katoh et al. [12] have been studied the role of MIBG examination in patients with chronic HF, but preserved ejection fraction. They observed poor clinical outcome in patients with significantly lower HMR and high WO — despite of normal ejection fraction. WO was not correlated with ejection fraction and had a weak correlation with plasma BNP. The authors concluded, that MIBG examination provides independent prognostic factor in examined group.

Ekman et al. [13] reported that an increase in the  $^{123}\text{I}$ -MIBG uptake better correlates with survival than the LVEF. The technique, which assesses the sympathetic system of the heart, may help to identify chronic HF patients with a poorer prognosis, a decreased HMR, and an increasing WO rate be-

ing prognostic. Thus  $^{123}\text{I}$ -MIBG scintigraphy may be used to predict survival in ischaemic and idiopathic cardiomyopathy. It may contribute to a better understanding of the adverse effect of adrenergic hyperactivity in HF, the development of improved treatments, and the achievement of better treatment outcomes.

Al Badarin et al. [14] found that  $^{123}\text{I}$ -MIBG scintigraphy is an independent tool to identify optimal therapy to use in HF, e.g. ICD implantation. It allows the investigation of arrhythmias due to enhanced sympathetic activity, including assessment of the risk for arrhythmias in HF patients with low LVEF. It may serve as a single predictor of arrhythmic events, even when other risk factors are not taken into consideration. In the foreseeable future, it may be used for patient-specific assessment of the risk for arrhythmias.

Travin et al. [15] emphasise the potential uses of  $^{123}\text{I}$ -MIBG in predicting the risk for HF in patients with a low ejection fraction. In particular, it may identify patients at low and increasing risk for cardiac death and potentially lethal ventricular arrhythmic events. In their opinion,  $\text{LVEF} \leq 35\%$  correlates with a low HMR and an increased risk for cardiac events in the following two years. Proportionally more arrhythmic events occur in patients with moderate abnormalities in  $^{123}\text{I}$ -MIBG uptake. The authors suggest that patients with regional alterations in  $^{123}\text{I}$ -MIBG uptake (in the region of preserved perfusion) are predisposed to denervation hypersensitivity with the resulting lethal ventricular arrhythmias.

Numerous studies have demonstrated that patients with preserved  $^{123}\text{I}$ -MIBG uptake have a high delayed HMR, which predicts a low risk for any cardiac events related to arrhythmic events [15].

The published studies discussed in this review provide ample evidence confirming the prognostic value of  $^{123}\text{I}$ -MIBG scintigraphy in patients with diagnosed chronic HF and at risk for HF, including the risk for sudden cardiac death and arrhythmic events.  $^{123}\text{I}$ -MIBG imaging may also aid in selecting appropriate treatment, including the need for ICD, and it may be used to assess treatment efficacy. This evidence suggests the need for reappraisal of  $^{123}\text{I}$ -MIBG scintigraphy use in cardiology and its introduction in clinical practice in Poland.

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