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Cardiac ^{123}I -MIBG Imaging beyond Heart Failure: Potential Clinical Indications

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Abstract

^{123}I -Iodine-meta-iodobenzylguanidine (^{123}I -MIBG) imaging can visualize cardiac sympathetic innervation by providing (semi-) quantitative information on the myocardial sympathetic activity.

Although there are lots of prognostic studies in patients with heart failure, clinical application of cardiac ^{123}I -MIBG outside Japan is still limited. However, the number of potential clinical indications for ^{123}I -MIBG imaging is growing as autonomic dysfunction is also present in other cardiac diseases.

The present review gives an overview of the potential clinical cardiac indications beyond heart failure of ^{123}I -MIBG imaging to evaluate the cardiac sympathetic activity. The focus of the manuscript is primarily based on studies that have been performed outside Japan.

Keywords: ^{123}I -MIBG imaging, Clinical indications, H/M ratio, Washout rate

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^{123}I -Iodine-meta-iodobenzylguanidine (^{123}I -MIBG) scintigraphy enables visualization of cardiac sympathetic innervation by providing (semi-) quantitative information of the myocardial sympathetic activity (1). From the early and late planar ^{123}I -MIBG images the heart-to-mediastinum (H/M) ratio can be obtained. This parameter represents the relative distribution of cardiac sympathetic nerve terminals and offers information about the neuronal function. In addition, the washout rate of the tracer between the early and late planar image can be gained providing information about the sympathetic drive. Furthermore, focal innervation defects can be detected with ^{123}I -MIBG single photon emission computed tomography (SPECT) (2).

Cardiac ^{123}I -MIBG scintigraphy is a well-known technique for the determination of prognosis in patients with heart failure (3). The late H/M ratio and washout rate appeared to be powerful predictors of survival and ventricular arrhythmias (4). In addition, ^{123}I -MIBG imaging can be used to monitor the effect of medical therapy (5). Therefore, the nuclear cardiology guidelines of the Japanese Circulation Society

recommend cardiac ^{123}I -MIBG in heart failure patients for assessment of heart failure severity and prognosis (6). Outside Japan the use of cardiac ^{123}I -MIBG scintigraphy is low in clinical practice since it has not been implemented in clinical guidelines (7,8). In addition, there is a lack of standardization and validation of cardiac ^{123}I -MIBG imaging and post-processing procedures (9). As well as the limited gains in cost-effectiveness and the long awaited FDA approval in the USA (10). However, clinical research with ^{123}I -MIBG imaging is growing and the number of potential clinical indications is promising (as depicted in Table 1) (11, 12). An obvious case whereby cardiac denervation is present and ^{123}I -MIBG imaging might give important information is after cardiac transplantation (13). Moreover, autonomic dysfunction can also be present beyond heart failure for instance in patients after a myocardial infarction (14), with arrhythmias (15) and amyloidosis (16). An area where ^{123}I -MIBG imaging provides additive information as well is for the evaluation of patients with cardiovascular risk factors such as diabetes mellitus (DM) (17), (resistant) hypertension (18), and obesity (19).

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Table 1 List of (potential) clinical application of cardiac ^{123}I -MIBG imaging beyond heart failure.

Clinical application of cardiac ^{123}I -MIBG imaging beyond heart failure	
Cardiac disease	Myocardial infarction Takotsubo cardiomyopathy Atrial fibrillation Post-heart transplantation Post-LVAD-implantation
Systemic disorders	Amyloidosis Diabetes mellitus Hypertension
Other	Obesity

This review examines recent trends for potential clinical indications in the future for cardiac ^{123}I -MIBG imaging. The focus of the article is primarily on clinical studies that have been performed outside Japan.

Cardiac diseases beyond heart failure

Myocardial infarction

The autonomic function in patients after an acute myocardial infarction (AMI) can be disturbed since damaged myocardial tissue (scar) caused by prolonged ischemia and hypoxia results in denervated sympathetic fibres. Compared to normal innervated myocardium, denervated regions are more sensitive to norepinephrine and therefore of value in the risk assessment for arrhythmias (20). The size of the denervated myocardium represented by the total ^{123}I -MIBG defect score correlates highly with the occurrence of ventricular arrhythmias resulting in appropriate ICD discharges (21). Similarly, inducible ventricular arrhythmias during electrophysiology testing are correlated with larger total ^{123}I -MIBG defect scores (22). In addition, the areas of myocardial autonomic denervation determined with ^{123}I -MIBG imaging often extent the infarct borders determined on myocardial perfusion imaging (MPI) SPECT (14, 23). This so called innervation/perfusion mismatch is due to the fact that neural tissue is more sensitive to hypoxia compared to myocardial fibres and the recovery time in neural tissue is increased (24, 25). The areas with innervation/perfusion mismatch are at increased risk of ventricular arrhythmias (26). However, there is an on-going debate whether the size of ^{123}I -MIBG innervation/perfusion mismatch on top of the size of innervation defect is associated with more ventricular arrhythmias since results are conflicting (26-28).

Another possible consequence of cardiac sympathetic denervation in post-AMI patients is a disturbance in the nocturnal blood pressure drop (29). The exact underlying mechanism of this disturbance is not yet fully elucidated.

However, acknowledged is the fact that the sympathetic activity is of importance as reports have demonstrated that the intrinsic catecholamine levels are strongly related to systemic blood pressure courses (30). Therefore, cardiac dysinnervation reflected by lower H/M ratio is associated with dysregulation of blood pressure variation with significantly worse prognosis in patients post-AMI evidenced by higher rates of all-cause mortality, myocardial infarction, coronary revascularization, and stroke (31).

Takotsubo cardiomyopathy

The clinical presentation of patients with a Takotsubo cardiomyopathy resembles AMI. However, in contrast to an AMI, no significant coronary lesions or thrombi are found on invasive coronary angiography. There are different pathophysiological hypothesis explaining the exact mechanism of a Takotsubo cardiomyopathy (32,33). The two main hypothesis are that Takotsubo cardiomyopathy is caused by a stress-induced neurohormonal event affecting the coronary microcirculation or by undetected spasm, and/or thrombotic epicardial artery occlusion (32,33). To diagnose Takotsubo cardiomyopathy, ^{123}I -MIBG imaging might be helpful since regional myocardial uptake of the radiotracer is in the left ventricle segments hypokinetic/akinetic (depicted in Fig. 1) (34). However, summarized data from 22 reviewed reports of 112 patients with Takotsubo cardiomyopathy who underwent ^{123}I -MIBG scintigraphy demonstrated that the first ^{123}I -MIBG scan was usually performed 1 to 2 weeks after the admission suggesting that this technique did not contribute to the diagnostic process (34). Though, investigation with ^{123}I -MIBG during the first day has to be performed to determine which abnormalities are already shown direct after admission and what the exact value of ^{123}I -MIBG scintigraphy will be in the diagnostic process.

In addition, Cimarelli et al. demonstrated in a case report that patients with a Takotsubo cardiomyopathy revealed a similar pattern of ^{123}I -MIBG and ^{18}F -FDG uptake underlying a relation between cardiac sympathetic function and insulin mediated glucose cellular intake and metabolism (35).

Atrial fibrillation

Activation of the autonomic nervous system plays an important role in the initiation and maintenance of atrial tachycardia as it induces various atrial electrophysiological changes with as result increased risk for atrial tachyarrhythmias, such as atrial fibrillation and atrial tachycardia (15).

In Japan, small studies have demonstrated the value of ^{123}I -MIBG imaging in patients with atrial fibrillation (36-38). In patients with idiopathic paroxysmal atrial fibrillation a lower H/M ratio was associated with vascular events (36) and the occurrence of permanent atrial fibrillation (37). In addition, in

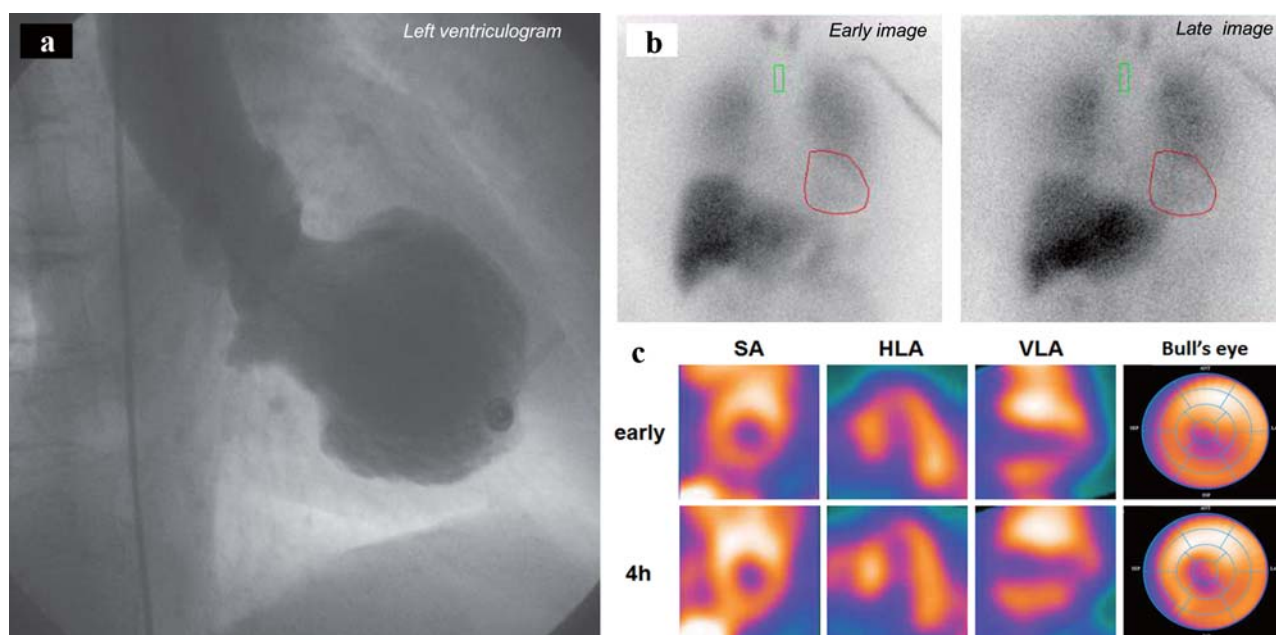


Fig. 1 ^{123}I -MIBG scintigraphy in a patient with Takotsubo cardiomyopathy

A female patient presenting with typical chest pain without significant coronary artery disease on coronary angiography with on left ventriculogram (a) a typical contraction pattern of the left ventricle suspected for Takotsubo cardiomyopathy. Additionally, on early and late planar ^{123}I -MIBG image (b) a decreased H/M ratio (1.68 and 1.46 respectively) and on SPECT ^{123}I -MIBG (c) reduced accumulation apical expanded to the inferior wall.

patients with atrial fibrillation treated with a Maze procedure an increase in denervation occurred in the early stage after the procedure (38). However, after 1 year significant reinnervation of those areas occurred.

Additionally, Wenning et al. demonstrated in 16 patients who underwent pulmonary vein isolation that new innervation deficits demonstrated on ^{123}I -MIBG SPECT images were associated with atrial fibrillation relapses (39).

Amyloidosis

In primary and familial amyloidosis, cardiac involvement is frequently manifest (40). However, the diagnosis is often difficult (41). To ease the diagnosis of cardiac amyloidosis ^{123}I -MIBG can be used, because it indirectly visualizes the effect of myocardial depositions of amyloid by evaluating the occurrence of sympathetic nerve destruction (16, 42). In patients with biopsy-proven systemic amyloidosis echocardiographic signs of amyloidosis are associated with a lower H/M ratio and higher washout rate (43). Moreover, results suggest that ^{123}I -MIBG imaging detects cardiac amyloid earlier than echocardiography (44). Therefore, it may play a pivotal role in the early detection of cardiac involvement of amyloidosis. This is of importance since current therapies (including liver transplantation) limit disease progression but not amyloid depositions. Consequently, the H/M ratio does not improve after liver transplantation in patients with cardiac amyloidosis (45).

In addition, ^{123}I -MIBG imaging can be useful as a

prognostic marker. In patients with amyloidosis with a V30M transthyretin mutation, Coutinho et al. demonstrated that the late H/M ratio was independent associated with all-cause mortality (46). As a consequence, the five-year mortality risk in patients with a late H/M ratio <1.60 was 6-fold higher compared with patients with a late H/M ratio ≥ 1.60 .

Cardiovascular risk factors

Diabetes Mellitus

The prevalence of DM is increasing in the western world, mainly consisting of type 2 DM (47). Several studies have examined the use of ^{123}I -MIBG imaging as a diagnostic and prognostic tool in patients with type 1 and 2 DM (17, 48, 49). DM is often complicated by diabetic neuropathy affecting different parts of the peripheral nervous system including the autonomic nerve fibres innervating the heart (50). This so called cardiovascular autonomic neuropathy (CAN) is one of the most severe complications of DM; it causes abnormalities in heart rate regulation and impairs vascular dynamics resulting in an increased risk of silent ischemia, life-threatening arrhythmias and sudden cardiac death (50). Hattori et al. demonstrated that in an early stage sympathetic impairment on ^{123}I -MIBG SPECT was mainly localized in the inferior wall, while global uptake determined on planar images remained within the normal range (51). However, gradually in a more advanced stage of CAN the adjacent segments were as well affected. Given that CAN is reversible if treated in an early stage, early evaluation to detection regional denervation

areas with ^{123}I -MIBG SPECT might be of value to achieve a better prognosis.

Non-insulin dependent DM appears to be more frequently related with ^{123}I -MIBG uptake impairment compared with insulin dependent DM. However, sympathetic myocardial dysinnervation is more common in patients with insulin-dependent DM than initially thought (49). Instead of measuring heart rate variability, ^{123}I -MIBG imaging is a more precise method to investigate the presence of CAN. This was demonstrated in a cohort of asymptomatic patients with type 2 DM with normal myocardial perfusion the prevalence of CAN diagnosed with ^{123}I -MIBG scintigraphy was much higher than by evaluation with heart rate variability, 58% versus 27%, respectively (17).

In addition, in patients with heart failure and DM the H/M ratio is significantly lower than in patients without DM (48, 52). Furthermore, patients with heart failure and DM with a H/M ratio <1.6 are at 3-fold higher 2-years risk of heart failure progression compared with patients with a late H/M ratio ≥ 1.6 (52).

Resistant hypertension

If the blood pressure remains too high regardless of three antihypertensive medications out of different classes or controlled with four or more agents, and secondary hypertension is excluded, resistant hypertension should be considered (53). It is important to treat resistant hypertension since it is a powerful predictor for cardiovascular morbidity and mortality. The sympathetic innervation of the kidney plays an important role in the pathophysiology of hypertension since efferent renal sympathetic outflow stimulates renin release, increases tubular sodium reabsorption and reduces renal blood flow (54). In addition, increased afferent renal signals stimulate central sympathetic outflow resulting in neurogenic hypertension. Investigations have suggested that renal sympathetic denervation of the artery might reduce the sympathetic overdrive and thereby lower the blood pressure (55). The effect of renal sympathetic denervation of the artery on the cardiac sympathetic overdrive can be assessed with ^{123}I -MIBG imaging. Studies demonstrated an increase in H/M ratio and decrease in washout rate, independently of blood pressure changes (18, 56). This improvement in cardiac innervation is of importance since studies have demonstrated controversial results of the effect of renal denervation on the blood pressure. Therefore, ^{123}I -MIBG imaging has the potential to evaluate the effect of renal denervation on arrhythmias and heart failure (18, 56). However, in contrast to above studies van Brussel et al. demonstrated no reduction in sympathetic activity on cardiac level in 16 patients with resistance hypertension who underwent bilateral renal artery sympathetic denervation (57). Therefore, the precise role in renal denervation needs to be

further evaluated in larger studies.

Obesity

Obese patients are at high risk for cardiovascular events. To fight obesity, activation of brown adipose tissue (BAT) is a new treatment target as it increases energy consumption and thereby inducement of weight loss. ^{18}F -FDG Positron Emission Tomography/Computed Tomography (PET/CT) is a common imaging tool to evaluate therapies targeting BAT activity (58). However, ^{123}I -MIBG imaging might also be indicated since BAT is activated mainly by adrenergic receptors. The increased number of adrenergic receptors on BAT visualized by ^{123}I -MIBG allows discrimination between brown and white adipose tissue since white tissue has only a limited number of adrenergic receptors. Okuyama et al. demonstrated in rats that ^{123}I -MIBG and ^{125}I -MIBG accumulates in BAT and not in white adipose tissue (19). In line with previous study, Admiraal et al. demonstrated in 10 healthy Caucasian men that ^{123}I -MIBG SPECT/CT compared with ^{18}F -FDG PET/CT classified the same anatomic regions as active BAT (59). Therefore, ^{123}I -MIBG SPECT/CT is indicated to visualize and quantify sympathetic stimulation of BAT.

However, the activity of sympathetic drive and BAT visualized by ^{123}I -MIBG SPECT/CT is age-dependent (60). In contrast, between lean and obese patients the visualized BAT volume did not differ in volume suggesting that ^{123}I -MIBG SPECT/CT is capable of detecting the sympathetic nervous system BAT activity in both patient groups.

Evaluation of chemotherapy-related cardiotoxicity

The survival rates in patients with cancer have increased tremendously over the last years because of improved therapeutic options. However, by prolonging life cardiologic side effects from treatments have become more clear (61). One of the best known cardiotoxic agent is anthracycline which causes dose-dependent permanent damage at cellular level with as the most frequent and serious side effect the onset of heart failure by reducing left ventricular ejection fraction (LVEF). Although dose reduction limits the cardiotoxicity, cardiologic evaluation around cancer treatment is necessary since decline in LVEF still occurs. Experts state that evaluation of the LVEF is the cornerstone in the cardiac imaging assessment (62). However, ^{123}I -MIBG imaging might be a novel approach in the early evaluation of cardiotoxicity (63). Early investigation by Wagasugi et al. suggests that in the early phase after chemotherapy the evaluation of cardiotoxic effects with ^{123}I -MIBG is more sensitive than LVEF since ^{123}I -MIBG accumulation in the heart shows a greater and more linear dose-dependent decrease than LVEF after doxorubicin therapy (64).

However, not only patients treated with anthracyclines

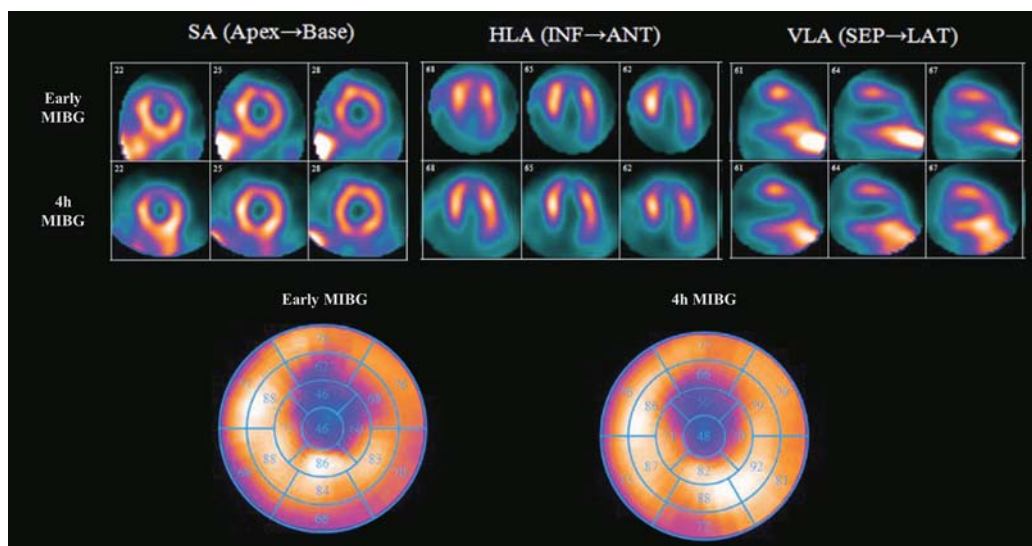


Fig. 2 Effects of trastuzumab on sympathetic activity

A 69-year old patient with a breast carcinoma treated with trastuzumab (Herceptin®) with on ^{123}I -MIBG SPECT a innervation defect in the anterior and apical region.

should be evaluated with ^{123}I -MIBG since the novel agent monoclonal antibody trastuzumab affects the heart as well by inducing transient reversible myocyte dysfunction independent of dose (as demonstrated in Fig. 2) (65).

^{123}I -MIBG parameters might indicate in patients treated with trastuzumab with an affected LVEF whether recovery of the LVEF occurs during follow-up since Stokkel et al. suggested in a pilot study that ^{123}I -MIBG scintigraphy might indicate whether recovery of LVEF will occur (66).

Heart transplantation and left ventricular assist device implantation

Complete denervation of the allograft occurs after heart transplantation. In some patients the catecholamine storage capacity is regained which is associated with improved response of the heart rate and contractile function to exercise (67). However, this is a slow process that takes often more than 1 year up to even 12 years and can be demonstrated by ^{123}I -MIBG imaging (13, 68). In addition, patients with idiopathic cardiomyopathy are less likely to re-gain innervation compared to other aetiologies of congestive heart failure, as well as in patients with DM (69).

Patients pending on or non-eligible for a heart transplantation can nowadays be treated with a left ventricular assist device (LVAD) to reduce mortality and improve quality of life. To evaluate the effects of LVAD on cardiac sympathetic innervation ^{123}I -MIBG imaging has demonstrated that after LVAD implantation the early and late H/M ratio increases and the washout rate decreases (70, 71).

Conclusion

This review provides an overview of the potential

increasing number of clinical indications of cardiac ^{123}I -MIBG imaging besides heart failure in the last few years.

However, first cardiac ^{123}I -MIBG has to be implemented in heart failure guidelines outside Japan, before other potential indications will. Until then other indications beyond heart failure will stay pre-clinical.

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Conflicts of interest

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