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How Do We Establish Cardiac Sympathetic Nervous System Imaging with ^{123}I-*m*IBG in Clinical Practice? Perspectives and Lessons from Japan and the US

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Abstract

Cardiac denervation is associated with progressive left ventricular (LV) dysfunction, ventricular arrhythmias, and sudden cardiac death (SCD) in heart failure (HF). In this regard, it is important to evaluate cardiac-specific sympathetic nervous system (SNS) function. The radiotracer Iodine-123 *meta*-iodobenzylguanidine (^{123}I-*m*IBG) can noninvasively evaluate presynaptic SNS function. Recent multicenter trials have shown ^{123}I-*m*IBG to have strong predictive value for fatal arrhythmias and cardiac death in HF. ^{123}I-*m*IBG was initially developed in the USA in the 1970s. In 1992, the Japanese Ministry of Health and Labour approved ^{123}I-*m*IBG for the assessment of cardiac function. Following approval, the Japanese nuclear cardiology community developed ^{123}I-*m*IBG imaging services in various medical centers. Japanese groups have been trying to establish the clinical utility of ^{123}I-*m*IBG and standardize parameters for data acquisition and image analysis. The US Food and Drug Administration (FDA) has approved clinical use of ^{123}I-*m*IBG for cardiac and non-cardiac imaging. However, clinical use of ^{123}I-*m*IBG in the USA has been very limited. The number of ^{123}I-*m*IBG studies in Japan has also been limited. There are similarities and differences between the two countries. To establish the clinical utility of ^{123}I-*m*IBG in both countries, it is important to characterize the situations of ^{123}I-*m*IBG in each.

Keywords: ^{123}I-*m*IBG imaging, Guidelines, Heart failure, Sympathetic nervous activity, Ventricular arrhythmias
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Radiolabeled *meta*-iodobenzylguanidine (*m*IBG) was initially developed in the United States (US) of America in the 1970s. In November 1992, the Japanese Ministry of Health, Labour and Welfare (JMHLW) approved ^{123}I-*m*IBG for clinical use and approved reimbursement (1, 2). The developmental steps in each country are described below.

Radiolabeled *m*IBG was first synthesized in the US at the University of Michigan in 1979. The compound arose from efforts beginning in 1963 by William H. Beierwaltes, University of Michigan Division of Nuclear Medicine Chief, to develop novel radiopharmaceuticals for adrenal imaging (3). Efforts to image the adrenal medulla began in 1967 with investigations of ^{14}C-epinephrine and its precursors which established the feasibility of using radiolabeled catecholamine analogs that concentrate in storage vesicles of adrenergic tissue. In 1972, University of Michigan organic chemist Don

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Wieland explored the biodistribution properties of bretylium analogs labeled with ^{125}I in various positions (i.e., ortho, para, and meta), as well as those of related guanethidine compounds including benzylguanidines. While [^{125}I] *para*-iodobenzylguanidine was found to have the highest adrenal uptake levels, iodine labeling in the *meta* position also showed satisfactory adrenal uptake and had the advantage of being more metabolically stable, thus establishing *m*IBG as the ideal tracer for adrenomedullary imaging (Figure 1).

At the same time, the potential for imaging cardiac sympathetic innervation was recognized, with the first imaging study in dogs published by Wieland et al. in 1981 (4), followed by Kline et al. performing the first human neurocardiac ^{123}I-*m*IBG imaging study (5). While concurrent work elsewhere was exploring cardiac radiotracer imaging to assess myocardial perfusion, particularly with ^{201}Thallium (^{201}Tl), University of Michigan investigators emphasized that *m*IBG was able to visualize sympathetic nerve function in cardiac disease, with Wieland contending that "although perfusion tracers like ^{201}Tl provided information on the 'plumbing' of the heart, *m*IBG provided clinicians with insights into the 'wiring' of the heart (3)."

A few years later, visiting Japanese fellow Masayuki Nakajo reported an inverse relationship between cardiac accumulation of ^{131}I-*m*IBG, and plasma and urinary catecholamine levels, finding the absence of cardiac tracer uptake in patients with pheochromocytomas (6). Upon returning to Japan, Nakajo reported in 1986 the importance of *m*IBG uptake into intraneuronal norepinephrine (NE) storage vesicles (7).

A few years later, Sisson et al. reported that regional cardiac denervation in dogs via phenol application to the myocardium was detectable with *m*IBG (8). In 1988, the research focus at the University of Michigan shifted to positron emission tomography (PET) adrenergic tracers, and consequently, the majority of clinical cardiac *m*IBG studies shifted elsewhere, largely to European and Japanese centers.

^{123}I-*m*IBG introduction in Japan

Although Japanese researchers contributed to the initial development of *m*IBG in the US, the introduction of *m*IBG in Japan occurred a decade later. Japanese investigation of ^{123}I-*m*IBG was initiated by Daiichi Radioisotope Laboratories (now FUJIFILM RI Pharma, Co. Ltd) in 1987 for the diagnosis of heart disease. During phase II and III clinical trials, the Japanese nuclear cardiology community conducted several ^{123}I-*m*IBG clinical trials, with the first report in 1991 of a 981-patient multicenter trial (9). Compared to the case for ^{201}Tl myocardial perfusion imaging at rest, ^{123}I-*m*IBG defects or perfusion/innervation mismatching defects were frequently observed in patients with myocardial infarction (Figure 2A),

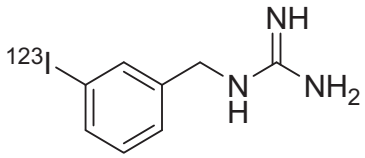

Figure 1 Chemical structure of *meta*-iodobenzylguanidine (*m*IBG).

angina pectoris, and unstable angina. An ^{123}I-*m*IBG-detected defect became more evident in the late (3–4 h) images in hypertrophic cardiomyopathy (HCM) (Figure 2B) (10), and the frequency of defects was particularly high in dilated cardiomyopathy (DCM). This multicenter trial established the diagnostic utility of ^{123}I-*m*IBG for detecting sympathetic nervous dysfunction in a clinical setting. Thereafter, in November 1992, MyoMIBG (111 MBq) was approved for clinical use by the Japanese Ministry of Health and Welfare (JMHW) (currently Japanese Ministry of Health, Labour and Welfare) (1, 2).

Safety aspects of ^{123}I-*m*IBG use in clinical settings

Since JMHW approval in 1992 (26 years ago) (Table 1), ^{123}I-*m*IBG has been used in Japan as part of clinical practice. According to a 2002 to 2012 survey by the Japanese Society of Nuclear Medicine on adverse reactions to radiopharmaceuticals, only 6 patients had ^{123}I-*m*IBG-related adverse effects between 1975 and 2007 with no ^{123}I-*m*IBG-related adverse effects between 2008 and 2012 (11). In addition, the annual frequency of ^{123}I-*m*IBG clinical studies has increased to 40,000 including applications for cardiology (27%), neurology (63%), and oncology (11%) (12).

Development of ^{123}I-*m*IBG in the US and Japan

Earlier preclinical and clinical investigations in the US and Japan

Preclinical investigations in the US. Investigators at a few US institutions expanded on the University of Michigan work, including at Indiana University where, under the direction of Douglas Zipes, investigations of the potential utility of cardiac *m*IBG imaging in identifying arrhythmic risk were undertaken. The group at Indiana University studied abnormalities of regional myocardial tracer uptake. Pathophysiologic investigations in dogs by Inoue et al. (13) and Kammerling et al. (14) established that sympathetic efferent denervation, produced either from latex embolization-induced infarction or by epicardial application of phenol, increased vulnerability to programmed ventricular stimulation induction of ventricular fibrillation, termed "denervation supersensitivity." Shortly thereafter, also in dogs, Minardo et al. (15) showed that such denervation could be imaged as an ^{123}I-*m*IBG defect apical to the site of intervention, and that the defect could be present

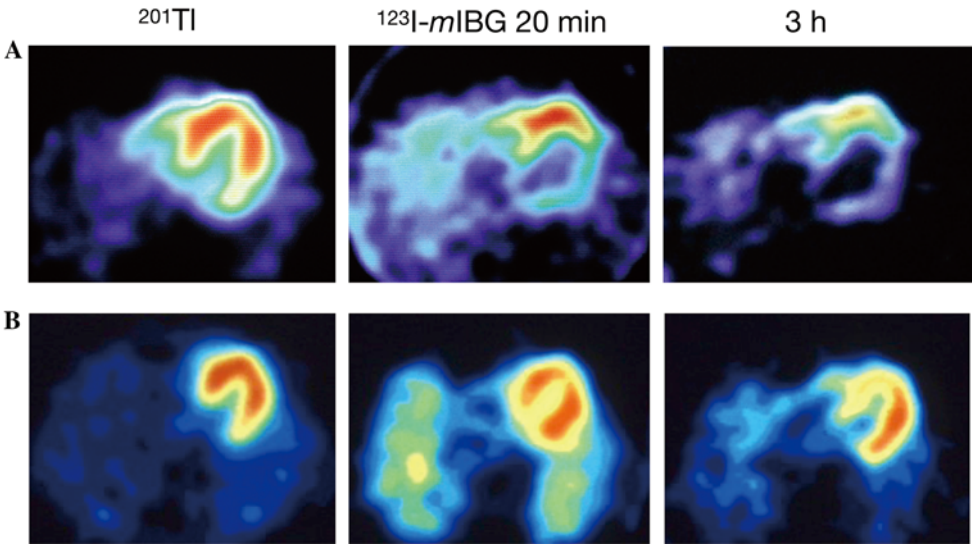

Figure 2 ^{201}Tl and ^{123}I-*m*IBG images from a clinical trial in Japan (1989, Kanazawa University Hospital). **A**: Transaxial images of a patient with inferolateral infarction after revascularization. Perfusion-innervation mismatch was clearly observed. **B**: A patient with hypertrophic cardiomyopathy, showing hypertrophic septum in a ^{201}Tl transaxial image, while septal ^{123}I-*m*IBG uptake is reduced, particularly in the late 4-hour image (Nakajima K. Am Heart J 1990; 119: 1320) (10).

Table 1 Approval and reimbursement of ^{123}I-*m*IBG

	US	Japan
Approval date	March 2013	November 1992
		March 2012—additional indication
Approved diseases or conditions	NYHA Class II to III heart failure with LVEF ≤35%	Evaluation of cardiac function (November 1992) Any cardiac disease (additional approval—March 2012, reimbursement by social insurance for Parkinson's disease and dementia with Lewy bodies)
Clinical role of ^{123}I *m*IBG by approval	FDA: lower 1- and 2-year mortality risks for HMR ≥1.6	JMHLW: not specifically addressed
Suppliers	GE healthcare others	FUJIFILM RI Pharma
Reimbursement Payment in 2018	$1202.60	$612
Tracer cost	10 mCi (370 MBq) approximate range: $2,200–$3,900	3 mCi (111 MBq) $398

FDA: food and drug administration, JMHLW: Japanese Ministry of Health, Labour and Welfare, HMR: heart-to-mediastinum ratio, LVEF: left ventricular ejection fraction, NYHA: New York Heart Association

even in the absence of a ^{201}Tl perfusion abnormality.

In 1989, Dae et al. (16) evaluated the feasibility of ^{123}I-*m*IBG scintigraphic imaging assessment of adrenergic innervation, combining this with reference ^{201}Tl perfusion imaging. These investigators found various patterns of *m*IBG denervation defects on 3-hour delayed images (the initial images showed homogenous uptake) despite an absence of perfusion abnormalities. In 2000, a visiting Japanese fellow, Koichiro Yoshioka, found that ^{123}I-*m*IBG regional defects produced by phenol epicardial application in rabbits were associated with an electrophysiologically demonstrated shortening or dispersion of activation recovery intervals, potentially increasing the likelihood of occurrence of a fatal arrhythmia (17).

Preclinical investigations in Japan. Since ^{123}I-*m*IBG became available, Japanese investigators have performed extensive experimental studies using mice (18), rats (19) hamsters (20), rabbits (21), and dogs (22). Early studies focused on ischemic heart disease using dog models (23), introducing the concept of denervated but viable [perfusion/innervation mismatch] myocardium. Abnormal ^{123}I-*m*IBG kinetics in heart failure was investigated in rodents. In a series of studies using rats, Wakasugi et al. (24, 25) importantly demonstrated that a reduction in myocardial ^{123}I-*m*IBG uptake was a sensitive marker of adriamycin-induced cardiomyopathy, which is related to accelerated exocytotic release of norepinephrine. Such reduction in cardiac ^{123}I-*m*IBG uptake is reportedly reversible in response to medical

treatments such as angiotensin-converting enzyme inhibitors (26, 27), beta-blockers (28, 29), and amiodarone (30).

Some patients with diabetes mellitus have autonomic neuropathy. Therefore, sympathetic neuronal imaging is a major research target. There are experimental ^{123}I-*m*IBG studies showing impaired sympathetic neuronal function in insulin-dependent (31, 32) and non-insulin dependent (33) diabetic animal models. These studies showed less myocardial ^{123}I-*m*IBG uptake in diabetic models compared with control animals.

Initial clinical investigations of ^{123}I-*m*IBG in the US establishing perfusion/denervation mismatch and washout ratio: the US contributions (prior to 2000)

In 1989, Stanton et al. (34) undertook a clinical human ^{123}I-*m*IBG imaging study of patients >1 week following myocardial infarction (MI). They found that the presence of ^{123}I-*m*IBG defects, indicative of sympathetic denervation, including in regions of perfused viable myocardium as demonstrated by preserved ^{201}Tl-uptake, was associated with spontaneous ventricular arrhythmias.

In 1988, under the direction of James Willerson at the University of Texas Southwestern in Dallas, Henderson et al. (35) compared 14 healthy controls to 16 patients with non-ischemic cardiomyopathy (NICM). Tomographic cardiac images were obtained 15 and 85 minutes after ^{123}I-*m*IBG administration in both groups. While the 15-minute images were similar in the two groups, regional analyses found tracer retention to be lower based on a higher washout rate (WR) between early and late images. The late images showed "significantly more 'patchy' or heterogeneous" uptake relative to controls. A few years later at the same institution, McGhie et al. (36) reported that in 27 patients 1–2 weeks post MI, ^{123}I-*m*IBG adrenergic defects were more extensive than ^{201}Tl perfusion defects, more severely abnormal in patients with anterior vs. inferior MI, inversely related to left ventricular ejection fraction (LVEF), and associated with increased ventricular ectopy including ventricular tachycardia in 3 patients. This study established the concept of denervation and perfusion mismatch in damaged myocardium.

Japanese contributions (prior to 2000s)

In 1994, Nakajima et al. (37) first reported a range for the heart-to-mediastinum uptake ratio (HMR) and the washout rate (WR) in normal subjects compared to patients with various cardiac diseases. Tsuchimochi et al. (38) systemically investigated the effects of age and gender on myocardial ^{123}I-*m*IBG distribution in 29 normal subjects, observing an age-related reduction in ^{123}I-*m*IBG uptake in the inferior wall on both planar and single-photon emission computed tomography (SPECT) images, particularly in men.

Technical parameters of ^{123}I-*m*IBG in Japan and the US

For the most part, in the US and Japan, ^{123}I-*m*IBG scintigraphic imaging is performed in similar ways. However, there are some differences in data-acquisition approaches that may impact image quality (Figure 3, 4).

Data-acquisition standard approaches: Japanese approaches

The standard Japanese protocol for ^{123}I-*m*IBG imaging is shown in Table 2. After administration of 111 MBq of ^{123}I-*m*IBG, early (15 to 30 minutes) and late (3 to 4 hours) images are obtained as an anterior planar view with data acquisition for 3 to 10 minutes. SPECT imaging with either a 360-degree or 180-degree rotation is obtained for both early and late phases. ^{123}I-*m*IBG SPECT images include standard short-axis, vertical long-axis, and horizontal long-axis slices (Figure 4). In patients with very low cardiac ^{123}I-*m*IBG uptake, since axes of the heart cannot be determined, transaxial slices are created for early images. Such diffusely decreased uptake is sometimes observed in cases of Lewy body diseases or severe HF conditions. Although dual-nuclide simultaneous injection of ^{123}I-*m*IBG and perfusion tracers might be useful, it has not been commonly performed in Japan.

US approaches

There is no standard protocol for performing clinical ^{123}I-*m*IBG imaging in the United States. Practitioners performing such a study would most likely follow procedures used in the "AdreView Myocardial Imaging for Risk Evaluation in Heart Failure" (ADMIRE-HF) trial (39). These are also summarized in the GE Healthcare AdreView™ package insert (40). Alternatively, they may follow the European Association of Nuclear Medicine (EANM) Cardiovascular Committee/ European Council of Nuclear Cardiology guidelines (41). Those with prior research experience would likely use techniques they had previously employed (35, 42).

A potential US standard (American Society of Nuclear Cardiology [ASNC]) was recently described in the "ASNC imaging guidelines for SPECT nuclear cardiology procedures: Stress, protocols and tracers (43)," as well as in a "How To" review by Soman et al. (44). The FDA-approved dosage for adult cardiac imaging is 10 mCi (370 MBq) (Table 2). Anterior planar images can be acquired using low-energy high-resolution (LEHR) collimation for 10 minutes, with the patient supine approximately 15 minutes (early) and again 3 hours 50 minutes (late) after tracer administration and stored in a 128 × 128 matrix. While the utility of SPECT imaging is uncertain, most US practitioners proceed with SPECT after late planar imaging, obtaining a minimum of 60 projections at 30 seconds/stop over a 180° arc (45° right anterior oblique to 45° left posterior oblique), which are stored in a 64 × 64 matrix. As with perfusion SPECT, ^{123}I-*m*IBG SPECT images

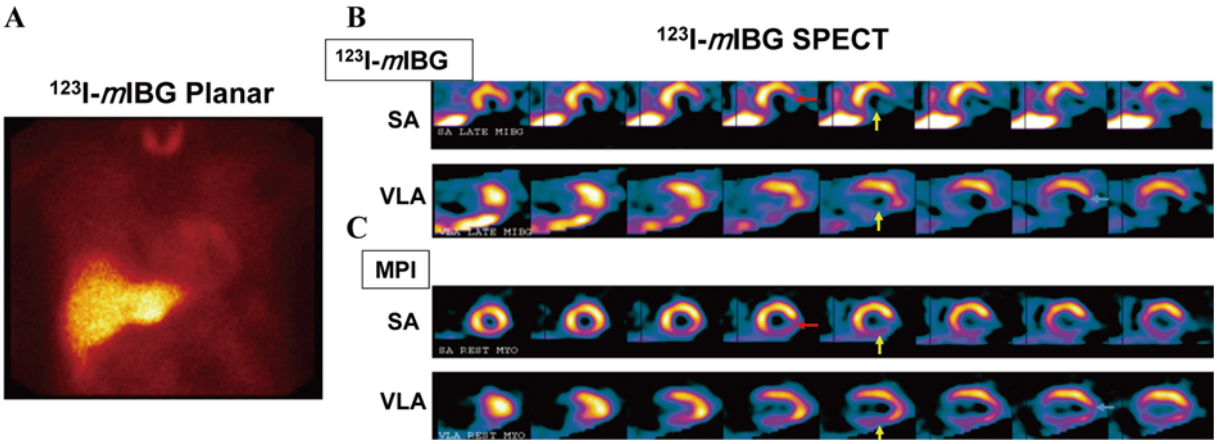

Figure 3 ^{123}I-*m*IBG images from the US of a 61-year-old man with non-ischemic cardiomyopathy, NYHA Class III, EF 25%. (**A**) Cardiac ^{123}I-*m*IBG uptake is mildly reduced with a heart-to-mediastinum ratio of 1.63. (**B**) Tomographic imaging demonstrates severe ^{123}I-*m*IBG defects involving the inferior (yellow arrows), lateral (red arrows), and apical (green arrows) walls, with preserved perfusion throughout most of these territories, i.e., adrenergic/perfusion mismatch.
HLA: horizontal long axis, MYO: myoview (^{99m}Tc-tetrofosmin), SA: short axis, VLA: vertical long axis.

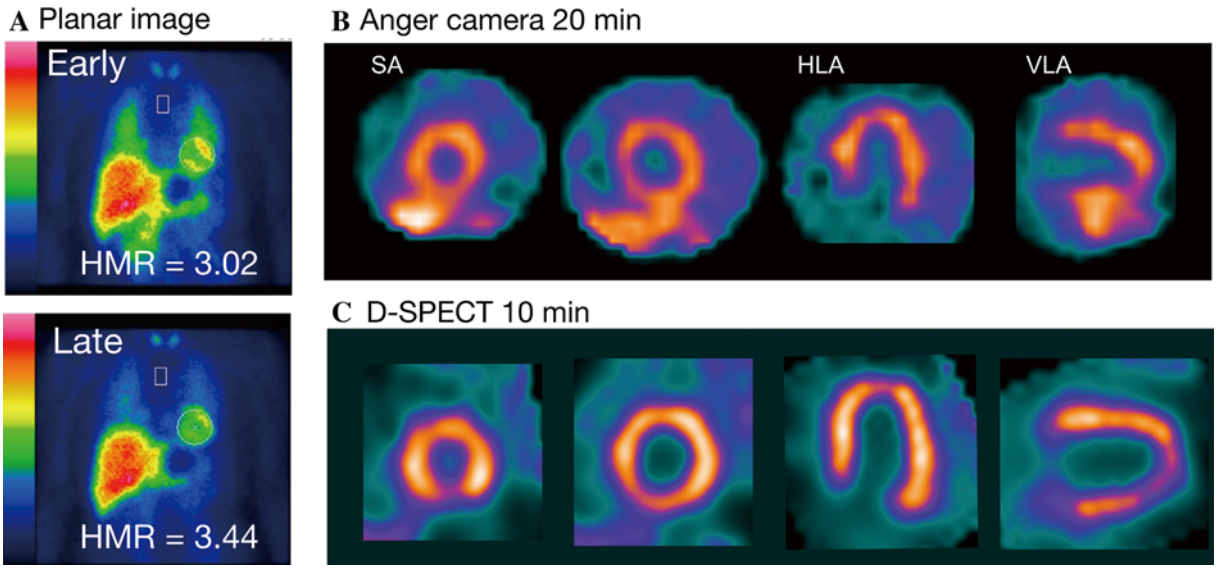

Figure 4 Typical ^{123}I-*m*IBG images in Japan: Early and late images with regions of interest overlapped with "smartMIBG" software (**A**). Short-axis (SA) and horizontal and vertical and long- axis (HLA, VLA) images captured by Anger camera (**B**) and D-SPECT (**C**).

are processed with either filtered back-projection or iterative reconstruction, and are displayed in standard short-axis, vertical long-axis, and horizontal long-axis slices. There are no recommendations regarding use of attenuation correction.

Data interpretation and semiquantitative parameter standards

Japanese nuclear cardiology communities have developed normal standards based on their experience with SPECT myocardial perfusion imaging (MPI) and ECG-gated SPECT. It is understood that standards developed in the US and elsewhere cannot simply be used in the Japanese population. In this regard, the Japanese Society of Nuclear Medicine (JSNM) working group has aimed to establish standard *m*IBG parameters for Japanese patients.

Japanese standards

The JSNM working group has accumulated a normal database for ^{123}I-*m*IBG (n=62), excluding patients with cardiac diseases or neurological disorders (45). The JSNM established normal cutoff values for the HMR and WR based on this database.

As differences in camera-collimator selection influence HMR, Japanese groups apply collimator-specific conversion coefficients for calibrating HMR to mediumenergy general purpose (MEGP) -collimator-equivalent standardized values (46, 47). By using these conversion coefficients, any institution can use the same diagnostic criteria for the HMR.

Table 2 Data acquisition and parameter settings

	US	Japan
Collimator	LEHR	LEHR, LEGP, ELEGP, LME, MEGP, MELP
Data acquisition	Planar SPECT	Planar SPECT
Filter	FBP, OSEM	FBP, OSEM
HMR	Mediastinum and heart ROIs	Mediastinum and heart ROIs; HMR standardized to MEGP-collimator condition
Washout rate	(Early heart counts/pixel—late heart counts/pixel)/early heart counts/pixel, with background and time decay correction*1	(Early heart count—late heart count)/early heart count with background and time decay correction*1
Normal values		
HMR	2.2 ± 0.3	HMR
		Early: 3.1 (2.2–4.0), late: 3.3 (2.2–4.4)*2
Washout rate	N/A	Decay and background corrected: 13% (0–34%), decay corrected 16% (6–30%)
Prognostic threshold for heart failure	HMR=1.6*3 (ADMIRE-HF, LEHR collimator)	HMR=1.68*4 (pooled database in Japan, LE collimator)

*1 Some studies use WR without background subtraction; *2 Standardized HMR ratios to MEGP collimator-equivalent values; standardized HMR to MEGP-collimator condition: 2.0 for both *3 and *4
ELEGP: extended low energy general purpose, FBP: filtered back-projection, HMR: heart-to-mediastinum ratio, LEGP: low energy general purpose, LEHR: low energy high resolution, LME: low medium energy, MEGP: medium energy general purpose, MELP: medium energy low penetration, OSEM: ordered subset expectation maximization, ROI: region of interest, WR: washout rate

With respect to SPECT imaging, normal polar map distributions with means and standard deviations have been prepared by the JSNM working group and can be used for defect scoring using QPS and 4DM software (48).

The Japanese Movement Disorder Society aimed to apply a standardized approach to ^{123}I-*m*IBG imaging parameters for use in clinical practice. The standardized HMR can be calculated by ^{123}I-*m*IBG-dedicated quantification software (49), which is convenient for creating a threshold HMR for Lewy body diseases and other related neurological disorders (49). The standardized HMR provides a strong basis also for estimating mortality risk in patients with chronic heart failure (50). HMR prognostic thresholds for heart failure patients were 1.60 and 1.68 in the ADMIRE-HF study (39) and Japanese-pooled database (51), respectively, both of which are converted to 2.0 when standardized to the MEGP-collimator condition. Normal ranges of washout rates with and without background subtraction correction have also been determined as 0–34% and 6–30%, respectively (12, 48).

US standards

The key parameter of image interpretation is the HMR obtained from the anterior planar images, with the value from the late image considered most important (Figure 5). A recommended technique for obtaining a planar HMR based on the ADMIRE-HF study is described in various publications (40, 43). A normal value has been considered to be 2.2 ± 0.3 (52). An HMR value of 1.6, two standard deviations below this “normal” mean, was the preset threshold for the ADMIRE-HF study. Heart failure patients with HMRs ≥1.6 were associated with lower 1- and 2-year mortality rates. There have been some investigations obtaining an HMR from SPECT images that might be needed for small-field-of-view cameras and SPECT-only systems, and that could also correct for higher-energy ^{123}I emissions (53).

Washout of tracer between early and delayed planar images has been extensively investigated in the Japanese literature but is sparse in the US investigations. The parameter is studied in a paper by Henderson et al. (35) from University of Texas in 1988, but the specific methodology is not detailed. The methodology described in the aforementioned ASNC guidelines (43) is based on the EANM/European Association of Nuclear Cardiology (EANC) guidelines. To our knowledge, no threshold for washout abnormality has been proposed in the US-published guidelines.

With regard to SPECT, investigators at the Emory University (54) described an algorithm they developed for deriving a summed segmental dysinnervation score, using an approach similar to that customary for SPECT perfusion but with the recognized need to factor in global cardiac uptake measured by the HMR. The technique was validated by showing a reasonable ability to distinguish ischemic from non-ischemic cardiomyopathy.

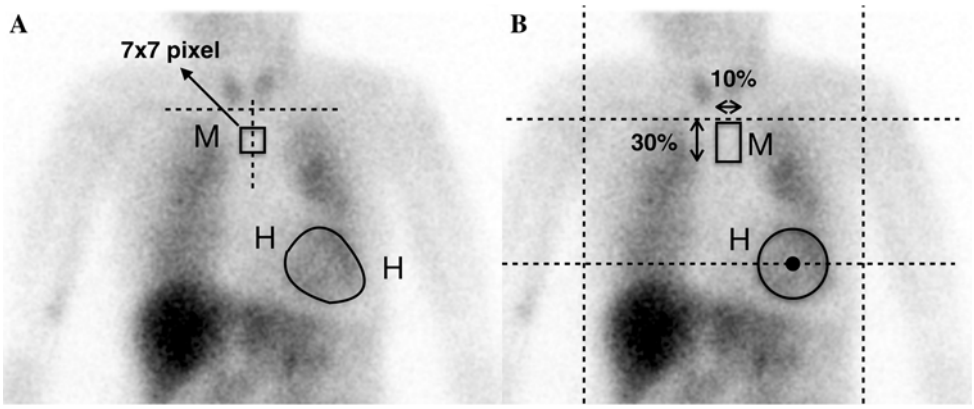

Figure 5 Regions of interest (ROI) for ^{123}I-*m*IBG imaging. Predefined rules for selecting ROI are recommended to improve reproducibility of HMR. In ASNC imaging guidelines, a heart ROI is drawn on the epicardial border, and an upper mediastinal ROI (7 × 7 pixel square) on the center vertical line (**A**) (43). In smartMIBG software used in Japan, after pointing at the center of the heart, a circular heart ROI is created, and a rectangular mediastinal ROI is automatically determined as the upper 30% height and 10% width of rectangular thoracic boundaries (**B**) (49).

Recent clinical investigations establishing the clinical roles of ^{123}I-*m*IBG in the US and Japan

US trials (after 2000) and US challenges without FDA approval

The US initially had very successful clinical studies of ^{123}I-*m*IBG, establishing important concepts and parameters for ^{123}I-*m*IBG use. However, given the absence of the US FDA approval until recently, investigations with larger cohorts or noninvestigational clinical experiences with cardiac ^{123}I-*m*IBG have been sporadic.

Focusing on management of pump failure in the setting of HF with reduced ejection fraction (HFrEF), Myron Gerson at the University of Cincinnati investigated the ability of ^{123}I-*m*IBG imaging to assess a patient's response to medical therapy. In 22 patients with HF secondary to dilated, non-ischemic cardiomyopathy, Gerson et al. (42) found that, after a mean of 7. 2 months of therapy with the β-blocker carvedilol, patients with a baseline HMR <1.4 had a significant increase in adrenergic tracer uptake accompanied by a significant improvement in LVEF from 25% to 37%. This study suggested that patients with lower baseline *m*IBG uptake are more likely to respond to such therapy. Another study by Gerson and colleagues (55) found that advanced HF patients with an HMR <1. 536 experienced a greater likelihood of undergoing cardiac transplant or suffering cardiac death, with the HMR superior to LVEF or maximum oxygen consumption for prediction of these endpoints.

The above summary represents much of the work in the US up to the early 2000s. These studies contained mostly small sample sizes owing to the absence of the US FDA approval. In fact, in a meta-analysis review published in 2008 by a group from the University of Amsterdam led by Verberne (56), of the 107 studies performed between 1980 and 2006, 18 of which were included in the final analyses, there was only one study from the US, the aforementioned study by Gerson et al. (55) regarding ^{123}I-*m*IBG image prediction of transplant-free survival.

The US moves toward establishing the clinical roles of ^{123}I-*m*IBG: issues related to ICD indications in heart failure

An important factor for a strong US interest developing toward the potential clinical use of ^{123}I-*m*IBG imaging was the publication of a series of large randomized studies including MADIT-2 (Multicenter Automatic Defibrillator Implantation Trial-II) (57), DINAMIT (Defibrillator in Acute Myocardial Infarction Trial) (58), DEFINITE (Defibrillators in Non-ischemic Cardiomyopathy Treatment Evaluation) (59), and SCD- HeFT (60), showing clear benefits to prophylactic use of an implantable cardiac defibrillator (ICD) for primary prevention of SCD in patients with HFrEF. However, while these studies resulted in the creation of guidelines establishing a Class IA recommendation for implantation of an ICD as primary prevention in patients with NYHA Class II-III symptoms and LVEF <35% (61), from the onset of this paradigm, it was recognized that basing such treatment predominantly on LVEF was flawed, as large numbers of patients receiving ICDs never used the anti-arrhythmic feature while being at risk of serious morbidities related to the device (62).

Possible role of ^{123}I-*m*IBG for decision-making on ICD implantation: the US and Japan collaboration

At Montefiore Medical Center in New York, Arora et al. performed ^{123}I-*m*IBG imaging on patients who already had an

ICD to investigate whether planar and SPECT findings correlated with the occurrence of ICD defibrillator discharges. The hypothesis was that ^{123}I-*m*IBG imaging could potentially identify who would benefit most from an ICD. Japanese medical groups and industry contributed to this study by supporting ^{123}I-*m*IBG production and labeling. Study results showed that ^{123}I-*m*IBG HMR did effectively separate the patients, with even better risk stratification when heart rate variability on a Holter monitor was also included (Figure 6A) (63). In addition, adrenergic defect extent/severity, as shown through tomographic imaging also correlated with ICD discharge (Figure 6B).

Shortly thereafter, a larger and more comprehensive follow-up study was undertaken in Sapporo, Japan under the direction of Nakata. This group prospectively followed 54 patients with an ICD and found that SCD or an arrhythmic-triggered ICD discharge strongly correlated with delayed ^{123}I-*m*IBG HMR, independent of other variables including LVEF (64).

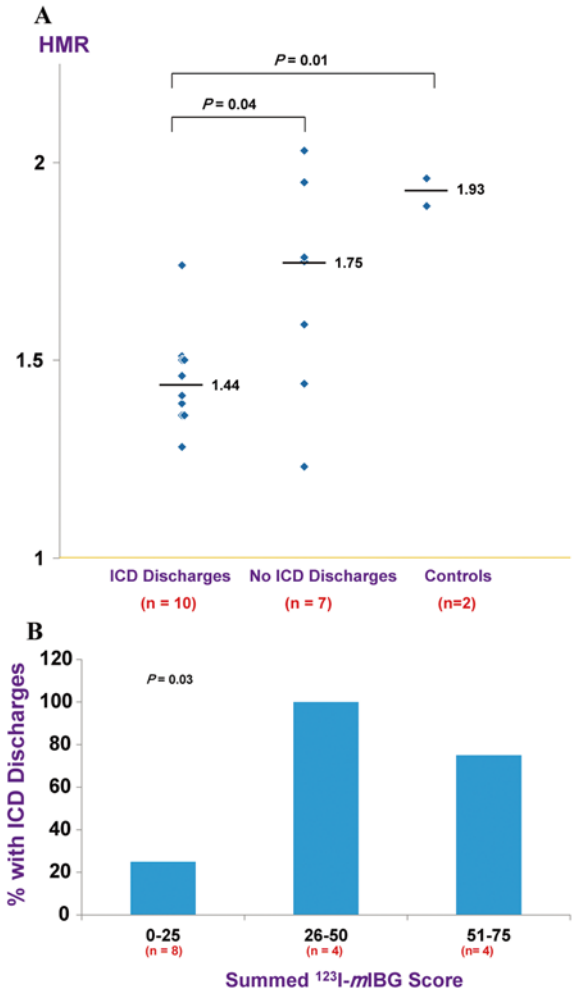

Figure 6 Relationship of ^{123}I-*m*IBG imaging findings with the occurrence of ICD discharges. (**A**) Heart-to-mediastinum ratio (HMR) on planar images in relation to the occurrence of ICD discharges. Heart failure patients with ICD discharges had a median HMR of 1.44 compared with 1.75 for those without discharges. Controls (no heart failure) had a median HMR of 1. 93. (**B**). Occurrence of ICD discharges in relation to summed ^{123}I-*m*IBG dysinnervation scores (note: summed dysinnerva- tion scores were derived analogously to perfusion summed stress scores, with SPECT images divided into 17 segments, and subjectively graded 0 for visually normal segmental ^{123}I-*m*IBG uptake, 1 for mildly decreased uptake, 2 for moderately decreased uptake, 3 for severely decreased uptake, and 4 for no uptake). (Data for figures is from Arora et al. JNC 2003 (63).

Multiple directions of Japanese ^{123}I-*m*IBG clinical studies after the ministry's approval

As previously discussed, the US groups have focused on establishing clinical roles for ^{123}I-*m*IBG, including guidance of ICD use, as well as establishing important clinical parameters. The limited availability of ^{123}I-*m*IBG in the US has been constraining. In contrast, ^{123}I-*m*IBG has been widely available in Japan for clinical practice as it has been covered by health insurance since 1992.

Japanese investigators have applied ^{123}I-*m*IBG imaging to a wide variety of cardiac and non-cardiac disease conditions, as summarized in Table 3. In particular, extensive clinical research has been performed in hypertrophic cardiomyopathy (HCM), Takotsubo cardiomyopathy, and vasospastic angina. Nakajima et al. (65) performed ^{123}I-mIBG scintigraphy in 29 HCM patients and found low ^{123}I-*m*IBG uptake relative to perfusion and fast washout in hypertrophied myocardium. Akashi et al. (66) found faster ^{123}I-*m*IBG washout in the acute phase (within 3 days after the onset) than in the chronic phase (3 months later) in 8 patients with takotsubo cardiomyopathy, suggesting neurogenic myocardial stunning. Heterogeneous results have been reported for ^{123}I-*m*IBG imaging in vasospastic angina. Takano et al. (67) showed reduced regional ^{123}I-*m*IBG uptake in the area of coronary vasospasm, whereas Sakata et al. (68) demonstrated faster ^{123}I-*m*IBG washout along with preserved ^{123}I-*m*IBG uptake in such areas.

Besides cardiac applications, applications of ^{123}I-*m*IBG imaging in non-cardiac diseases such as diabetes mellitus (69) and sleep apnea syndrome (70) have been discussed in a number of publications. Unfortunately, to date, these applications have been investigational and have not been extended to clinical practice.

Japanese groups have developed a wide range of clinical uses for ^{123}I-*m*IBG and have published extensively, but most studies have consisted of small sample sizes and lacked randomization. While these studies have been very useful, adopting some of the more rigorous US-style study designs could prove helpful within Japanese nuclear cardiology communities.

Roles of industry in ^{123}I-*m*IBG supply: US ^{123}I-*m*IBG supplier

An important event for potential *m*IBG use in the US occurred in 2003–2004 when the General Electric Company

Table 3 Clinical applications of ^{123}I-*m*IBG imaging in various diseases reported by Japanese groups in Japanese Clinical Studies

Cardiac applications	Atrial fibrillation	Contributions to clinical practice
	Athlete's heart	
	Brugada syndrome	Part of JCS guidelines
	Familial amyloidosis polyneuropathy	
	Hypertrophic cardiomyopathy	
	Takotsubo cardiomyopathy	Included in diagnostic guidelines
	Vasospastic angina	
Non-cardiac applications	Chronic obstructive pulmonary disease	
	Diabetes mellitus	
	Hypothyroidism	
	Liver cirrhosis	
	Renal failure	
	Sleep apnea syndrome	
	Systemic sclerosis	
	Parkinson's disease, dementia with Lewy bodies	Movement society guidelines
	Paraganglioma	
	Pheochromocytoma	JSNM draft guidelines for radiotherapy with ^{131}I-*m*IBG
United States	HF: ICD	Potential to help determine ICD implantation indication

ICD: implantable cardioverter defibrillator, HF: heart failure

(GE) acquired the United Kingdom biotech firm Amersham, one of several companies manufacturing and supplying radiolabeled *m*IBG (71). Restructured into GE Healthcare, the new entity undertook further investigation of the clinical potential of ^{123}I-*m*IBG, aiming to obtain the US FDA approval (labeling it "Adreview™") for cardiac and non-cardiac imaging (Table 1).

In 2005, GE Healthcare organized and sponsored a prospective, multicenter, international observational cohort study that became known as "AdreView Myocardial Imaging for Risk Evaluation in Heart Failure" (ADMIRE-HF). The trial demonstrated strong prognostic utility of ^{123}I-*m*IBG cardiac imaging in patients with New York Heart Association (NYHA) functional Class II-III HFrEF (≤35%) (39).

The US ^{123}I-*m*IBG FDA approval in 2013 and reimbursement

Based largely on the results of the ADMIRE-HF trial, in March 2013, ^{123}I-*m*IBG (GE Healthcare "Adreview™ Iobenguane I 123 Injection") received the US FDA approval for scintigraphic assessment of sympathetic innervation of the myocardium by measurement of the heart-to-mediastinum (H/M) ratio of radioactivity uptake in patients with NYHA Class II or Class III heart failure and LVEF ≤35%" (Table 1). This approval covers a specific condition in HF patients.

In contrast, the Japanese Ministry of Health, Labour and Welfare's approval covers any cardiac disease, a significant difference between the US and Japanese approvals (72). The US FDA approval states that "Among these patients, AdreView may be used to help identify patients with lower one- and two-year mortality risks, as indicated by an HMR ≥1.6. (40)" The US approval adds the limitation that "In patients with congestive heart failure, AdreView utility has not been established for: selecting a therapeutic intervention or for monitoring the response to therapy; [or] using the HMR to identify a patient with a high risk for death."

Shortly thereafter, "T" (for an emerging technology) billing codes were assigned to cardiac imaging with ^{123}I-*m*IBG, 0331T for "myocardial sympathetic innervation imaging, planar qualitative and quantitative assessment," and 0332T for "myocardial sympathetic innervation imaging, planar qualitative and quantitative assessment; with tomographic SPECT (73)." Currently, the Centers for Medicare and Medicaid Service (CMS) Hospital Outpatient Prospective Payment Systems (HOPPS) Calendar Year 2018 (CY2018) proposed payment rates for these codes are $1202.60 (74), with rates having earlier ranged from $1108.46 to $1140.59 since 2015 (75).

Reasons for underuse of ^{123}I-*m*IBG in the US

Despite the US FDA approval existing for approximately 5 years till the time of this writing, clinical use in the US has been rare as ^{123}I-*m*IBG (Adreview) is priced significantly higher than CMS reimbursement rates, with the tracer cost ranging from $2,200 to $3,900 per dose (Table 1) (76). In addition, cardiac ^{123}I-*m*IBG imaging is covered insufficiently, if at all, by other third-party private payers.

An example of the situation in the US is described in

statements from October 28, 2014, to May 2, 2017, in the Clinical Review Criteria of the state of Washington's Kaiser Foundation Health Plan. After reviewing the relevant literature, the plan's Medical Policy Committee concluded that while "there is evidence that myocardial MIBG innervation imaging provides prognostic information for cardiac events… there is a lack of evidence that the prognostic information will lead to improved health outcomes," further stating that "The use of I MIBG Imaging for Heart Failure does not meet *Kaiser Permanente Medical Technology Assessment Criteria* (77)."

Similarly, Blue Cross/Blue Shield of North Carolina (BCBSNC), in documents from July 2013 to May 2017, stated that "myocardial sympathetic innervation imaging with ^{123}Iodine meta-iodobenzylguanidine (MIBG) is considered investigational for patients with heart failure," and that "BCBSNC does not provide coverage for investigational services or procedures (78)."

Efforts by ASNC to encourage ^{123}I-*m*IBG payment coverage in the US

To encourage third-party payers to consider reimbursing cardiac ^{123}I-*m*IBG imaging, ASNC and the Society of Nuclear Medicine and Molecular Imaging (SNMMI), in an effort to provide patients access to promising new technologies, published a model policy coverage document of expert consensus evaluation of the current peer-reviewed literature that supports the use of ^{123}I-*m*IBG myocardial sympathetic innervation for clinical imaging (79). In this document, the authors highlighted specific clinical scenarios and indications in which ^{123}I-*m*IBG could provide incremental risk stratification and guide further management. A major focus of the model policy were decisions regarding use of an ICD for which Class I indications are determined largely by LVEF. However, it is widely understood that basing implantation of the device on LVEF is flawed. In consideration of the aforementioned ADMIRE-HF study and of similar data from large observational studies in Europe (80) and Japan (51) showing that patients with a high ^{123}I-*m*IBG HMR are at extremely low risk for SCD, the model coverage policy document designated as a "Specific Indication" that ^{123}I-*m*IBG be recommended "for patients with NYHA Class II-III HF with LVEF ≤35% to help stratify risk and to promote more informed clinical decision-making when the result of ^{123}I-*m*IBG study is likely to influence the decision regarding ICD implant (79)." A situation designated as a "Potential/Emerging" indication was "For patients who received an ICD for primary and/or secondary prevention of SCD who subsequently underwent complete device and lead removal due to definite infection [and] there [was] uncertainty on the part of [the] treating physician to proceed with ICD replacement, when the result of ^{123}I-*m*IBG study is likely to influence the decision regarding device placement (79)."

^{123}I-*m*IBG clinical guidelines in the US and Japan

The US and Japan share the issue of underuse of ^{123}I-*m*IBG in the clinical setting. In the US, third-party reimbursement is strongly influenced by clinical guidelines published by recognized professional societies. In Japan, there have been no efforts to increase reimbursement by healthcare systems. While clinical guidelines do not impact payments at this time, physicians in Japan tend to choose the diagnostic tests referred to in them. Therefore, the professional societies of both countries have endeavored to include the use of ^{123}I-*m*IBG in clinical guidelines.

The US ^{123}I-*m*IBG clinical guidelines

In support of cardiac ^{123}I-*m*IBG imaging in the US, protocol and image interpretation details were included in the most recent (2016) "ASNC Imaging Guidelines for SPECT nuclear cardiology procedures: Stress, protocols, and tracers (43)." Unfortunately, societies members of which would be expected to have an interest in potential patient benefits from ^{123}I-*m*IBG imaging, such as the Heart Rhythm Society and the Heart Failure Society of America (HFSA), are as yet unwilling to recommend in their guidelines that ^{123}I-*m*IBG imaging could be helpful in assessing patients with these conditions. HFSA withdrew support for the aforementioned model policy coverage document despite a prominent member of their society being on the writing committee.

The contention has been that there is not yet any prospective, randomized trial documenting the benefits of ^{123}I-*m*IBG imaging in directing ICD or other therapies, as opposed to the case with the aforementioned randomized trials upon which the current standard of care is based. A major fear is the risk of using "unproven" ^{123}I-*m*IBG imaging to inform a decision to not place an ICD into a patient who, following current guidelines that recommend implantation based on LVEF, would otherwise receive one.

Japanese ^{123}I-*m*IBG clinical guidelines: JCS guidelines

In 2011, the Japanese Circulation Society (JCS) formulated a comprehensive update for clinical use of nuclear cardiology. Subsequently, in 2012, the JCS nuclear cardiology committee published an English version of the updated JCS guidelines (81). In these guidelines, ^{123}I-*m*IBG imaging was assigned a Class I recommendation for the assessment of severity and prognosis of heart failure based on the published evidence, and Class IIa for the assessment of effects of heart failure treatment (Table 3).

Neurology society guidelines

Neurological applications of ^{123}I-*m*IBG, particularly for

Table 4 ^{123}I-*m*IBG in guidelines, criteria, and academic societies' tasks

Academic Society	＊＊	Indications	Comments	Publication
Japanese Circulation Society's guidelines	Japan	Assessment of severity of heart failure and prognosis	Class I recommendation	Circ J 2012; 76: 761–767
		Assessment of effects of heart failure treatment	Class IIa recommendation	
		Arrhythmogenic disease	Class IIb recommendation	
EANM Cardiovascular Committee and the European Council of Nuclear Cardiology	Europe	Proposal for standardization of ^{123}I-*m*IBG	Data acquisition and processing protocols	Eur J Nucl Med Mol Imaging 2010; 37:1802–1812
Japanese Society of Nuclear Medicine working group	Japan	Normal databases of planar and SPECT studies	Japanese normal values for ^{123}I-*m*IBG (H/M ratio, washout rate, SPET polar maps)	Ann Nucl Med 2010; 24: 125–135 Ann Nucl Med 2016; 30: 188–199
Movement Disorder Society (MDS) clinical diagnostic criteria for Parkinson's disease		Parkinson's disease	Supportive criteria for Parkinson's disease	Movement Disorder 2015; 30 (12): 1591–1599
Fourth consensus report of the dementia with Lewy bodies (DLB) Consortium		Diagnosis and management of DLB	Abnormal (low) ^{123}I-*m*IBG uptake as an indicative biomarker for DLB	Neurology 2017; 89: 88–100
ASNC imaging guidelines	US	New York Heart Association Class II or Class III HF and left ventricular ejection fraction ≤35%	Potential indication of ^{123}I-*m*IBG for ICD candidate and for sudden cardiac death	J Nucl Cardiol 2016; 23: 606–639

ASNC: American Society of Nuclear Cardiology, DLB: dementia with Lewy bodies, EANM: European Association of Nuclear Medicine, ICD: implantable cardioverter defibrillator

Lewy body diseases including Parkinson's disease and dementia with Lewy bodies (DLBs), are common in Japan. JMHLW began reimbursement for these indications in 2012, as well as for the diagnosis of cardiac diseases (Table 1). Initial application to Parkinson's disease began in 1994, and subsequent Japanese and European studies supported the use of ^{123}I-*m*IBG, showing a diagnostic accuracy of 80–90% (82, 83). After 2000, it was also found that ^{123}I-*m*IBG uptake was clearly decreased in the heart in patients with DLB (84). The use of ^{123}I-*m*IBG was addressed in guidelines for diagnosis of Parkinson's disease by the Movement Disorder Society as one of the supportive criteria (Table 3) (85). In addition, in 2017, the fourth consensus report of the DLB consortium identified ^{123}I-*m*IBG uptake as one of the indicative biomarkers for the clinical diagnosis of probable and possible DLB (Table 4) (86).

In the Japanese multicenter studies for differentiating DLB and Alzheimer disease, standardized HMR based on the phantom study was employed to overcome camera-collimator differences (87). While the frequency of cardiac ^{123}I-*m*IBG studies has not changed, the total number of ^{123}I-*m*IBG studies has gradually increased secondary to the increased use for neurology applications, demonstrating the importance of academic society endorsements.

How should we overcome the current issues for ^{123}I-*m*IBG?

While the US and Japanese groups and societies have established the clinical utility of ^{123}I-*m*IBG, both countries have had great challenges with the underuse of ^{123}I-*m*IBG in clinical settings. To overcome current limitations, both countries have undertaken several approaches to promote ^{123}I-*m*IBG.

In the US, a GE Healthcare-sponsored prospective study planned to randomize >2000 subjects with NYHA Class II-III HF and LVEF 25%–35% to ^{123}I-*m*IBG HMR-guided ICD implantation rather than using a guidelines-directed approach. The study would compare occurrences of all-cause mortality and various secondary outcomes, including ventricular arrhythmias, over a 2. 75 to 3-year follow-up period (88). Unfortunately, the study was discontinued in March 2018 due to insufficient patient and site recruitment. Subsequent studies remain uncertain at this point.

As of now, the future of cardiac ^{123}I-*m*IBG imaging in the US is unclear. Similar circumstances exist in Europe, where its use is predominately in clinical trials (1). At the same time, efforts are under way to develop alternative positron emission tomographic (PET) adrenergic agents (89–91). Cardiac magnetic resonance imaging is also considered a promising tool for ventricular arrhythmic risk stratification (62).

Perhaps it may be advantageous, at least for the time being, to increase focus on more limited uses, such as deciding whether to replace an ICD generator secondary battery at the end of life or to avoid replacing infected devices in patients no longer believed to be at clinical risk. Its potential use in detecting non-arrhythmic conditions, such as myocardial ischemia, myocardium at risk during an acute myocardial infarction, and hidden risk in diabetic patients, should also be considered (92, 93). Current evidence indicates that cardiac adrenergic imaging can offer much benefit to patient well-being.

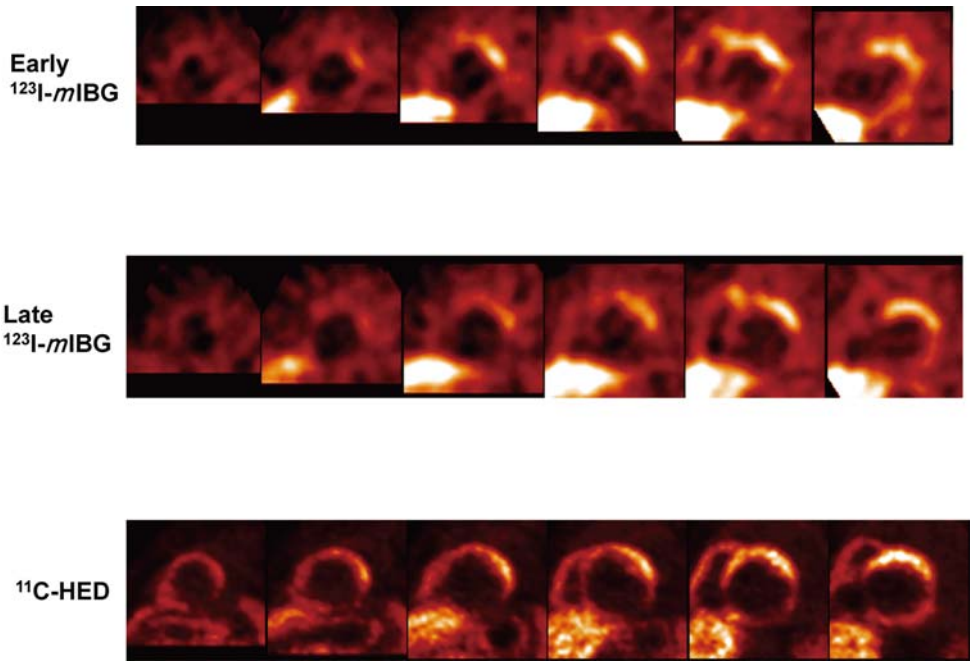

Figure 7 ^{123}I-*m*IBG SPECT and ^{11}C-hydroxyephedrine PET/CT short-axis images showing inferior defect from a male patient with inferior myocardial infarction. HED: hydroxyephedrine.

Conclusions

The ability of cardiac adrenergic imaging with ^{123}I-*m*IBG and related PET tracers such as ^{11}C-hydroxyephedrine (Figure 7) to contribute to evaluation of patients with various cardiac conditions beyond that of conventional techniques has been consistently demonstrated through the US and Japanese studies. The potential for such imaging to improve patient management is strong. Unfortunately, clinical use in the US has been hampered by the lack of a prospective randomized trial demonstrating value and by the cost of the tracer relative to reimbursement.

In Japan, in light of JMHLW approval, clinical use is common including for neurologic conditions. It is hoped that this review comparing practices in each country can help increase technical sophistication in performing and interpreting test results, and provide the impetus to undertake studies needed to increase clinical use, which the authors believe will improve patient outcomes.

New knowledge gained

^{123}I-*m*IBG was initially developed in the USA in the 1970s, with the first human images published in 1981. The first approval for clinical use was in 1992 in Japan. In accord with national health insurance coverage guidelines, Japanese nuclear cardiologists have used ^{123}I-*m*IBG imaging in patients with various pathophysiological conditions. In this regard, ^{123}I-*m*IBG clinical indications have been included in Japanese circulation Societies guidelines and Movement Disorder Society Guidelines. US cardiologists and nuclear physicians have sought to establish evidence supporting clinical roles for ^{123}I-*m*IBG, particularly to help better guide ICD implantation in relation to current recommendations. US and Japan have had different approaches to cardiac ^{123}I-*m*IBG imaging, but both countries aim to establish the clinical roles. Use of this very promising radiotracer has been impeded in both Japan and the US, as well as in other parts of the world. It is hoped that consideration of the successes and obstacles in both countries described here will encourage scientists and clinicians to perform the necessary further investigations required to allow ^{123}I-*m*IBG or PET analogues of it to be used clinically, in order to better evaluate and manage patients with various cardiac diseases, thereby improving patient outcome and well-being.

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Conflicts of interest

The authors declare that there are no conflicts of interest.

Abbreviations

^{123}I-*m*IBG	Iodine-123 *meta*-iodobenzylguanidine
FDA	Food and Drug Administration
HF	Heart failure

HMR	Heart-to-mediastinum ratio
ICD	Implantable carioverter defibrillator
JMHLW	Japanese Ministry of Health, Labour and Welfare
SCD	Sudden cardiac death
SNS	Sympathetic nervous system
SPECT	Single-photon emission computed tomography

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