

## REVIEW ARTICLE—ASNC INTERNATIONAL SESSION

# Present Status of Medical Radiation and Nuclear Cardiology Usage in Japan: A Discussion at the American Society of Nuclear Cardiology Joint Symposium

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Received: May 15, 2018/Revised manuscript received: June 6, 2018/Accepted: June 16, 2018

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## Abstract

The indications and methods for and volumes of nuclear cardiology procedures differ among countries, and each country has specific nuclear cardiology characteristics. Nuclear cardiology practice in Japan has the following specific characteristics: 1) stress myocardial perfusion imaging is severely underused; 2) thallium-201 ( $^{201}\text{Tl}$ ) is frequently used for perfusion imaging, which might increase the public radiation burden; 3) iodine-123-labeled beta-methyl-iodophenyl pentadecanoic acid ( $^{123}\text{I}$ -BMIPP) is readily available for cardiac imaging, which has resulted in large amounts of evidence about the utility of this technique being collected in Japan; and 4)  $^{123}\text{I}$ -meta-iodobenzylguanidine (MIBG)-based imaging is readily available for examining cardiac and neurological disease, especially Parkinson's disease. In some respects, Japan is behind the global standard and must follow the lead of other countries (issues 1 and 2). However, in other areas Japanese nuclear cardiologists can pave the way for other countries (issues 3 and 4). These issues were presented and discussed at the annual meeting of the American Society of Nuclear Cardiology in 2017.

**Keywords:** ASNC, BMIPP, Medical radiation, MIBG, MPI, Thallium

*Ann Nucl Cardiol* 2018; 4 (1): 142–148

The indications and methods for and volumes of nuclear cardiology procedures differ between countries. Thus, close international communication is essential for facilitating the standardization of such procedures and advancing nuclear cardiology. An International Atomic Energy Agency (IAEA) global initiative session was held at the annual meeting of the American Society of Nuclear Cardiology in 2017 (ASNC2017), which provided us with a precious opportunity to discuss issues related to nuclear cardiology with nuclear cardiologists from all over the world. Specifically, we had the opportunity to summarize the specific characteristics of nuclear cardiology practice in Japan.

### What is special about Japanese nuclear cardiology?

What is special about nuclear cardiology in Japan? Of course, there are many specific characteristics of Japanese

nuclear cardiology. Here, we want to focus on four issues.

- 1) The severe underusage of stress myocardial perfusion imaging (MPI)
- 2) The frequent usage of thallium-201 ( $^{201}\text{Tl}$ ) for perfusion imaging
- 3) The availability of iodine-123-labeled beta-methyl-iodophenyl pentadecanoic acid ( $^{123}\text{I}$ -BMIPP) for cardiac imaging
- 4) The availability of  $^{123}\text{I}$ -meta-iodobenzylguanidine ( $^{123}\text{I}$ -MIBG) for examining cardiac and neurological disease

### The underusage of MPI

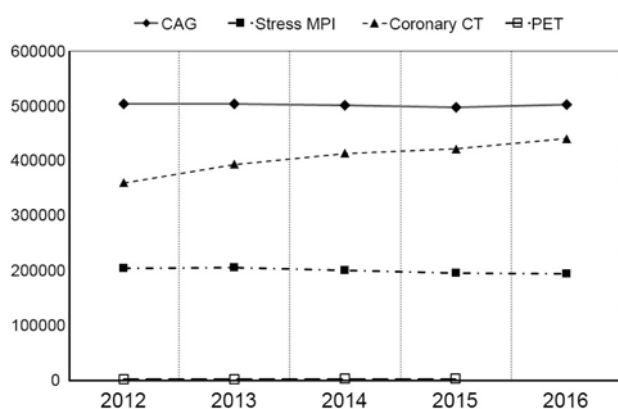
If there is one well known fact about nuclear cardiology in Japan, it is that Japan is a giant of medical radiation. The United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) reported that medical radiation

doi: 10.17996/anc.18-00071

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**Fig. 1** Recent trends in the numbers of imaging procedures performed in Japan (data from the J-ROAD registry).

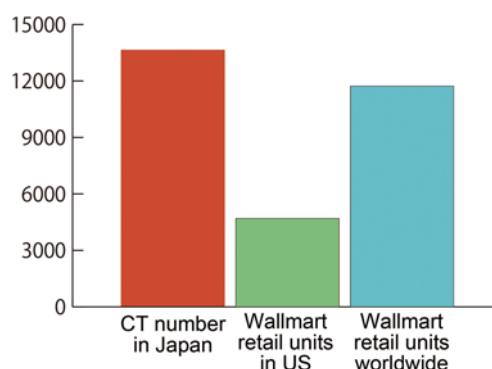
accounts for roughly 20% of the public radiation burden around the world (1). However, the contribution of medical radiation is much larger in developed countries, and each country has its own specific characteristics.

The US is a major user of nuclear cardiology. Thus, approximately 10% of the public radiation burden in the US is caused by nuclear cardiology procedures alone, and roughly 50% is from medical procedures (2). In Japan, medical radiation is more important because roughly two thirds of the public radiation burden is due to medical radiation, which is a much larger proportion than is seen in the US (3). However, the contribution of nuclear cardiology to the public radiation burden is quite small in Japan. In fact, the sum of all nuclear medicine procedures (not only those related to cardiology) only contributes about 1% to the public radiation burden (3). The major reason for this difference is the heavy underusage of nuclear cardiology procedures in Japan.

Information about the number of imaging examinations performed each year in Japan is presented in Fig. 1 (data from JROAD: The Japanese Registry of All Cardiac and Vascular Diseases) (4). Briefly, the number of MPI procedures carried out each year is much lower than the number of coronary angiography scans and even lower than that of coronary computed tomography angiography (CTA) scans. As shown in Fig. 1, the number of cardiac CTA examinations conducted in Japan is very high and is rapidly increasing. On the other hand, the number of stress MPI procedures performed in Japan has declined slightly. The annual number of pharmacological stress MPI procedures has increased slightly; however, the increase was not enough to compensate for the reduction in the number of exercise MPI procedures. In addition, the number of cardiac positron emission tomography (PET) scans has tended to increase, but it is still so low as to be negligible compared with the frequencies of other examinations.

The incredibly high and increasing usage of cardiac CT scans is probably due to their easy availability in Japan. As is

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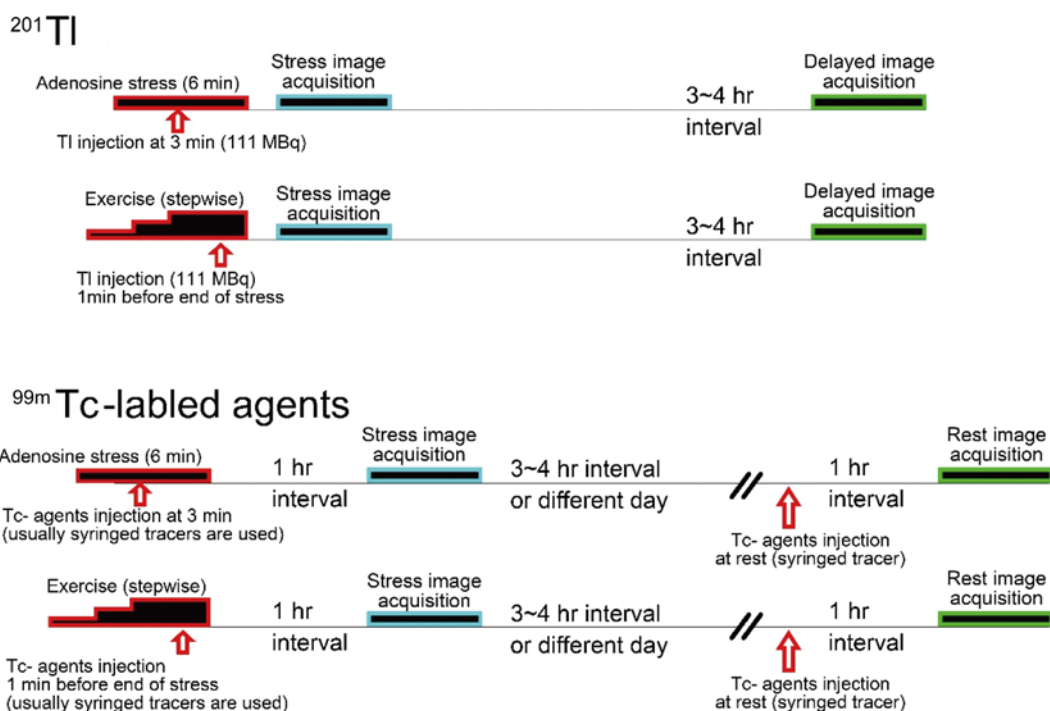


**Fig. 2** A comparison of the total number of CT scanners in Japan and the numbers of Walmart retail stores in the US and around the world (Walmart data available from <https://corporate.walmart.com/our-story/our-locations>).

well known, the number of CT scanners per population is higher in Japan than anywhere else in the world (there were 101.28 scanners per million population in 2011). In fact, the figure for Japan is almost twice as high as that for the country with the second highest number of CT scanners per population (Australia: 59.61 scanners per million population in 2015) (5). In addition, the total number of CT scanners in Japan is almost equal to the number of Walmart stores around the world (Fig. 2).

These statistics indicate that in Japan current practice regarding ischemic heart disease centers around percutaneous coronary interventions/CTA, and so patients with ischemic heart disease might be being treated without appropriate non-invasive examinations of physiological ischemia, such as stress MPI scans.

Thus, Japanese nuclear cardiologists are heavily underusing stress MPI. However, recently the importance of the physiology of myocardial perfusion has begun to be recognized by many cardiac interventionalists in Japan. Numerous studies have indicated that physiological ischemia, which can be assessed based on the fractional flow reserve (FFR) or instantaneous wave-free ratio (iFR), is an important determinant of prognosis in ischemic heart disease and that information about physiological ischemia can aid decision-making in such cases (6-9). These findings have resulted in a strong trend towards the measurement of the FFR and iFR during “invasive” coronary angiography. This in turn seems to have encouraged the use of MPI, which has made many interventionalists realize that stress MPI is the optimal method for “non-invasively” assessing the physiology of myocardial perfusion. The Japanese Society of Nuclear Cardiology (JSNC) is working on facilitating greater MPI usage in Japan. The JSNC considers that young cardiologists who are not yet familiar with nuclear cardiology are the most important targets of programs for facilitating nuclear cardiology. Therefore, we are publishing a nuclear cardiology textbook, which covers everything from basic aspects of nuclear cardiology to



**Fig. 3** Common MPI protocols in Japan.  
<sup>99m</sup>Tc-labeled agents are provided in syringe form. The majority of MPI studies are performed using these syringe-based tracers.

**Table 1** Estimated effective doses for common nuclear cardiology protocols

	Thallium	Tetrofosmin		MIBI		BMIPP	MIBG
		Exe	Rest	Exe	Rest		
Effective dose (mSv/MBq)	0.14	0.0069	0.008	0.0079	0.009	0.016	0.013
Typical actual dose at the time of injection (MBq)	111	418	660	523	660	111	111
Estimated effective dose per injection (mSv)	15.54	2.884	5.28	4.132	5.94	1.776	1.443
Estimated effective dose per procedure (mSv)	15.54	8.164		10.072		1.776	1.443

In Japan, syringe-based <sup>99m</sup>Tc-labeled MPI agents are usually used. Thus, dose estimates were calculated based on the assumption that a small syringe (296 MBq of tetrofosmin or 370 MBq of MIBI) would be injected at 9:00 for stress imaging, and a large syringe (740 MBq of either tracer) would be injected at 13:00 for rest imaging without any dose modification.

practical protocols. In addition to information about perfusion imaging, it also provides information about metabolic and sympathetic imaging, which are mentioned later in this review. This textbook is frequently revised, and the present version is more than 120 pages long. We are also hosting local workshops twice a year in eight areas of Japan to help young cardiologists understand the basics of nuclear cardiology.

### <sup>201</sup>Tl usage and medical radiation

Around the world, <sup>201</sup>Tl has been replaced with <sup>99m</sup>Tc-labeled myocardial perfusion tracers [methoxyisobutylisonitrite (MIBI) and tetrofosmin]. However, in Japan <sup>201</sup>Tl is still used as the major radiopharmaceutical for stress MPI. This might result in a higher patient/public radiation burden from MPI. Japanese nuclear cardiologists probably realize this. However, we do not have any objective data regarding this

issue.

Recently, several nationwide surveys have been performed to assess the present state of radiopharmaceutical usage in Japan. A survey by Otsuka and Fukuchi (10) not only revealed present radiopharmaceutical usage in Japan, but also estimated the radiation doses administered to typical patients who undergo standard Japanese MPI procedures. They reported that most MPI procedures are performed well, with <20 mSv radiation being administered per procedure, which is the recommended upper limit per procedure (11) [which was calculated from the occupational dose limit (100 mSv) for adults over 5 years] (12). Even when <sup>201</sup>Tl is administered at the typical dose employed in Japan (111 MBq), the aforementioned limit is not broken in most of the examinations conducted in Japan. Otsuka and Fukuchi also estimated that almost one third of MPI procedures involve a radiation dose of

< 9 mSv, which is the target dose recommended by the American Society of Nuclear Cardiology in 2010 (13). These findings indicate that the radiation burden placed on patients by nuclear cardiology procedures in Japan is not excessive. A typical stress MPI procedure and the estimated effective doses for each protocol are described in Fig. 3 and Table 1, respectively (14, 15).

However, this is only due to a fortunate coincidence. The rules for the delivery of and reference doses for long half-life tracers were changed in April 2016, and the abovementioned survey was performed after the new rules came into force. We do not have any objective data that were collected before April 2016; thus, we cannot calculate the radiation doses administered before that time. Probably, a significant percentage of the MPI procedures conducted before April 2016 involved doses slightly over 20 mSv.

Due to the changes in the delivery rules for  $^{201}\text{Tl}$ , the actual injected dose significantly reduced after April 2016. This should have resulted in a significant deterioration of the image quality of  $^{201}\text{Tl}$ -based MPI. However, only a minority of facilities switched from  $^{201}\text{Tl}$ -to  $^{99\text{m}}\text{Tc}$ -labeled tracers (personal communication, not yet published). Otsuka and Fukuchi also surveyed the reasons why  $^{201}\text{Tl}$  was still used at the majority of facilities and revealed that the major reasons were 1) familiarity with the  $^{201}\text{Tl}$  procedure, which made clinicians hesitant to switch, and 2) apprehension about increasing the workload of physicians, as  $^{99\text{m}}\text{Tc}$ -based imaging procedures require a second tracer injection (10). Although this survey was performed before April 2016, the aforementioned reasons probably continued to apply after April 2016. In Japan, most radiopharmaceuticals are injected by physicians (mainly by cardiologists in the case of MPI), rather than by nurses or technologists. Thus, the very high workload of Japanese cardiologists often makes it hard to find a doctor to perform a second radiopharmaceutical injection.

As the reasons given for the continued use of  $^{201}\text{Tl}$  represent practical rather than scientific issues, it will be very hard to change this situation rapidly. However, to improve this situation, the JSNC created a working group for “optimizing the radiation burden associated with nuclear cardiology procedures”. We are planning to distribute the first version of our guidelines in 2018. It is considered that switching from  $^{201}\text{Tl}$  to  $^{99\text{m}}\text{Tc}$  would cut the radiation burden by almost 50% and result in better image quality (mainly due to an improved signal to noise ratio). In our guidelines, we are planning to compare the radiation burdens associated with  $^{201}\text{Tl}$ -and  $^{99\text{m}}\text{Tc}$ -based imaging and recommend that clinicians use  $^{99\text{m}}\text{Tc}$  instead of  $^{201}\text{Tl}$ .

### Usage of $^{123}\text{I}$ -BMIPP in cardiology

$^{123}\text{I}$ -BMIPP (BMIPP) is the only commercially available

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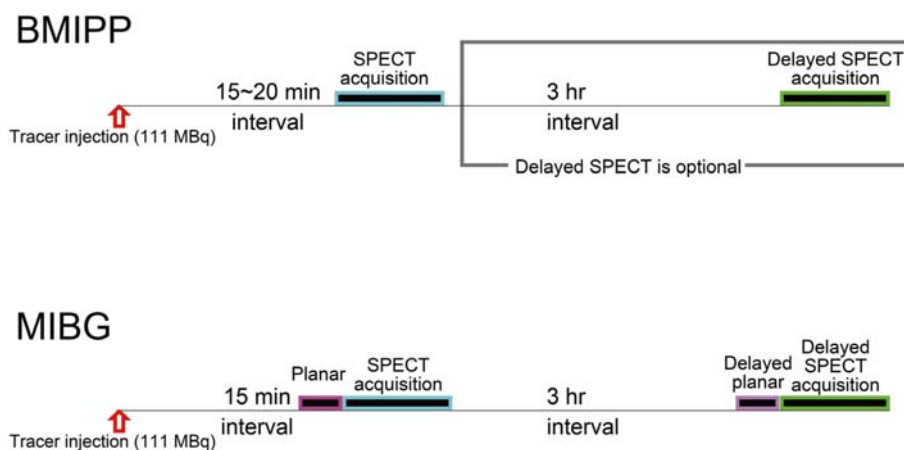
radiopharmaceutical that can be used to assess myocardial fatty acid metabolism with single-photon emission computed tomography (SPECT). It is a branched long-chain fatty acid labeled with  $^{123}\text{I}$ . During fatty acid transport, it accumulates in the myocardium. A common BMIPP imaging procedure is described in Fig. 4. Contrary to fluorodeoxyglucose (FDG), which accumulates in damaged myocardial tissue, BMIPP uptake is suppressed in damaged myocardial tissue. Thus, BMIPP imaging provides a reverse image compared with FDG imaging. In Japan, BMIPP was approved for clinical use in 1993, while it is still not clinically available in Europe or the US. Since its commercial release in 1993, many Japanese researchers have performed imaging with BMIPP and obtained evidence about the best way to use this tracer.

The Japanese Cardiology Society, Japanese College of Cardiology, Japanese Society of Pediatric Cardiology and Cardiac Surgery, Japanese Radiology Society, Japanese Society of Nuclear Medicine, and JSNC jointly developed the “Guidelines for the Clinical Use of Cardiac Nuclear Medicine” in 2005. The most recent version of these guidelines was published in 2010 (JCS2010 version) (16).

In these guidelines, BMIPP usage is mainly recommended for the diagnosis of ischemic heart disease and risk stratification. In particular, BMIPP imaging is recommended (class I, level B evidence) for the diagnosis of unstable angina.

BMIPP imaging has many applications. One typical application is for patients with severe chronic kidney disease (CKD) (17, 18), especially those who are on hemodialysis (HD) (19-23). CKD is one of the most important risk factors for ischemic heart disease. However, performing stress MPI regularly in all CKD/HD patients would generate an unrealistically large volume of examinations. BMIPP imaging is very simple, as it is performed under resting conditions. The standard imaging protocol involves a resting injection and the acquisition of a SPECT scan roughly 20 min after the injection. BMIPP imaging can detect severe ischemic damage without a stress procedure; thus, it can be helpful for reducing the number of patients with CKD/HD that need to undergo stress MPI. Fig. 5 shows typical cases in which HD patients with and without ischemic damage were examined with dual-isotope ( $^{201}\text{Tl}$ /BMIPP) simultaneous SPECT imaging.

A multicenter cohort study evaluating the utility of BMIPP imaging for estimating cardiac mortality among HD patients (the B-SAFE trial) revealed that clear risk stratification can be achieved using the BMIPP scoring system (24). In this cohort study, cardiac mortality, including sudden death, accounted for roughly one third of all-cause mortality, and 16% of deaths were classified as cerebrovascular or other vascular deaths. The remaining deaths were non-cardiac/vascular deaths. In the B-SAFE study, patients with low (<4) and high (>8) BMIPP scores exhibited good (95.7%) and very poor (78.8%) 3-year



**Fig. 4** Common BMIPP and MIBG imaging protocols in Japan.

For BMIPP imaging, delayed images are optional. Sometimes, dual-tracer imaging (BMIPP/ $^{201}\text{Tl}$ ) is performed. For MIBG imaging, delayed images are usually considered mandatory. On the other hand, SPECT images are sometimes considered optional, especially in cases involving the differential diagnosis of PD.

cardiac-related death-free survival, respectively. Interestingly, such clear risk stratification was only observed for cardiac-related mortality.

However, considering the huge number of HD patients being treated in Japan, it would still be unrealistic to perform BMIPP imaging regularly in all HD patients. When CKD patients are included as well, the number of potential examinations is even greater. Thus, we should consider “triaging” such patients in order to identify those who would benefit most from BMIPP imaging.

A study by Nakata et al. provided a good roadmap for selecting appropriate CKD/HD patients for BMIPP imaging (19). They combined electrocardiography (ECG), blood tests, and BMIPP imaging and selected an abnormal Q wave on ECG, a C-reactive protein (CRP) level of  $>2.38$ , and a BMIPP score of  $>16$  as prognostic markers for such patients. They found that the prognosis of the patients who displayed only one of the three markers was similar to that of the patients who exhibited none of the three markers. On the other hand, the patients who possessed two or three of these markers had critically poor prognoses. These findings indicate that it is possible to select appropriate patients for BMIPP imaging with simple and inexpensive ECG and blood sampling. BMIPP imaging should only be performed in patients who exhibit abnormal Q waves or CRP levels of  $>2.38$ .

One of the major concerns about the usage of BMIPP is the additional radiation burden it places on the patient. The radiation burden produced by a standard BMIPP procedure (Table 1) is roughly around 1.8 mSv/procedure (0.016 mSv/MBq, 111 MBq/procedure). We do not consider this to be excessively high because only patients who it is considered would derive sufficient benefit from BMIPP imaging (relative to the associated risks) are selected to undergo such

procedures. However, if it were possible to choose another PET tracer, such as  $^{11}\text{C}$  palmitate and/or  $^{18}\text{F}$  fluoro-6-thia-heptadecanoic acid (FTHA), which are used as PET tracers for fatty acid imaging, it would allow more patient-friendly assessments of myocardial fatty acid metabolism. Considering the low availability of these tracers, efforts should be made to facilitate their use.

In Japan, we have a relatively long history of BMIPP usage and have accumulated a lot of evidence and experience about it. The JSNC are willing to collaborate with doctors and academic societies in other countries to facilitate the usage of BMIPP.

#### Usage of $^{123}\text{I}$ -MIBG for cardio-neurology (rather than neuro-cardiology)

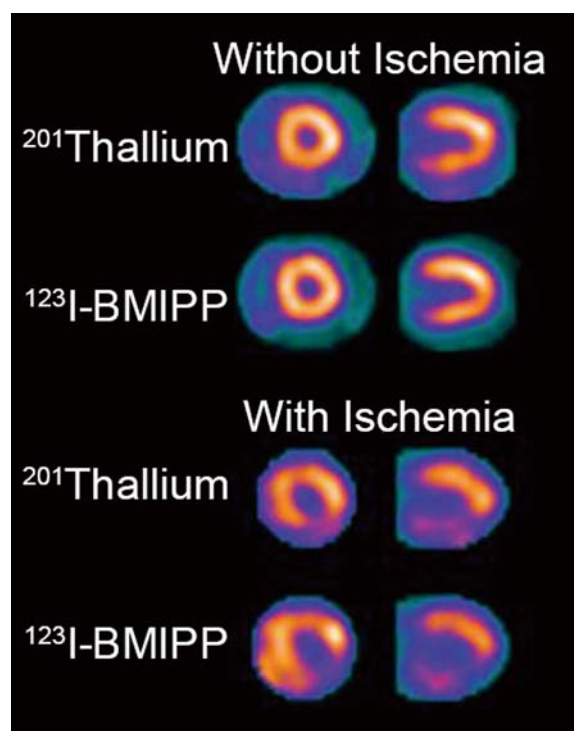
In Japan,  $^{123}\text{I}$ -MIBG (MIBG) was approved for clinical usage in 1992, just before BMIPP. Since then, we have accumulated much experience about the use of this tracer. A common MIBG imaging procedure is described in Fig. 4.

The jointly developed “Guidelines for the Clinical Use of Cardiac Nuclear Medicine” also include guidelines about MIBG usage (16). The guidelines list 7 types of MIBG usage. Unlike for BMIPP, MIBG usage is mainly recommended for diagnosing heart failure and arrhythmic disease, rather than for ischemic heart disease. Specifically, it is recommended (class I, level B evidence) that MIBG should be used to evaluate disease severity/prognosis in patients with heart failure.

However, over the past few years the usage of MIBG in Japan has changed. Recently, MIBG has been mainly used in neurology, rather than in cardiology, in Japan.

Nakajima et al. reported that in 2012, 62% of MIBG-based procedures conducted in Japan were performed to obtain a neurological diagnosis (25). This phenomenon arose due to the





**Fig. 5** Typical  $^{201}\text{Tl}$ /BMIPP images of HD patients with (bottom group) and without (top group) ischemia.

fact that many clinicians realized that MIBG is very useful for the differential diagnosis of Parkinson's disease (PD) and related disorders [e.g., dementia with Lewy bodies (DLB)] (26).

According to a patient survey published in 2014, there were 163,000 PD patients in Japan. This survey indicated that the number of PD patients is increasing and is becoming a huge problem for society (27). Among neurological diseases, DLB is the second most common cause of dementia (the most common is Alzheimer's disease). Differential diagnosis is important in such cases because there are many diseases that present with similar symptoms to PD (Parkinson syndromes, such as progressive supranuclear palsy, multiple systemic atrophy, etc.) and DLB (other types of dementia, such as Alzheimer's disease, argyrophilic grain dementia, etc.). In PD and DLB, markedly decreased myocardial uptake of MIBG is seen (28). This phenomenon is specific to PD/DLB and is not found in other degenerative diseases that cause Parkinson syndromes (non-PD PS). This indicates that MIBG can be used to clearly distinguish between PD and non-PD PS. According to these important findings, MIBG is classified as an "indicative" biomarker for the diagnosis of PD in the 4th consensus report of the DLB consortium (29).

As is the case for BMIPP, the usage of MIBG also raises questions regarding the radiation burden placed on patients. The estimated radiation dose delivered during the standard MIBG procedure (Fig. 4) is roughly 1.5 mSv/procedure (0.013 mSv/MBq, 111 MBq/procedure). Like BMIPP imaging,

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MIBG imaging is also only performed in selected patients. Thus, we do not consider that the associated radiation burden is too high. However, considering the large number of PD patients, we should carefully choose patients who would receive clear benefits from the use of this tracer. Thus, MIBG imaging should not be used as a screening test for PD.

## Conclusion

There are many differences between the nuclear cardiology procedures performed in Japan and those conducted in other countries. In some respects, Japan is behind the global standard and must follow the lead of other countries. However, in other areas Japanese nuclear cardiologists can pave the way for other countries.

## Acknowledgments

The author gratefully thanks for Prof. Kazuki Fukuchi (Osaka University) for the helping to summarize the work and providing important information.

## Source of funding

This work was partly supported by JSPS KAKENHI Grant Number 17K10447.

## Conflicts of interest

None.

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