

# Usefulness of MIBG scintigraphy in idiopathic REM sleep behavior disorder: a systematic review

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**Background and purpose:** It has been widely demonstrated that Parkinson's disease (PD) and dementia with Lewy bodies (DLB) share one clinicopathological entity; Lewy body disease (LBD) has thus become a general term for these diseases. LBD presents an impairment of adrenergic function and consequently an abnormal myocardial metaiodobenzylguanidine (MIBG) innervation imaging. Like PD and DLB, other Lewy body disorders, including pure autonomic failure and idiopathic rapid eye movement sleep behavior disorder (RBD), have been reported to develop cardiac sympathetic denervation. This study is designed to systematically review whether iodine-123-MIBG scintigraphy in patients with RBD demonstrates reduced myocardial uptake thereby suggesting cardiac sympathetic denervation, a typical finding of LBD, in these patients.

**Methods:** A comprehensive computer literature search of studies published through December 2010 regarding MIBG scintigraphy in patients with RBD was performed in PubMed/Medline and EMBASE databases. Only studies in which MIBG scintigraphy was performed in more than two patients with RBD were selected.

**Results:** Ultimately, six studies comprising a total of 139 patients with RBD were identified and discussed.

**Conclusions:** RBD usually show a markedly reduced cardiac MIBG uptake, consistent with a sympathetic denervation, a typical finding of a LBD.

**Keywords:** metaiodobenzylguanidine, REM sleep behavior disorder, Lewy body disease

## Introduction

Radiolabeled metaiodobenzylguanidine (MIBG) is considered as an established sympathetic neuron imaging agent useful to study the organs richly innervated by the sympathetic nervous system.<sup>1-4</sup>

In recent years, it has been revealed that Parkinson's disease (PD) and dementia with Lewy bodies (DLB) share one clinicopathological entity: Lewy body disease (LBD) has thus become a general term for these diseases.<sup>5</sup>

LBD presents an impairment of adrenergic function and consequently an abnormal myocardial MIBG innervation imaging: the involvement of myocardial postganglionic sympathetic nerves may account for the reduction of myocardial MIBG uptake in patients with DLB, as well as in patients with PD.<sup>2-5</sup>

Like PD and DLB, other Lewy body disorders, including pure autonomic failure and idiopathic rapid eye movement (REM) sleep behavior disorder (RBD), have been reported to develop cardiac sympathetic denervation. Several MIBG studies have demonstrated that cardiac sympathetic denervation occurs in patients with LBD.<sup>2-4,6-8</sup>

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Recent evidence supports the notion that myocardial sympathetic involvement is a very early event in the evolution of LBD in humans, occurring prior to the deposition of  $\alpha$ -synuclein pathology in the central nervous system in many patients.<sup>9,10</sup>

Several investigators have, therefore, suggested that myocardial MIBG scintigraphy could be used to identify those with underlying LBD regardless of the other clinical features being exhibited; therefore, reduced myocardial MIBG uptake may be one of the most specific biomarkers for underlying LBD.<sup>10</sup>

RBD is a parasomnia manifested by vivid, often frightening dreams associated with simple or complex motor behavior during REM sleep. RBD is characterized by loss of normal skeletal muscle atonia during REM sleep with prominent motor activity and dreaming. The polysomnographic features of RBD include increased electromyographic tone with dream enactment behavior during REM sleep.<sup>10</sup>

The term idiopathic RBD refers to RBD occurring in the absence of any other obvious associated neurologic disorder. There is a large amount of recent data suggesting that many patients with idiopathic RBD actually represent an evolving neurodegenerative disorder.<sup>10</sup>

Over 50% of patients with idiopathic RBD will develop a synuclein-mediated neurodegenerative disorder, including PD, DLB, and multiple system atrophy (MSA).<sup>10–13</sup>

Braak and colleagues have proposed a staging system for the neuropathologic characterization of the phenotype of PD, and this system may be applicable to the timing of the evolution of RBD in the context of evolving LBD regardless of the clinical phenotype evolving as PD or DLB.<sup>9,10</sup> This staging system posits a temporal sequence of  $\alpha$ -synuclein pathology in the brain, beginning mainly in the medulla (and olfactory bulb) and gradually ascending to more rostral structures. This temporal sequence of pathology could explain why RBD precedes parkinsonism, cognitive decline, and dementia in many patients with Lewy body pathology.<sup>9,10</sup>

LBD is, therefore, a more systemic process that clearly affects the peripheral autonomic nervous system, and in some cases, actually may begin in the spinal cord prior to the brain and the peripheral autonomic system even before the central nervous system.<sup>9,10</sup>

The purpose of this study is to systematically review published data to evaluate whether MIBG scintigraphy in patients with RBD demonstrates reduced myocardial uptake thereby suggesting cardiac sympathetic denervation, a typical finding of LBD, in these patients.

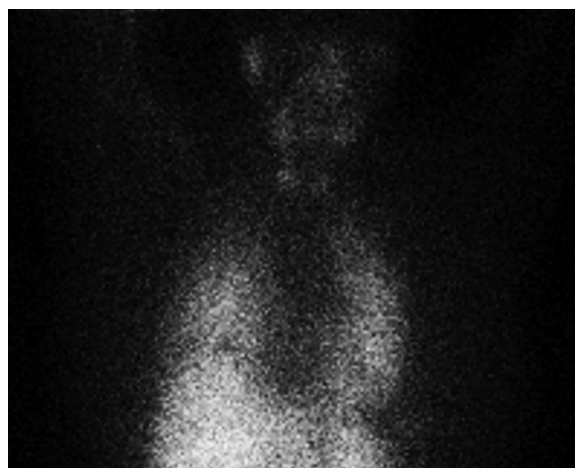
## Methods

### Scintigraphic method

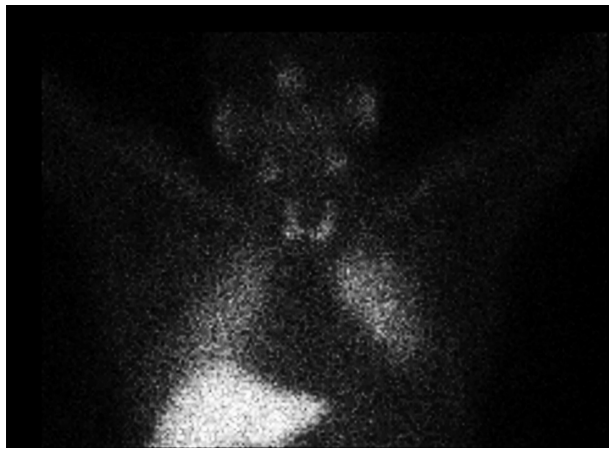
MIBG is an analog of guanethidine and is taken up by the postganglionic presynaptic nerve endings of the adrenergic nervous system. After depolarization, MIBG is released into the synaptic cleft like norepinephrine, but is not metabolized. Labeling MIBG with iodine-123 permits the visualization of adrenergic innervation *in vivo*; MIBG scintigraphy not only displays the presence of noradrenergic innervation, but also its functional capability.<sup>1–4</sup>

About myocardial innervation imaging, radiolabeled MIBG is intravenously administered at rest, and early (from 10 to 30 min after injection) and delayed (from 3 to 4 h after injection) images are obtained (see Figures 1 and 2). Planar images with anterior view are adequate for the evaluation of cardiac sympathetic function. Tomographic images (single photon emission computed tomography) are often acquired to evaluate the three-dimensional myocardial uptake pattern.<sup>1–4</sup>

The most common semiquantitative indices used for interpretation of myocardial innervation images are the heart to mediastinum (H/M) ratio and the washout rate (WR) obtained from the anterior planar images. Regions of interest (ROIs) are set in the heart (H; target region) and the mediastinum (M; background region) in early and delayed images to obtain the mean count in each ROI, after which the H/M ratio is calculated. Based on the resulting ratio, the degree of uptake in the heart is evaluated. The WR is an index that indicates the rate at which MIBG is washed out between the early image and the delayed image, via comparison of cardiac counts in the early image. Normal values of these indices have been



**Figure 1** Normal uptake pattern of I-123-MIBG scintigraphy (anterior view at 4 h after injection of 111 MBq); the tracer uptake in salivary glands, liver, heart, and lungs is considered as physiological.



**Figure 2** Abnormal uptake pattern of I-123-MIBG scintigraphy (anterior view at 4 h after injection of 111 MBq) in a patient with RBD. No tracer uptake is observed in the heart suggesting a sympathetic denervation, a typical finding of Lewy body disease.

calculated performing MIBG scintigraphy in control patients and are different between various institutions depending on acquisition conditions.<sup>1-4</sup>

## Search strategy

A comprehensive computer literature search of the PubMed/MEDLINE and EMBASE databases was conducted to find relevant published articles on the usefulness of MIBG scintigraphy in patients with RBD. We used a search algorithm that was based on a combination of the terms: *a*) 'MIBG' or 'metaiodobenzylguanidine' and *b*) 'REM' or 'RBD'. No beginning date limit was used; the search was updated until December 12, 2010. No language restriction was used.

## Study selection

Studies or subsets in studies investigating MIBG scintigraphy in patients with RBD were eligible for inclusion. Review articles, editorials or letters, comments, and case reports (studies with no more than two cases of RBD) were excluded from this review.

Two researchers (GT and FC) independently reviewed the titles and the full-text version of the retrieved articles to determine their eligibility for inclusion.

## Data abstraction

For each included study, information was collected concerning basic study (author names, journal, year of publication, and country of origin), patient characteristics (mean age, sex, number of patients in whom MIBG scintigraphy was performed, and number and types of disease investigated), and MIBG scintigraphy parameters (tracer, early and delayed H/M, WR).

## Results

### Literature search

The comprehensive computer literature search from the PubMed/MEDLINE and EMBASE databases revealed 16 articles that were retrieved in full-text version. After reviewing the full text, 2 articles were excluded as review,<sup>4,14</sup> 1 article was excluded as letter,<sup>15</sup> 1 article was excluded because MIBG scintigraphy was not performed in patients with RBD,<sup>16</sup> 6 articles were excluded as case reports or studies, including no more than 2 cases of RBD.<sup>17-22</sup>

Finally, 6 studies, comprising a total sample size of 139 patients with RBD, met all inclusion and exclusion criteria, and they were included in this systematic review.<sup>23-28</sup>

The characteristics of the included studies are presented in Tables 1 and 2.

### Literature data discussion

In 2006, Miyamoto et al<sup>23</sup> performed cardiac MIBG scintigraphy in 13 patients with confirmed idiopathic RBD, 12 age-matched patients with PD, and 8 age-matched controls. The authors reported a markedly reduced cardiac MIBG uptake, consistent with a sympathetic denervation, in idiopathic RBD; they also demonstrated that this reduction is of the

**Table 1** Basic study and patients characteristics

Authors	Year	Country	Number of patients who performed MIBG	Mean age (years)	Male (%)	RBD	Other LBD	Other diseases
Miyamoto et al <sup>23</sup>	2006	Japan	25 + 8 Controls	69	61	13	12 PD	0
Miyamoto et al <sup>24</sup>	2008	Japan	86 + 9 Controls	68	63	31	26 PD; 6 DLB	10 MSA; 13 PSP
Miyamoto et al <sup>25</sup>	2009	Japan	63	64	81	47	0	16 OSAS
Kashihara et al <sup>26</sup>	2010	Japan	235 + 50 Controls	73	55	13	222 PD	0
Nomura et al <sup>27</sup>	2010	Japan	49	70	37	26	23 PD; no RBD	0
Fujishiro et al <sup>28</sup>	2010	Japan	9	71	78	9	0	0

**Abbreviations:** PD, Parkinson's disease; LBD, Lewy body disease; DLB, dementia with Lewy bodies; RBD, REM sleep behavior disorder; MSA, multiple system atrophy; PSP, progressive supranuclear palsy; OSAS, obstructive sleep apnea syndrome; MIBG, metaiodobenzylguanidine.

Table 2 MIBG parameters and results in the included studies

Authors	Tracer	H/M ratio in RBD	H/M ratio in other LBD	H/M ratio in other diseases	H/M ratio in controls	WR in RBD
Miyamoto et al <sup>23</sup>	I-123-MIBG	Delayed: 1.34 ± 0.20 ( $P < 0.001$ compared to controls)	Delayed in PD: 1.43 ± 0.20 ( $P < 0.001$ compared to controls)	NA	Delayed: 3.01 ± 0.39	NA
Miyamoto et al <sup>24</sup>	I-123-MIBG	Early: 1.70 ± 0.39 ( $P < 0.05$ compared to PD and $P < 0.001$ compared to MSA, PSP, and controls) Delayed: 1.49 ± 0.39 ( $P < 0.001$ compared to PD, MSA, PSP, and controls)	Early in PD: 2.08 ± 0.55 Delayed in PD: 1.80 ± 0.68 ( $P < 0.001$ compared to MSA, PSP, and controls) Early in DLB: 1.52 ± 0.13 Delayed in DLB: 1.29 ± 0.12 ( $P < 0.001$ compared to MSA, PSP, and controls)	NA Early in MSA: 2.57 ± 0.49 Delayed in MSA: 2.91 ± 0.53 Early in PSP: 2.86 ± 0.34 Delayed in PSP: 3.03 ± 0.41	Early: 2.81 ± 0.37 Delayed: 3.06 ± 0.39	NA
Miyamoto et al <sup>25</sup>	I-123-MIBG	Early in RBD with $AHI < 5/h$ : 1.34 ± 0.19 Early in RBD with $5 \leq AHI < 15/h$ : 1.67 ± 0.62 Early in RBD with $AHI \geq 15/h$ : 1.36 ± 0.27 ( $P < 0.001$ compared to OSAS without RBD) Delayed in RBD with $AHI < 5/h$ : 1.34 ± 0.19 Delayed in RBD with $5 \leq AHI < 15/h$ : 1.67 ± 0.62 Delayed in RBD with $AHI \geq 15/h$ : 1.36 ± 0.27 ( $P < 0.001$ compared to OSAS without RBD) Early: 1.57 ± 0.37 ( $P < 0.001$ compared to controls) Delayed: 1.39 ± 0.40 ( $P < 0.001$ compared to controls)	NA Early in OSAS without RBD: 2.82 ± 0.56 Delayed in OSAS without RBD: 2.82 ± 0.56	NA Early in OSAS without RBD: 2.82 ± 0.56 Delayed in OSAS without RBD: 2.82 ± 0.56	NA Early: 2.36 ± 0.26 Delayed: 2.57 ± 0.35	NA
Kashihara et al <sup>26</sup>	I-123-MIBG	Early: 1.57 ± 0.37 ( $P < 0.001$ compared to controls) Delayed: 1.39 ± 0.40 ( $P < 0.001$ compared to controls)	Early in PD: 1.74 ± 0.38 ( $P < 0.001$ compared to controls) Delayed in PD: 1.55 ± 0.45 ( $P < 0.001$ compared to controls)	NA	NA	NA
Nomura et al <sup>27</sup>	I-123-MIBG	Clinical RBD had significantly lower values of delayed H/M ratio compared to both the group with subclinical RBD ( $P < 0.01$ ) and the group with PD and normal REM sleep ( $P < 0.01$ ). There were no significant differences in H/M ratio between the PD group with subclinical RBD and the group with normal REM sleep	NA	NA	NA	NA
Fujishiro et al <sup>28</sup>	I-123-MIBG	Early: 1.81 ± 0.28 Delayed: 1.40 ± 0.25	NA	NA	NA	63.4 ± 14.2

**Note:** Values are expressed as means ± SD.

**Abbreviations:** PD, Parkinson's disease; LBD, Lewy body disease; DLB, dementia with Lewy bodies; RBD, REM sleep behavior disorder; MSA, multiple system atrophy; PSP, progressive supranuclear palsy; OSAS, obstructive sleep apnea syndrome; AHI, apnea and hypopnea index; NA, not applicable; MIBG, metaiodobenzylguanidine; REM, rapid eye movement.



same magnitude as that found in patients with PD. The delayed H/M ratio was reduced in patients with either idiopathic RBD or PD compared to controls (each  $P < 0.001$ ). The results are consistent with the hypothesis that idiopathic RBD may be an LBD.

In 2008, Miyamoto et al<sup>24</sup> compared cardiac MIBG uptake between idiopathic RBD, PD, MSA, DLB, progressive supranuclear palsy (PSP), and control subjects. A markedly reduced cardiac MIBG uptake was detected in both the early and the delayed images in 29 of 31 (93.5%) patients with idiopathic RBD, 21 of 26 (75%) patients with PD, and 6 of 6 (100%) patients with DLB. The cardiac MIBG uptake was normal in patients with MSA ( $n = 10$ ), PSP ( $n = 13$ ), and controls ( $n = 9$ ). The early and delayed H/M ratio was significantly reduced in patients with idiopathic RBD compared to MSA, PSP, and controls ( $P < 0.001$  in each subject group) and PD in early images ( $P < 0.05$ ). There was a correlation between the early and delayed H/M ratio and the duration of disease in the idiopathic RBD group (early:  $r = -0.477$ ,  $P = 0.0066$ ; delayed:  $r = -0.3578$ ,  $P = 0.0481$ ). In conclusion, a marked reduction in cardiac MIBG uptake was found in patients with idiopathic RBD compared to control subjects and patients with clinically diagnosed PSP and MSA, but similar to those with clinically diagnosed PD and DLB.

In 2009, Miyamoto et al<sup>25</sup> investigated whether idiopathic RBD complicated with moderate-to-severe obstructive sleep apnea could be differentiated from obstructive sleep apnea syndrome (OSAS) without RBD based on cardiac MIBG scintigraphic pattern. These authors studied 63 age-matched patients with idiopathic RBD ( $n = 47$ ) and moderate-to-severe OSAS ( $n = 16$ ). Cardiac MIBG uptake, based on early and delayed H/M, was significantly decreased in idiopathic RBD compared with OSAS patients ( $P < 0.001$ ). Five of the 16 patients (31.2%) in the OSAS group had a history of dream-enactment behavior, mimicking a RBD, but they did not have a decrease in cardiac MIBG uptake. These findings demonstrated that cardiac MIBG scintigraphy was a useful, supportive diagnostic indicator for LBD in moderate-to-severe OSAS patients.

Recently, Kashiwara et al<sup>26</sup> performed cardiac MIBG scintigraphy in patients with RBD and compared the findings with those of idiopathic PD. A total of 13 RBD, 222 PD, and 50 controls underwent MIBG scintigraphy. H/M ratios were significantly lower in patients with RBD and PD when compared to the control group ( $P < 0.001$ ). H/M ratios were lower for delayed than for early images in patients with RBD and idiopathic Parkinson's disease (IPD) ( $P < 0.001$ ), whereas the controls had higher H/M ratios for delayed

images ( $P < 0.001$ ). H/M ratios did not differ significantly between patients with RBD and PD; nevertheless, H/M ratio were significantly lower for patients with RBD than for those with IPD at Hoehn and Yahr stages 1 and 2 ( $P < 0.001$ ) and equaled those with PD at Hoehn and Yahr stages 3, 4, and 5. These findings demonstrated that: *a*) RBD has features of cardiac MIBG uptake reductions in common with other LBD; *b*) cardiac MIBG uptake was more markedly reduced in patients with RBD than in patients with early-stage PD; therefore, RBD may not necessarily be a prodromal condition of PD with respect to MIBG scintigraphic results.

Recently, Nomura et al<sup>27</sup> have investigated the association between MIBG scintigraphic findings and RBD measures among PD patients in order to clarify whether the existence of RBD accelerates autonomic dysfunction in PD; the authors performed clinical interviews to assess RBD symptoms, polysomnogram recordings, and MIBG scintigraphy on 49 PD patients. The patients were divided into 3 groups (PD with clinical RBD, PD with subclinical RBD, and PD with normal REM sleep). PD patients with clinical RBD had reduced cardiac MIBG uptake, as determined by delayed H/M ratio, compared to those with subclinical RBD and those with normal REM sleep. Multiple linear regression analysis revealed that only the existence of RBD symptoms was significantly associated with reduced MIBG uptake among PD patients without dementia after adjusting for demographic and PD symptom-related variables. The authors concluded that PD patients with clinical RBD might suffer from wider  $\alpha$ -synuclein pathology, including reduced cardiac sympathetic ganglia function as reflected by a lowered MIBG uptake.

Recently, Fujishiro et al,<sup>28</sup> based on the prevailing evidence that RBD often precedes the onset of DLB, compared <sup>18</sup>F-FDG PET scans of nine nondemented patients reporting recurrent nocturnal dream-enactment behavior with the normative database using three-dimensional stereotactic surface projection images. All patients underwent clinical and neuropsychological examinations as well as cardiac MIBG scintigraphy. None had dementia or met the clinical criteria for DLB or PD. Four patients were found to have diffuse areas of reduced cerebral metabolic rate of glucose (CMRglc), predominantly in the occipital lobe, which is the preferentially affected region in DLB patients. In contrast, 5 patients showed no such occipital hypometabolism; instead, these 5 patients showed hypometabolism in the left anterior cingulate gyrus, right frontal lobe, and right anterior temporal lobe, which are the preferentially affected regions in PD rather than DLB. All patients showed reduced cardiac

MIBG uptake, consistent with underlying LBD; there were no differences in the H/M ratio between the groups with and without diffuse occipital hypometabolism. The authors concluded that variations in  $^{18}\text{F}$ -FDG PET scans raise the possibility that the specific pattern of CMRglc reduction may predict developing DLB in patients with idiopathic RBD.

## Limitations

One possible limitation of this systematic review is that the study population in the final reviewed articles was only composed by Japanese patients. Therefore, the results might not always account for all patients with RBD, because of the racial difference. A possible explanation of these data is the wide number of Japanese studies about the application of MIBG scintigraphy in the field of neurology.<sup>2</sup>

Additional work with myocardial MIBG scintigraphy in RBD, particularly in countries outside of Japan, is clearly warranted to confirm the usefulness of this technique in this field.

All the studies included in this review used the H/M ratio to evaluate sympathetic denervation in patients with RBD. WR is an important index, as well as H/M ratio, in the assessment of myocardial sympathetic denervation. Nevertheless, only 1 out of 6 studies selected reported WR values in patients with RBD. A possible explanation of this finding is that considering the very low MIBG uptake in the heart in patients with RBD and other LBD, both in the early and in the delayed images, the WR from the heart is not cited.<sup>2</sup>

## Conclusion

From the literature analysis, we conclude that RBD patients usually show a markedly reduced cardiac MIBG uptake, consistent with a sympathetic denervation, a typical finding of a LBD.

## Disclosure

The authors report no conflicts of interest in this work.

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