

Different patterns of cardiac sympathetic denervation in tremor-type compared to akinetic-rigid-type Parkinson's disease: Molecular imaging with ^{123}I -MIBG

A. CHIARAVALLOTTI¹, A. STEFANI^{2,3}, M. TAVOLOZZA¹, M. PIERANTOZZI^{2,3}, D. DI BIAGIO¹, E. OLIVOLA^{2,3}, B. DI PIETRO¹, M. STAMPANONI^{2,3}, R. DANIELI¹, G. SIMONETTI¹, P. STANZIONE^{2,3} and O. SCHILLACI^{1,4}

Departments of ¹Biopathology and Diagnostic Imaging and ²Neurological Sciences, University Tor Vergata, Rome; ³IRCCS Fondazione S. Lucia, Rome; ⁴IRCCS Neuromed, Pozzilli, Italy

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Abstract. The aim of this study was to evaluate the correlation between the clinical motor phenotypes of Parkinson's disease (PD) and ^{123}I -MIBG myocardial uptake. In total, 53 patients with PD [31 males and 22 females, mean age 62 ± 10 years; 19 Hoehn & Yahr (H&Y) stage 1, 9 stage 1.5, 15 stage 2 and 10 at stage 3] were examined and subdivided into different clinical forms on the basis of dominance of resting tremor ($n=19$, TDT) and bradykinesia plus rigidity ($n=34$, ART). This status was correlated with the semi-quantitative analysis of ^{123}I -MIBG myocardial uptake. An age-matched control group of 18 patients was recruited (8 males and 10 females, mean age 62.4 ± 16.3 years). ^{123}I -MIBG myocardial uptake significantly correlated with disease duration in early ($r^2=0.1894$; $P=0.0028$) and delayed images ($r^2=0.1795$; $P=0.0037$) in PD patients, while no correlation was found when considering age at examination, UPDRS III motor examination section score and H&Y score. PD patients showed a reduced ^{123}I -MIBG myocardial uptake compared to the control group in early ($P=0.0026$) and delayed images ($P=0.0040$), and ^{123}I -MIBG myocardial uptake was significantly lower in delayed images in TDT patients compared with ART patients ($P=0.0167$). A decrease was detected in the heart-to-mediastinum (H/M) ratio in delayed images compared to that of the early images in TDT patients ($P=0.0040$) and in the whole PD population ($P=0.0012$), while no differences were found in ART patients ($P=0.1043$). The results of the present study revealed that the cardiac sympathetic system is more severely impaired in TDT than in ART patients and ^{123}I -MIBG molecular imaging has the potential help in improving therapeutic planning in these patients.

Introduction

^{123}I -metaiodobenzylguanidine (^{123}I -MIBG), a physiological analogue of noradrenaline, is actively transported into noradrenaline granules at sympathetic nerve terminals by a noradrenaline transporter and allows the quantification of cardiac sympathetic innervation *in vivo* (1). In Parkinson's disease (PD), neuronal damage in the areas associated with motor functions, particularly the superordinate centers of the somatomotor, visceromotor and limbic systems, has been reported (2). In particular, structures such as the dorsal motor nucleus of the vagal nerve and intermediate reticular zone are involved in the early stages, while the substantia nigra and other nuclear gray of the midbrain and forebrain become the focus of initially slight, and then severe, pathological changes in the late stages (2). These findings are consistent with cardiac sympathetic denervation shown by means of myocardial ^{123}I -MIBG scintigraphy, indicating an impairment of the nigrostriatal dopaminergic and myocardial sympathetic systems in the majority of the patients with PD, even in the earliest clinical stage of the disease (3).

In total, 50% of PD patients complain of slowness of movement at presentation (4). The symptoms of PD involve the initiation and execution of movements, particularly sequential and volitional actions (4). Approximately 40% of patients are likely to complain of tremulousness of the hand at rest, which improves with action and 80% of patients have an asymmetrical 3-5 Hz rest tremor evident on examination (5). The two subtypes of PD have different courses, which are concordant with the differences in brain biochemical abnormalities (5), and it has been reported that PD progresses more rapidly in akinetic rigid-type (ART) patients than in tremor dominant-type (TDT) patients (6). Previous studies suggested that ^{123}I -MIBG cardiac uptake is increased in PD patients with bradykinesia as compared with tremor patients (7). Additionally, Spiegel *et al* found that at all Hoen & Yahr (H&Y) stages, myocardial MIBG uptake was significantly higher in TDT patients than in ART patients (8).

In this study, ^{123}I -MIBG myocardial uptake was compared in patients with different subtypes of PD in order to assess the correlation between the clinical phenotype and sympathetic

Correspondence to: Professor Orazio Schillaci, Department of Biopathology and Diagnostic Imaging, University Tor Vergata, Viale Oxford 81 00173 Rome, Italy
E-mail: orazio.schillaci@uniroma2.it

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denervation. Moreover, the results concerning the PD population were evaluated in comparison with those of a control group (CG).

Materials and methods

Patients. The study involved 53 patients with PD [31 males and 22 females, mean age 62 ± 10 years; 19 H&Y stage 1, 9 stage 1.5, 15 stage 2 and 10 at stage 3]. A clinical examination was conducted by an experienced neurologist (P.S.) and PD was diagnosed using United Kingdom Parkinson's Disease Society Brain Bank (UKPDSBB) criteria (9). The motor part of the UKPDSBB criteria was used to assess the severity of disease (10). On the basis of the predominant motor features in UPDRS III motor examination section score, patients were subtyped into one of two clinical groups, ART and TDT, following the methods described in previous studies (11-14). The Mini Mental State Examination (MMSE) did not reveal any cognitive deficit. Nineteen patients had TDT and 34 had ART. A 'tremor score' and a 'non-tremor score' were calculated for each patient (11,15). The data concerning the clinical subtypes of patients with PD are shown in Table I. The tremor score was derived from the sum of UPDRS items 20 (tremor at rest) and 21 (action or postural tremor of hands) divided by 7 (the number of the single subitems included). The non-tremor score was derived from the sum of UPDRS items 18 (speech), 19 (facial expression), 22 (rigidity), 27 (arising from the chair), 28 (posture), 29 (gait), 30 (postural stability) and 31 (body bradykinesia and hypokinesia) divided by 12 (the number of the single subitems included). The patient was classified as tremor-dominant type when the tremor score was at least twice the non-tremor score. An age-matched control group (CG) of 18 patients was recruited (8 males and 10 females, mean age 62.4 ± 16.3 years). The CG patients underwent a ^{123}I -MIBG scintigraphy for a suspected adrenal mass, which was then revealed to be negative on image evaluation. Prior to their inclusion in our study, the subjects were evaluated for the absence of clinical signs of PD by an experienced neurologist (A.S.). Exclusion criteria for the PD and CG patients included diabetes, a history of neuropathy, previous relevant cardiac disease or any other medical condition that potentially affected the autonomic nervous system or the myocardial ^{123}I -MIBG uptake. None of the subjects were undergoing treatment with drugs that have been previously reported to affect ^{123}I -MIBG uptake at the sympathetic terminals (15,16). Informed consent was obtained in all cases from the patients themselves or from their families, in accordance with the Declaration of Helsinki. This study was approved by the ethics committee of the University of Tor Vergata.

Data acquisition. Each PD patient was intravenously injected in 60 sec with 111 MBq of ^{123}I -MIBG (Amersham, Eindhoven, The Netherlands) and 185-200 MBq was injected in CG patients in 5 min. The radio-labeled compound was administered at the same time of the day under the same experimental conditions in each patient.

Data were collected by means of a dual head gamma-camera (Millennium VG; General Electric Medical Systems, Milwaukee, WI, USA) equipped with low-energy high-resolution parallel-hole collimators with static planar images

in a 128x128 matrix. Images were captured 30 min (early images) and 4 h (delayed images) after the injection of the radio-labeled compound (Fig. 1). A region of interest (ROI) was manually drawn over the myocardium, including the left ventricular cavity. ROIs were then set over the upper mediastinum and a heart-to-mediastinum (H/M) count-ratio was calculated, which was defined as the average counts/pixel in the myocardium, divided by that of the upper mediastinum (1).

Statistical analysis. The means and standard deviation were calculated for age, UPDRS III score, H&Y grade, disease duration and the results of the semi-quantitative analysis for the early and delayed H/M count-ratio. To detect differences in the cardiac sympathetic innervation between the subgroups (semi-quantitative analysis, non-parametric data) a Mann-Whitney U test was used. Differences in early and delayed H/M in the PD subgroups (ART and TDT) and CG patients were analyzed by means of a Wilcoxon matched-pairs test. The Spearman's correlation was used to determine the relationship among UPDRS motor scores, H&Y stage, age at examination and early and delayed H/M count-ratio. Multiple regression analysis was applied to observe the effect of disease duration. The Chi-square test was used to assess differences in the H&Y stage and disease phenotype. An unpaired t-test was used to assess differences between age, disease duration, UPDRS and disease phenotype. A hypothesis was considered valid when $P \leq 0.05$.

Results

Patient characteristics and analysis of early and delayed H/M count-ratio. Differences in age, gender, disease duration and H&Y stage between ART and TDT patients were not significant. Patient characteristics are shown in Table I.

The results of the semi-quantitative analysis of the early and delayed H/M count-ratio are shown in Table II. A reduced ^{123}I -MIBG myocardial uptake was detected in PD patients as compared to CG patients in early ($P=0.0026$) and delayed images ($P=0.0040$). The H/M ratio was lower in ART patients as compared to CG patients only in early images ($P=0.0017$), while no statistically significant differences were observed in delayed acquisitions ($P=0.0691$). A lower H/M ratio was detected in TDT patients as compared to the CG ones in both the early and delayed images ($P=0.0016$; $P=0.0002$). A significant decrease in the H/M ratio was found between delayed images as compared to that of the early images in TDT patients ($P=0.0040$), CG patients ($P=0.0175$) and in the entire PD population ($P=0.0012$), while no statistically significant differences were found when comparing early and delayed H/M ratio in ART patients ($P=0.1043$). No statistically significant differences were detected when comparing early H/M count ratios in TDT and ART patients ($P=0.1727$), while ^{123}I -MIBG myocardial uptake was significantly lower in delayed images in TDT ($P=0.0167$) compared to ART patients (Fig. 2).

Effects on UPDRS score. The UPDRS score was higher in ART patients as compared with TDT patients ($P=0.0192$). The early and delayed H/M ratio of PD patients was not associated with UPDRS ($r=-0.1236$, $P=0.4297$; $r=-0.0057$, $P=0.9708$). Early and delayed ^{123}I -MIBG myocardial

Table I. General overview of the PD population examined.

	Population (n=53)	TDT (n=19)	ART (n=34)
Gender			
Males	31	10	21
Females	22	9	13
Disease duration (months \pm SD)	50.7 \pm 60.6	66.1 \pm 68.2	41.4 \pm 54.7
UPDRS III (mean \pm SD)	23.3 \pm 11.1	18.2 \pm 6.6	26.3 \pm 12.3
Hoehn & Yahr score			
1	19	7	12
1.5	9	4	5
2	15	6	9
3	10	2	8

PD, Parkinson's disease; TDT, tremor-dominant type; ART, akinetic-rigid type; UPDRS III, UPDRS motor examination section score III.

Table II. Early and delayed H/M ratio of the ^{123}I -MIBG myocardial uptake in clinical PD subtypes and the CG patients.

	CG	PD	TDT	ART	Comparison	P-value
Early H/M	1.97 \pm 0.28	1.68 \pm 0.36	1.59 \pm 0.34	1.72 \pm 0.36	PD vs. CG	0.0026
					TDT vs. CG	0.0016
					ART vs. CG	0.0017
					TDT vs. ART	0.1727
Delayed H/M	1.88 \pm 0.27	1.58 \pm 0.36	1.43 \pm 0.38	1.66 \pm 0.33	PD vs. CG	0.0040
					TDT vs. CG	0.0002
					ART vs. CG	0.0691
					TDT vs. ART	0.0167

CG, control group; PD, Parkinson's disease; TDT, tremor-dominant type; ART, akinetic-rigid type; H/M, heart-to-mediastinum; ^{123}I -MIBG, ^{123}I -metaiodobenzylguanidine. Values are expressed as the means \pm SD.

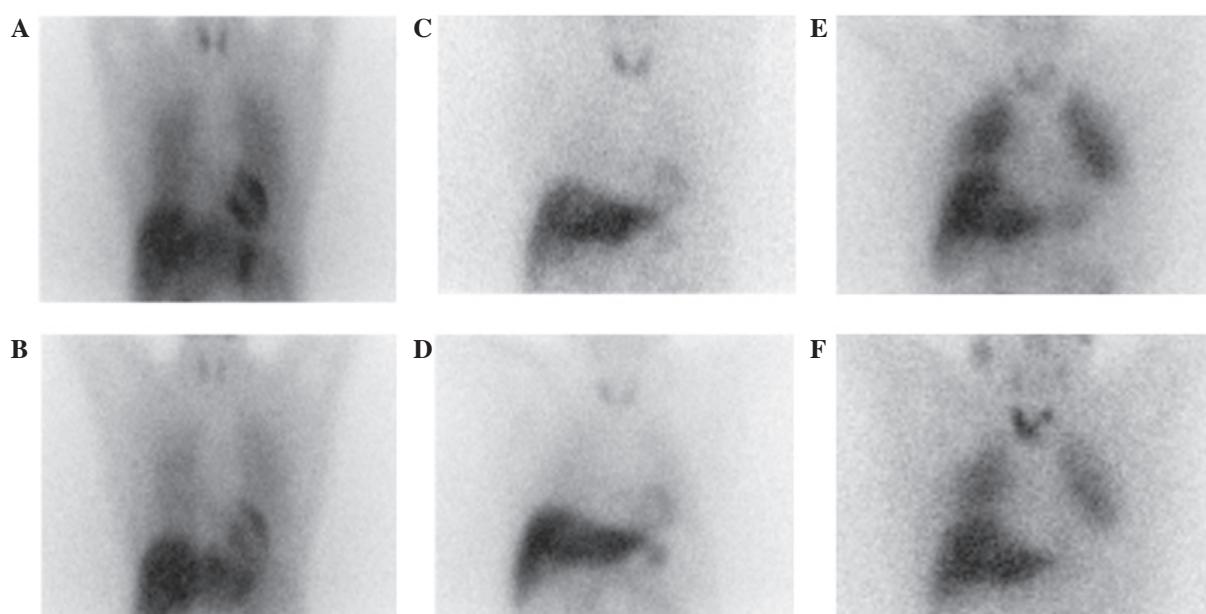


Figure 1. Sample images of ^{123}I -MIBG myocardial uptake in a CG patient: (A) early, (B) delayed; an ART patient: (C) early, (D) delayed; and a TDT patient: (E) early, (F) delayed. ^{123}I -MIBG, ^{123}I -metaiodobenzylguanidine; CG, control group; TDT, tremor-dominant type; ART, akinetic-rigid type.

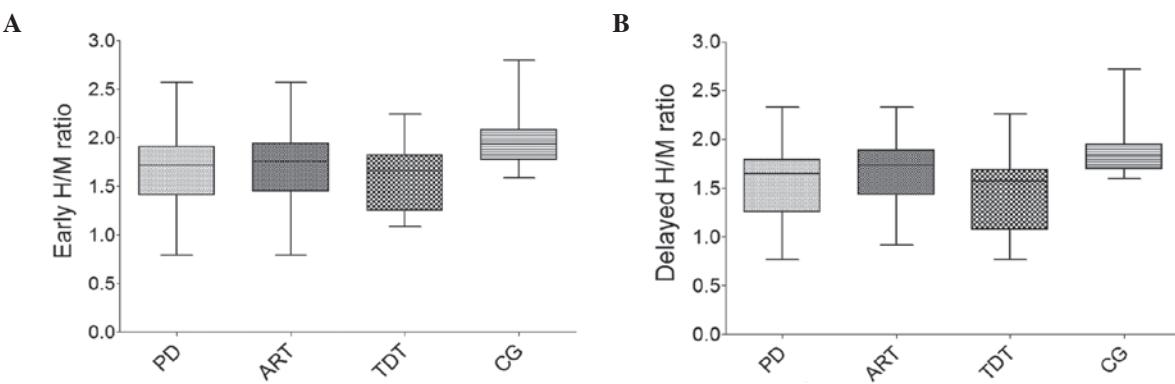


Figure 2. Examination of ^{123}I -MIBG myocardial uptake in the studied population. (A and B) The early and delayed H/M ratios were lower in the PD population as compared to the CG population. (B) ^{123}I -MIBG myocardial uptake was significantly lower in delayed images in TDT patients when compared to that in ART patients. ^{123}I -MIBG, ^{123}I -metaiodobenzylguanidine; H/M, heart-to-mediastinum; PD, Parkinson's disease; CG, control group; TDT, tremor-dominant type; ART, akinetic-rigid type.

uptake was not correlated with UPDRS in ART ($r=-0.3132$, $P=0.1117$; $r=-0.2128$, $P=0.2865$) and TDT patients ($r=0.07985$, $P=0.7688$; $r=0.04546$, $P=0.8672$). The H/M ratio was not associated with H&Y stage in PD patients in early ($r=-0.2411$, $P=0.0821$) or delayed ($r=-0.1969$, $P=0.1577$) scans. ^{123}I -MIBG myocardial uptake was also not correlated with the H&Y stage in the early ($r=-0.1909$, $P=0.2794$) and delayed images ($r=-0.1491$, $P=0.4002$) in ART patients. No correlation was found between H&Y stage and early ($r=-0.4047$, $P=0.0856$) and delayed ($r=-0.4352$, $P=0.0626$) H/M ratios in TDT patients.

Correlation of ^{123}I -MIBG myocardial uptake and disease duration. ^{123}I -MIBG myocardial uptake was significantly correlated with disease duration in early ($r^2=0.1894$, $P=0.0028$) and delayed images ($r^2=0.1795$, $P=0.0037$) in PD patients. The same correlation was found with this parameter when considering the ART population in early ($r^2=0.2651$, $P=0.0051$) and delayed images ($r^2=0.2193$, $P=0.0120$). No significant relationships were detected with disease duration in the TDT population in either the early ($r^2=0.0916$, $P=0.2375$) or delayed ($r^2=0.0983$, $P=0.2204$) image set.

Correlation of ^{123}I -MIBG myocardial uptake and age. No significant correlation was found when considering ^{123}I -MIBG myocardial uptake and age in PD patients at examination in early ($r=-0.1506$, $P=0.2817$) and delayed images ($r=-0.2430$, $P=0.0796$). The same results were obtained in the CG in the early ($r=-0.2687$, $P=0.2970$) and delayed images ($r=-0.2221$, $P=0.3916$). Considering the single subsets of the PD population, no significant correlations were found with aging in early ($r=-0.1905$, $P=0.2806$) and delayed ($r=-0.2700$, $P=0.1225$) images and with the H/M ratio of ART patients and TDT patients in early ($r=0.0537$, $P=0.8272$) and delayed images ($r=-0.04178$, $P=0.8652$).

Discussion

One of the key findings of the present study was the reduction of ^{123}I -MIBG myocardial uptake in PD patients as compared to the CG patients. This finding was more marked for the

delayed compared to the early images (Figs. 1 and 2), in agreement with several previous studies (4,7,8,16-20). The use of ^{123}I -MIBG has been suggested as a useful marker in the diagnosis of PD (19) and as a sensitive tool in the early detection of silent autonomic dysfunction (18). Being an analogue of noradrenaline (8), ^{123}I -MIBG uptake reflects presynaptic sympathetic integrity, while a reduced myocardial uptake of this tracer is consistent with cardiac sympathetic dysfunction or denervation (21). Nevertheless, Matsui *et al* demonstrated that there were no significant correlations between orthostatic hypotension or constipation and cardiac ^{123}I -MIBG uptake, indicating that not all components of the autonomic nervous system are uniformly affected in PD (19).

In the population of this study, a strong contribution to the lower H/M count-ratio in PD patients as compared with the CG was due to the TDT patients. When the single ART population was analyzed, only the early, but not the delayed, H/M ratio was lower than the CG.

In the comparison between TDT and ART, the TDT group showed markedly reduced H/M values in the delayed images (Figs. 1 and 2). Moreover, TDT patients showed a reduction of the H/M ratio in the delayed images as compared to the early images, while no differences were found in the ART patients. These latter findings are consistent with an increased wash-out of ^{123}I -MIBG in the myocardium of TDT patients (18), and together with previously mentioned results, indicate a more extensive involvement of the cardiac sympathetic system (due to denervation, a reduced uptake by storage vesicles, abnormalities in reuptake function, and increased norepinephrine release or an increased catecholamine turnover) in PD patients with the tremulous phenotype (22).

Previous studies have shown that in the early stage of PD the dopaminergic system is more severely impaired in ART compared to the other subgroups of patients, in particular when compared to TDT (11,12). To the best of our knowledge, only a few studies have evaluated the ^{123}I -MIBG myocardial uptake in different Parkinson's phenotypes (7,8,20). In their study, Spiegel *et al* found that myocardial ^{123}I -MIBG uptake was significantly less impaired in TDT patients than in ART patients at the same stage of the disease (8). Similar results were demonstrated by Saiki *et al* when comparing a tremor phenotype population of

PD with a phenotype characterized by postural instability gait difficulty, which could correspond to the ART phenotype (20). A significant correlation was found when comparing the early and delayed H/M ratio with the severity of hypokinesia and rigidity, a finding showing that the H/M ratio was negatively associated with the severity of these clinical features (8), whereas no correlations have been found with the severity of the resting tremor (8). By contrast, Suzuki *et al* did not find such a correlation in their population where ¹²³I-MIBG myocardial uptake was correlated only with the severity of bradykinesia but not with tremor or rigidity (7). In our study, ¹²³I-MIBG myocardial uptake was significantly lower in TDT patients when compared to ART patients ($P=0.0167$), findings that are in contrast with those of other studies (7,8,20). These discrepancies may be due to the different disease duration in these two subgroups. Even if differences in disease duration between TDT and ART patients did not reach statistical significance, TDT patients showed a longer disease duration than ART, which potentially affected our results. However, while the H/M ratio was significantly associated with disease duration in ART patients, no such correlation was found in TDT patients, supporting the hypothesis that a longer illness duration does not correlate with a worsening of the sympathetic system in this last group. Moreover, no difference was detected between ART and TDT patients in H&Y stage, with TDT patients scoring better than ART patients in UPDRS III, reflecting a lower disability level in these patients (9).

No significant correlations were found in either early or delayed images with H&Y stage and UPDRS motor score in PD patients. Additionally, no statistically significant relationships were evident when comparing the single populations of ART or TDT patients with these aspects of the disease. The lack of a clear relationship of ¹²³I-MIBG myocardial uptake with disease severity detectable by means of UPDRS and H&Y stage has been previously described (8,19). In their study performed on a pool of 143 patients, Suzuki *et al* hypothesized that 61.3% of the variation in the observed early H/M ratio and 68.2% of that in the delayed H/M ratio could be explained by their linear relationship with disease duration, gender, H&Y stages and the clinical features of their population (7). Nevertheless, their data indicated no such correlation with clinical disease severity of PD (H&Y stage) and ¹²³I-MIBG myocardial uptake (7). A comparison of both early and delayed H/M ratios of PD patients with disease duration yielded a lower H/M ratio in patients with a longer disease duration. In our population, the mean disease duration was 50.7 ± 60.6 months, which was lower as compared to that reported in previously published studies in which the same relationship was found and the disease duration was 86.4 ± 73.2 months (18). This finding suggests that cardiac sympathetic dysfunction occurs relatively early in PD and the longer the disease duration, the lower the myocardial ¹²³I-MIBG uptake and the more sympathetic degeneration occurred. In their study, Kashihara *et al* found that ¹²³I-MIBG myocardial uptake was lower in patients with a long history of PD and the duration of the illness was inversely correlated with the H/M ratio (18). Our data suggest that myocardial sympathetic impairment detectable in PD remains with a worsening in the disease course over time (23). However, such a correlation is controversial (24). It has been shown that disease duration was not significantly correlated with either the early or delayed

H/M ratio in a pool of 88 patients with PD, while both age at examination and age at onset were negatively correlated (17). Hamada *et al* suggested that a later onset of the disease rather than the length of disease duration may be associated with a lower ¹²³I-MIBG uptake in PD. Our results are slightly different from those of Hamada *et al* when considering disease duration and the number of subjects examined, and it is possible that a larger standard deviation in our data may play a role in these discrepancies (17).

Of note, no significant differences were detected in cardiac ¹²³I-MIBG uptake in terms of aging in either CG or PD patients. This observation is in agreement with a previous study reporting a reduced ¹²³I-MIBG uptake in the inferior heart regions in older patients, but no significant decrease in the whole myocardium with age (1).

In this study, the planar H/M values for quantification in the CG (early 1.97 ± 0.28 , and delayed 1.88 ± 0.27) were similar to the values reported by Somsen *et al* and Merlet *et al* in healthy volunteers (1,25). Morozumi *et al* reported higher values of early and delayed H/M ratios: 2.80 ± 0.25 and 3.02 ± 0.47 , respectively (26). Differences in these measurements have already been explained with the ROI size for the upper mediastinum and the matrix size used (1). In particular, the small ROI used by Morozumi *et al* for non-specific mediastinal uptake is less affected by non-specific lung uptake leading to a lower mediastinal count density and a larger variability with a larger SD for late H/M (26). Notably, in the CG, differences in the early and delayed H/M ratios were statistically significant (Fig. 1). This finding is in agreement with other studies that reported a decrease in H/M ratio from early and delayed images in normal subjects (17,27,28). Nevertheless, several studies reported a stability or an increase in the H/M ratio over time (1,20,25). A high interindividual and within-subject variability in ¹²³I-MIBG uptake has been shown and may explain the differences with the previously mentioned studies (1).

In conclusion, the results of the present study have shown that the cardiac sympathetic system is more severely impaired in TDT than in ART patients. Thus, in contrast to the other movement symptoms of PD, tremor is caused by separate mechanisms and is anatomically different from rigidity and bradykinesia (29,30). Therefore, resting tremor is comparatively less affected by dopamine than other motor symptoms, and the evidence of lesser efficacy of dopaminergic therapy on PD tremor than on other main symptoms emphasizes the contribution of non-dopaminergic mechanisms (12). The scintigraphic findings in TDT are possibly associated with a greater autonomic impairment in these patients with ¹²³I-MIBG molecular imaging being capable of improving therapeutic planning. However, more studies on this subject are required.

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