



# What new can we learn from cardiac sympathetic neuroimaging in synucleinopathies?

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Received: 11 February 2022 / Accepted: 12 February 2022 / Published online: 24 February 2022  
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**Keywords** MIBG · SPECT · PET · Fluorodopamine · Parkinson disease · Multiple system atrophy

## Introduction

Neuroimaging evidence indicating cardiac sympathetic denervation in the Lewy body (LB) synucleinopathy Parkinson disease (PD) and generally intact innervation in the non-LB synucleinopathy multiple system atrophy (MSA) was first reported using <sup>18</sup>F-dopamine (<sup>18</sup>F-DA) positron emission tomography (PET) imaging [1]. Numerous studies since then, mainly using <sup>123</sup>I-metaiodobenzylguanidine (<sup>123</sup>I-MIBG) single-photon emission computed tomographic (SPECT) scanning, have confirmed these findings. Of 21 studies in English on this topic involving at least 50 patients, all 21 have reported a significant group difference in the direction of cardiac noradrenergic deficiency in PD (Table 1).

The issue of whether cardiac sympathetic neuroimaging can aid the differential diagnosis of PD vs. MSA seems settled, to the extent that it can be settled. <sup>123</sup>I-MIBG SPECT scanning for this purpose has been approved for several years in Europe and Asia. In the United States, however, <sup>123</sup>I-MIBG SPECT scanning is rarely done for this indication, due to lack of reimbursement by third-party payers. Cardiac PET neuroimaging is conducted only in research settings.

## Intra-cardiac regional differences in sympathetic abnormalities

In this issue of *Clinical Autonomic Research*, Eckhardt and colleagues report a small, cross-sectional study of patients diagnosed clinically with idiopathic PD or the parkinsonian form of MSA (MSA-P) [2]. Anatomic co-registration of <sup>123</sup>I-MIBG SPECT images and low-dose chest computed tomography (CT) enabled the examination of regional <sup>123</sup>I-MIBG-derived radioactivity within the left-ventricular myocardium. Digital thresholding was applied based on voxel intensity to identify 3 different patterns of radioactivity, homogeneous, non-homogeneously reduced, and absent. Among 10 patients with homogeneous radioactivity, 8 had MSA-P and 2 PD; among 7 with non-homogeneously reduced radioactivity, 3 had MSA-P and 4 PD; and among 9 with absent radioactivity, 1 had MSA-P and 8 PD. Non-homogeneously reduced tracer uptake was most common in the apex and the infero-lateral left-ventricular myocardium.

The same non-homogeneous pattern has been found by <sup>18</sup>F-DA [3] and <sup>11</sup>C-hydroxyephedrine [4] PET scanning in subgroups of PD patients. The present report confirms these findings using <sup>123</sup>I-MIBG SPECT.

## Relevance of orthostatic hypotension

In synucleinopathies, a cardinal manifestation of autonomic failure is neurogenic orthostatic hypotension (OH). Abnormal cardiac sympathetic neuroimaging is more consistently found in PD + OH than in PD without OH, by both <sup>123</sup>I-MIBG SPECT scanning [5] and <sup>18</sup>F-DA PET scanning [6]. In the study by Eckhardt et al., OH was present in only 9/28 (32%) patients (5 PD, 4 MSA-P) [2]. This limits the implication of the study for clinical autonomic research, because in autonomic centers, OH

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**Table 1** Studies using cardiac sympathetic neuroimaging in patients with Parkinson disease (PD) and multiple system atrophy (MSA)

PMID	First author	Year	Country	PD N	MSA N	TotalN	PD≠MSA <sup>a</sup>
9366173	Yoshita	1997	Japan	25	25	50	Yes
10406987	Orimo	1999	Japan	46	7	53	Yes
10979878	Goldstein	2000	USA	29	24	53	Yes
10853813	Taki	2000	Japan	41	9	50	Yes
10872011	Takatsu	2000	Japan	40	12	52	Yes
15654042	Nagayama	2005	Japan	122	14	136	Yes
20396485	Shin	2006	Korea	40	23	63	Yes
16818943	Kashihara	2006	Japan	130	11	141	Yes
19418293	Escamilla-Sevilla	2009	Spain	51	9	60	Yes
20127386	Yamashita	2010	Japan	38	20	58	Yes
21840242	Kikuchi	2011	Japan	42	42	84	Yes <sup>b</sup>
22082889	Kurata	2011	Japan	113	16	139	Yes
21342781	Tateno	2011	Japan	90	14	104	Yes
23613784	Umamura	2013	Japan	118	20	138	Yes
26303385	Mochizuki	2015	Japan	191	42	233	Yes
27812167	Fujita	2016	Japan	101	21	122	Yes
30324423	Gabilondo	2018	Spain	85	40	125	Yes
31715596	Ikeda	2019	Japan	77	35	112	Yes
34316615	Sakuramoto	2019	Japan	70	16	86	Yes
33392714	Iwabuchi	2021	Japan	90	9	99	Yes
33981791	Lenka	2021	USA	50	68	118	Yes

<sup>a</sup>Statistically significant difference between PD and MSA

<sup>b</sup>Statistically significant difference between PD and MSA as a group. No difference between PD and MSA-P ( $N=19$ ). Statistically significant difference between PD and MSA-C ( $N=23$ )

with central neurodegeneration is often the relevant differential diagnostic issue. A recent retrospective analysis of <sup>18</sup>F-DA PET imaging separated patients with PD + OH from MSA-P with high sensitivity (92%) and specificity (96%) [7].

### Functional correlates of cardiac noradrenergic deficiency

Eckhardt et al. also investigated relationships of <sup>123</sup>I-MIBG imaging with physiological indices of autonomic function. An absence of a blood pressure overshoot above baseline after performance of the Valsalva maneuver, a measure of baroreflex-sympathoneural failure, was associated with low myocardial <sup>123</sup>I-MIBG-derived radioactivity in PD but not in MSA [2]. This association could reflect postganglionic sympathetic noradrenergic impairment but also central baroreflex-sympathoneural failure.

Eckhardt and colleagues noted a lack of association between cardiac sympathetic innervation and autonomic symptom burden or OH; however, the number of patients with OH may have been too small to conduct meaningful statistical testing.

### Clinical significance of cardiac noradrenergic deficiency

Inconsistent results have been reported in the literature regarding the association between motor symptoms and cardiac noradrenergic deficiency in PD. The extent to which cardiac noradrenergic deficiency contributes to cardiovascular dysfunction in synucleinopathies is still unclear and requires further research.

Cardiac sympathetic neuroimaging may provide a better understanding of the pathophysiology of other non-motor symptoms, such as anosmia, rapid eye movement behavior disorder, fatigue, and cognitive dysfunction, all of which have been associated with evidence of myocardial noradrenergic deficiency [8]. Mechanisms for the associations between these non-motor symptoms and cardiac noradrenergic deficiency in PD remain unknown.

## Progression biomarkers

There is a push to develop quantifiable biomarkers of disease progression for use in clinical trials for neurological diseases. Longitudinal studies are far less common than cross-sectional studies such as that by Eckhardt et al. Using  $^{18}\text{F}$ -DA PET imaging, we have found that  $^{18}\text{F}$ -DA-derived radioactivity decreases by a median of 4% per year in PD [9]. Because of individual variability in the rate of decline, a clinical trial of a disease-modifying approach using  $^{18}\text{F}$ -DA-derived radioactivity as an outcome measure would require about 70 patients in each of the experimental treatment and standard treatment groups to detect a 50% decrease in the loss of cardiac noradrenergic innervation over a 5-year-period, which would represent a substantial study. Thus, cardiac neuroimaging may be more fitted as a secondary outcome or as part of a composite outcome, in which multiple endpoints are combined. Importantly, there is evidence that decreased vesicular uptake in cardiac sympathetic nerves is present upon initial evaluation of patients with LB synucleinopathies and may provide a biomarker of catecholaminergic dysfunction early in the disease process [9].

Neuroimaging evidence of cardiac noradrenergic deficiency can precede striatal dopamine deficiency and the onset of motor signs in PD [10]. In the prospective, longitudinal intramural NINDS PDRisk study, in individuals at high risk for developing PD (at least 3 of the following risk factors: genetic susceptibility, olfactory dysfunction, dream enactment, and OH), low cardiac  $^{18}\text{F}$ -DA-derived radioactivity has been reported to predict a diagnosis of PD by 3 years of follow-up [11]. The findings indicate the potential of cardiac sympathetic neuroimaging for providing a preclinical biomarker of PD; however, the generalizability to the broader population of individuals with fewer risk factors is unknown.

## Dysfunction vs. denervation

PET imaging agents such as  $^{18}\text{F}$ -DA,  $^{11}\text{C}$ -epinephrine, and  $^{11}\text{C}$ -phenylephrine are substrates for metabolism by monoamine oxidase (MAO). After uptake into the neuronal cytoplasm, these agents have two alternative fates. The main fate is vesicular uptake; oxidative deamination via MAO is a minor fate. By measuring the deaminated metabolite of  $^{18}\text{F}$ -DA simultaneously with  $^{18}\text{F}$ -DA, one can examine the efficiency of vesicular sequestration. It was by applying this approach that decreased intra-neuronal vesicular uptake was discovered in LB diseases [6]. Confirmation of this finding has come from tracking the

radioactivity during the testing session. PD + OH is associated with accelerated loss of  $^{18}\text{F}$ -DA-derived radioactivity [12]. The implications for treatment of this functional abnormality are substantial. Put simply, you cannot treat dead neurons, whereas neurons that are dysfunctional but extant (“sick-but-not-dead”) might be salvaged.

This functional abnormality cannot be quantified by  $^{123}\text{I}$ -MIBG SPECT or by  $^{18}\text{F}$ -hydroxyephedrine PET, since neither imaging agent is a substrate for MAO. On the other hand, accelerated loss (“washout”) of  $^{123}\text{I}$ -MIBG-derived radioactivity might provide a biomarker of increased sympathetically mediated exocytosis. This possibility can be tested by determining effects of sympatholysis on  $^{123}\text{I}$ -MIBG-derived radioactivity.

## PAF as a prototype of “body-first” PD

A model of brain-first versus body-first subtypes of PD has been proposed by Borghammer and colleagues [13]. In the brain-first (top-down) type,  $\alpha\text{S}$  pathology initially occurs in the brain, with secondary spreading to the peripheral autonomic nervous system; whereas in the body-first (bottom-up) type, the pathology originates in the enteric or peripheral autonomic nervous system and then spreads to the brain. The Lewy body form of PAF can evolve to PD or dementia with Lewy bodies (DLB) [14]. Measuring CSF levels of catecholamines and analyzing post-mortem data in autonomic synucleinopathy patients and controls, we reported recently that the synucleinopathies have in common evidence of central noradrenergic deficiency but differ in extents of central dopaminergic deficiency—prominent in PD and MSA, less pronounced in PAF [15]. Therefore, PAF may be the prototype for peripheral-to-central disease progression in LB diseases. Only a minority of PAF patients seem to develop symptomatic central synucleinopathy; however, these patients might be identifiable based on biomarkers of central nervous system involvement, such as by  $^{18}\text{F}$ -DOPA PET scanning [10] or by brainstem neuromelanin magnetic resonance imaging [16].

## PET vs. SPECT imaging

PET scanning offers several advantages over SPECT scanning. These include better spatial resolution, a smaller amount of injected radioactivity, the possibility of measuring radioactivity concentrations in tissues in absolute terms, and, importantly, the analysis of curves relating tissue radioactivity vs. time (time-activity curves), which provides valuable information about not only innervation but also functional abnormalities in residual nerves, such as a vesicular storage defect [6]. The time frames involved with PET and

SPECT scanning differ. Injected cardiac sympathetic neuroimaging agents exit the bloodstream almost instantly and are taken up by sympathetic nerves extremely rapidly. Although the initial  $^{123}\text{I}$ -MIBG SPECT scan, at about 15–30 min, is called “uptake,” peak  $^{18}\text{F}$ -DA-derived radioactivity normally occurs by about 5 min after tracer injection.

Comparing  $^{18}\text{F}$ -DA PET with  $^{123}\text{I}$ -MIBG SPECT scanning in the same patients with autonomic synucleinopathies would provide valuable information, and we would welcome investigators outside the NIH to join in the IND covering  $^{18}\text{F}$ -DA PET scanning, with a view toward a multi-center collaborative study.

## Implications

Research on cardiac sympathetic neuroimaging in synucleinopathies is not dead. Early involvement of the autonomic nervous system should be the focus of future studies. In patients for whom the pathophysiological process starts in the periphery and propagates to the brain, understanding and modulating the peripheral process might not only help alleviate the associated non-motor symptoms but also prevent the central degeneration that leads to the motor signs and symptoms. Cardiac sympathetic neuroimaging combined with other measurable and robust biomarkers of preclinical disease may serve as a tool to target catecholaminergic neurodegeneration at the earliest stages of LB diseases.

**Acknowledgements** Dr. Goldstein’s research is supported by the Division of Intramural Research, NINDS, NIH.

**Funding** No funding to declare.

## Declarations

**Conflict of interest** The authors declare that they have no competing interest.

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