J Neural Transm (2015) 122:1441–1446
DOI 10.1007/s00702-015-1393-5

Heart rate variability shows different cardiovascular modulation in Parkinson's disease patients with tremor dominant subtype compared to those with akinetic rigid dominant subtype

Paolo Solla[1] · Christian Cadeddu[2] · Antonino Cannas[1] · Martino Deidda[2] · Nicola Mura[2] · Giuseppe Mercuro[2] · Francesco Marrosu[1]

Received: 9 January 2015 / Accepted: 9 March 2015 / Published online: 24 March 2015

Abstract Parkinson's disease (PD) can present with different motor subtypes depending on the predominant symptoms (tremor or rigidity/bradykinesia). Slower disease progression and less cognitive decline are observed in tremor-dominant patients compared to those with akinetic-rigid subtype. Autonomic cardiovascular disorders have been described in parkinsonian patients, although the definite correlations with different subtypes of PD are not clear. In this context, heart rate variability (HRV) analysis represents a non-invasive and established tool in assessing cardiovascular autonomic modulation. We investigate cardiovascular autonomic modulation in PD patients with tremor dominant subtype in comparison to akinetic rigid dominant subtype subjects using HRV analysis. Twenty-eight PD patients (17 with tremor dominant subtype and 11 with akinetic rigid dominant subtype) were enrolled and compared to 17 age and sex-matched healthy controls. HRV was analyzed in time- and frequency-domains. Low-frequency (LF) values were significantly lower in the akinetic rigid dominant subtype than in the tremor dominant group [LF 41.4 ± 13.6 vs 55.5 ± 11.6 ($p < 0.007$)] indicating that the disease led to a more evident impairment of the baroreflex modulation of the autonomic outflow mediated by both sympathetic and parasympathetic systems in the first class of patients. These findings support the biological relevance of clinical subtypes supporting the idea of a different pathophysiological process between these subtypes. These differences also suggest that different subtypes may also result in different responses to therapy or in the possible development of cardiovascular side effects of dopaminergic drugs in these different populations.

Keywords Cardiovascular modulation · Dysautonomia · Parkinson's disease · Tremor dominant subtype · Akinetic rigid dominant subtype · Heart rate variability

Introduction

Parkinson's disease (PD) is commonly defined as a neurodegenerative movement disorder characterized by resting tremor, rigidity and bradykinesia. Patients affected by PD can present different subtypes according to the predominant symptoms (tremor or rigidity/bradykinesia) with clear clinical proof that these different subtypes can have a different clinical course (Jankovic et al. 1990). Slower progression of the disease and less cognitive decline are observed in tremor-dominant patients. These clinical observations have been confirmed by neuroimaging and clinic–pathologic findings describing a more favorable outcome in tremor-dominant patients than in akinetic-rigid subjects, in concordance with different brain biochemical abnormalities (Rossi et al. 2010; Eggers et al. 2011; Lewis et al. 2011). Moreover, PD is often hampered by the appearance of non-motor symptoms (NMS), which in recent

P. Solla and C. Cadeddu contributed equally to this study.

G. Mercuro and F. Marrosu are senior authors and contributed equally to this study.

✉ Christian Cadeddu
cadedduc@unica.it

[1] Department of Public Health, Clinical and Molecular Medicine, Movement Disorders Centre, University of Cagliari, Cagliari, Italy

[2] Department of Medical Sciences "Mario Aresu", University Hospital of Cagliari, University of Cagliari, Strada Statale 554, Km 4.500, Monserrato, 09042 Cagliari, Italy

years are gaining increasing attention (Langston 2006; Chaudhuri et al. 2006). Among the NMS, autonomic cardiovascular disorders have been associated with significant morbidity and mortality and with variable manifestations in patients affected by PD (Goldstein 2003), although the definite correlations with different subtypes of PD are not clear. In this context, analysis of heart rate variability (HRV) represents a not invasive and established tool in assessing cardiovascular autonomic modulation in different extrapyramidal disorders, especially in PD patients (Friedrich et al. 2008; Valappil et al. 2010; Maetzler et al. 2014).

In this context, it was decided to study cardiovascular autonomic modulation in PD patients with tremor dominant subtype in comparison to akinetic rigid dominant subtype, and compare them with normal subjects using HRV analysis with the aim to investigate the biological relevance of clinical subtypes and possible different pathophysiological process between these subtypes.

Methods

PD patients were selected among individuals attending the Movement Disorders Centre of University of Cagliari, Italy. Inclusion criteria were a diagnosis of probable Parkinson's disease, defined according to the United Kingdom (UK) brain bank criteria (Hughes et al. 1992) and done by one neurologist specialized in movement disorders, age 40–80 years, and stable medication use.

Patients with moderate-to-severe dementia with the mini-mental state examination (MMSE) (Folstein et al. 1975) of <24 or with incapacity to give an informed consent were excluded from the study. In addition, any patient with atypical Parkinson's syndromes such as multiple system atrophy (MSA), vascular parkinsonism, drug-induced parkinsonism, and progressive supranuclear palsy (PSP) was excluded.

Twenty-eight consecutive PD patients (17 with tremor dominant subtype and 11 with akinetic rigid dominant subtype) were selected and compared. These two groups were also compared to 17 age and sex-matched healthy controls. Patients with medical disorders that could alter autonomic function (e.g. diabetes, hematological disorders, collagen diseases, malignancies, and neuropathy) were excluded.

Anticholinergic anti-Parkinson's drugs were withdrawn whenever possible, or reduced to the lowest dosage that allowed appropriate cooperation during the test. In this regard, biperidene, an anticholinergic drug used to decrease tremor in PD patients, was withdrawn in a single patient enrolled in the dominant group. No other patients were taking anticholinergic drugs.

Whenever possible, cardiac drugs that could alter HRV results (i.e. beta-receptor blockers, I_f-current blockers, calcium-channel blockers, mineral corticoids) were discontinued or reduced to the lowest dosage that allowed appropriate cooperation during the test. If therapeutic modification was clinically impossible patients were excluded. Medications such as ACE-inhibitors, angiotensin receptor blockers and diuretics were allowed. Cardiac drugs that could alter HRV results were discontinued only in one patient of PD patients with tremor dominant subtype who was taking propranolol. This drug was gradually discontinued before HRV evaluation.

Patients underwent complete neurological examination, including disease duration (time passed from diagnosis), measures of disease severity such as Hoehn and Yahr stage (Hoehn and Yahr 1967), the Unified Parkinson's Disease Rating Scale (UPDRS) pars-III score (Goetz 2003), and total levodopa equivalent daily dose (LEDD) was also recorded.

LEDD was calculated, as previously described by Evans et al. (2004), with the following formula: levodopa dose + levodopa dose × 1/3 if on entacapone + bromocriptine (mg) × 10 + cabergoline or pramipexole (mg) × 67 + ropinirole or rotigotine (mg) × 20 + pergolide (mg) × 100 + apomorphine (mg) × 8.

The scales were rated during an "off" phase (12 h off drugs). We defined the clinical subgroups tremor-dominant and akinetic-rigid for each patient in a manner similar to Lewis et al. (2005). The tremor score was obtained from the sum of UPDRS items 20 and 21 divided by 7. The non-tremor score was obtained from the sum of UPDRS items 18, 19, 22, 27, 28, 29, 30, and 31, divided by 12. PD patients were classified as tremor-dominant if the tremor score was at least twice the non-tremor score, as akinetic-rigid patients if the non-tremor score was at least twice the tremor score. ECG 24-h recordings were performed in all subjects at the same time with a digital three-channel recorder (Del Mar-Aria recorder; Del Mar Medical, Irvine, CA). During the ECG recording all patients were free to carry out daily tasks to the extent allowed by hospital regimen. All RR interval time series were automatically edited first. Manual editing was not performed due to the insignificant presence of artifacts and premature beats. For final analysis, 24-h HR-variability data were divided into segments of 3600 ms, and only segments with >85 % sinus beats were included in analysis. Quantitative time domain analysis was performed on normal–normal (NN or RR) interval, and the following data were computed: mean, SDNN (standard deviation of NN intervals), SDNN index (mean of the standard deviations of NN intervals), SDANN (standard deviation of the averaged NN intervals), SDSD (standard deviation of successive NN differences), RMSSD (square root of the mean squared difference of the

consecutive NN intervals), pNN50 (proportion of NN intervals differing more than 50 ms to the total number of NN intervals), and TINN (the integral of the density distribution of the number of all NN intervals plotted in a histogram divided by the maximum of the density distribution). An autoregressive model was used to estimate the power-spectrum densities of HR variability (Kay and Marple 1981). Power spectra were quantified by measuring the area in three frequency bands: 0.005–0.04 Hz (very low frequency, VLF), 0.04–0.15 Hz (low frequency, LF), and 0.15–0.4 Hz (high frequency, HF).

Spectral power of HRV was reported in normalized units (representation of the relative value of each power component in proportion to the total power minus the VLF component).

ECG data were transferred for the analysis of HR variability on Impresario Holter Analysis System (Del Mar Reynolds Medical INC, Irvine, CA).

Finally, PD patients were compared to the age and sex-matched healthy controls. Written informed consent was obtained from all participants before screening, consistent with the Declaration of Helsinki.

Statistical analysis

Categorical data are presented as percentages, and quantitative data as mean ± SD. Differences between groups were calculated using a one-way analysis of variance (ANOVA) for repeated measures, and categorical variables were compared with the Fisher's exact test. Subsequently, values were normalized for age at onset, HY and UPDRS. A two-tailed value of $p < 0.05$ was considered statistically significant.

Results

Twenty-eight PD patients (17 with tremor dominant subtype and 11 with akinetic rigid dominant subtype) were selected and compared to 17 age and sex-matched healthy controls. Demographic characteristics of patients (subdivided in tremor dominant and akinetic-rigid subtypes) and health subjects involved in the study are summarized in Table 1. The mean age was 65.5 ± 6.5 in PD patients with akinetic rigid dominant subtype, 63.4 ± 8.6 in PD patients with tremor dominant subtype, 65.2 ± 9.8 in control subjects. Both, the control and the PD groups had similar height and weight characteristics. Other clinical characteristics were not significantly different between PD patients groups and healthy control, with the exception of motor disability scores between PD patients. Indeed, HY resulted significantly higher in akinetic-rigid PD patients compared to tremor dominant subtype: 2.7 ± 0.8 vs 2.1 ± 0.4 ($p < 0.03$), and UPDRS-III was also significantly greater in akinetic-rigid PD patients compared to tremor dominant subtype: 27.5 ± 14.5 vs 18.9 ± 4.4 ($p < 0.03$).

Among time and geometric domains parameters, summarized in Table 2, SDSD was significantly enhanced in PD patients compared to controls ($p = 0.04$), while SDNN index and HRV were significantly decreased in PD patients compared to controls ($p = 0.03$).

No differences in these parameters were found between akinetic-rigid PD patients compared to tremor dominant subtype.

Among frequency domain parameters, summarized in Table 3, both PD groups and healthy control subjects showed significant differences in LF, LF/HF ratio and HF. In particular, LF values were lower both in akinetic-rigid PD patients ($p < 0.0001$) and tremor dominant subtype PD patients ($p = 0.043$) compared to controls, HF values were higher both in akinetic-rigid PD patients ($p = 0.006$) and tremor dominant subtype PD patients ($p = 0.041$) compared to controls, while LF/HF ratio were lower both in akinetic-rigid PD patients ($p = 0.007$) and tremor dominant subtype PD patients ($p = 0.018$) compared to controls.

Moreover, it was observed that LF values were significantly lower in the akinetic rigid dominant subtype than in the tremor dominant group (LF 41.4 ± 13.6 vs 55.5 ± 11.6; $p = 0.007$), while the LF/HF ratios tended to be lower in akinetic rigid dominant subtype, although no statistical differences were found. To exclude a possible bias due to HY, UPDRS and age at observation (although the last difference was not significant), low-frequency values were normalized for these variable. Normalized LF were significantly lower in the akinetic rigid dominant subtype than in the tremor dominant group: normalized LF for HY were 16.2 ± 7.6 vs 26.9 ± 7.0, $p = 0.001$; normalized LF for UPDRS were 2.0 ± 1.4 vs 3.1 ± 0.9; $p = 0.021$; normalized LF for age at observation were 0.6 ± 0.3 vs 0.9 ± 0.3; $p = 0.023$. Thus, normalization of LF value for these variables did not change the significant difference between tremor dominant subtype and akinetic rigid dominant subtype subjects.

Discussion

In PD patients two different clinical phenotypes are commonly described, namely a tremor dominant subtype and an akinetic-rigid subtype. The first subtype of patients is usually characterized by slower disease progression, a lower degree of cognitive impairment and minor incidence of neuropsychiatric disorders compared with the latter group (Lewis et al. 2005; Oh et al. 2009).

Table 1 Demographic characteristics of patients (subdivided in tremor dominant and akinetic-rigid subtypes) and healthy subjects involved in the study

	Tremor-dominant PD	Akinetic-rigid PD	Controls	*p*
Subjects	17	11	17	
Gender (male/female)	10/7	6/5	10/7	0.8
Age, years (SD)	63.4 (8.6)	65.5 (6.5)	65.2 (9.8)	0.5
Height, cm (SD)	169.4 (6.9)	167.5 (5.5)	168.4 (6.5)	0.7
Weight, kg (SD)	69.2 (7.1)	66.1 (8.6)	68.5 (7.6)	0.4
Disease duration, years (SD)	6.0 (1.8)	7.9 (5.5)	NA	0.3
Modified Hoehn and Yahr stage (SD)	2.1 (0.4)	2.7 (0.8)	NA	**0.03**
UPDRS-III, mean score (SD)	18.9 (4.4)	27.5 (14.5)	NA	**0.03**
Total LEDD, mg/day (SD)	606 (140)	586 (267)	NA	0.9

Significant *p* values ($p < 0.05$) are highlighted in bold

PD Parkinson's disease, *SD* standard deviation, *UPDRS* unified PD rating scale, *LEDD* levodopa equivalent daily dose

Table 2 Heart rate variability measures: time and geometric domains

Parameters	Tremor-dominant PD	Akinetic-rigid PD	Controls	*p*		
				C vs AR	C vs T	T vs AR
SDNN (SD)	120.9 (24.8)	104.8 (33.9)	122.9 (22.7)	0.101	0.811	0.164
RMSSD (SD)	36.1 (16.4)	38.2 (27.8)	28.4 (7.8)	0.180	0.100	0.804
SDSD (SD)	30.0 (16.6)	30.4 (21.5)	20.4 (6.0)	0.081	**0.037**	0.961
HRV (SD)	16.5 (4.1)	13.9 (5.2)	18.0 (4.0)	**0.027**	0.303	0.159
TINN (SD)	507.4 (133.2)	483.9 (210.7)	558.8 (129.1)	0.252	0.269	0.723
SDNN index (SD)	39.8 (9.9)	35.6 (17.3)	48.5 (12.2)	**0.029**	**0.031**	0.429
PNN50 (SD)	5.0 (3.4)	8.0 (14.1)	5.4 (4.8)	0.101	0.811	0.398

Significant *p* values ($p < 0.05$) are highlighted in bold

PD Parkinson's disease, *C* controls, *T* tremor dominant, *AR* akinetic-rigid, *SD* standard deviation, *SDNN* standard deviation of NN intervals, *RMSSD* square root of the mean squared difference of the consecutive NN intervals, *SDSD* standard deviation of successive NN differences, *HRV* heart rate variability, *TINN* the integral of the density distribution of the number of all NN intervals plotted in a histogram divided by the maximum of the density distribution, *SDNN index* mean of the standard deviations of NN intervals, *pNN50* proportion of NN intervals differing more than 50 ms to the total number of NN intervals

Table 3 Heart rate variability measures: frequency domain

Parameters	Tremor-dominant PD	Akinetic-rigid PD	Controls	*p*		
				C vs AR	C vs T	T vs AR
LF (SD), n.u.	55.5 (11.6)	41.4 (13.6)	64.7 (13.6)	**0.000**	**0.043**	**0.007**
HF (SD), n.u.	31.7 (8.5)	36.5 (9.8)	25.1 (9.4)	**0.006**	**0.041**	0.194
LF/HF (SD)	2.4 (1.2)	1.9 (1.4)	3.8 (1.9)	**0.007**	**0.018**	0.242

Significant *p* values ($p < 0.05$) are highlighted in bold

PD Parkinson's disease, *C* controls, *T* tremor dominant, *AR* akinetic-rigid, *SD* standard deviation, *LF* low frequency; *HF* high frequency, *n.u.* normalized unit, *LF/HF* LF/HF ratio

These data reflect pathological differences where tremor dominant subtype patients presented with more severe impairment of the middle part of the substantia nigra pars compacta and lesion of retrorubral area A8, while patients with akinetic-rigid subtype presented with a major degeneration in the ventrolateral part of the substantia nigra pars compacta (Jellinger 1999).

However, neurodegeneration in PD not only involves brain areas, but can also be present externally of central nervous system with the occurrence of severe non-motor features (Langston 2006; Chaudhuri et al. 2006). Among them, symptoms of cardiovascular dysautonomia are a common occurrence in Parkinson's disease, often occurring prior to motor impairment (Mathias 1998; Goldstein 2003). Previously, SPECT studies with 123I-metaiodobenzylguanidine (MIBG) indicated a cardioselective, postganglionic denervation in PD patients (Taki et al. 2004; Mitsui et al. 2006).

This data explicates how the damage to the postganglionic sympathetic efferences in PD patients may be the main cause of dysautonomia (Ziemssen and Reichmann 2010).

HRV parameters reflect cardio-vagal modulation, sympathetic excitation (Pagani et al. 1997) and sympathovagal balance (Eckberg 1997) and can be quantified and displayed using spectral analysis (Cadeddu et al. 2010). Among the power spectrum frequency bands, the HF band is thought to reflect the parasympathetic activity mediated by the vagus nerve, whereas the LF band is thought to reflect the baroreflex modulation of the autonomic outflow mediated by both sympathetic and parasympathetic systems (Goldstein et al. 2011).

Given that, this study shows LF values significantly lower in the akinetic rigid dominant subtype compared to tremor dominant control group, indicating that the disease led to a more evident impairment of the baroreflex modulation of the autonomic outflow mediated by both sympathetic and parasympathetic systems in the first class of patients. Thus, there was a significant alteration in autonomic parameters in PD patients with akinetic rigid dominant compared to tremor dominant subtype.

Moreover, using time domain analysis of HRV, we found that despite the normal mean resting heart rate (as measured by RR interval) in PD subjects, there was a notable reduction in HRV and SDNN (estimate of overall HRV) when compared with normal controls. Total HRV and SDNN index correlate to the total power of the analysis when applied on a 24-h measurement (Camm et al. 1996) underlining the value of the reduction of the LF components of the power spectrum. On the other hand, the increase of SDSD, which correlates to the HF components of the power spectrum when applied on a 24-h measurement (Camm et al. 1996), confirms the imbalance of the autonomic components evidenced with the power spectrum analysis.

These findings support the biological relevance of clinical subtypes backing the idea of a different pathophysiological process between these subtypes. These differences are not only important for a better classification between PD patients, but also suggest that different subtypes may also result in different responses to therapy or in the possible development of cardiovascular side effects of dopaminergic drugs in these different populations.

This study also confirms previous results on significant abnormalities in sympathetic function of PD patients compared to controls and suggests the presence of an enhanced autonomic dysfunction in PD patients, especially in patients with akinetic-rigid PD subtypes. The presence of cardiovascular autonomic dysfunction might represent an important cause of comorbidity in these specific forms of PD, with possible effects on cardiovascular symptoms.

Acknowledgments Authors gratefully thank Mr. Barry Mark Wheaton for his editorial and linguistic assistance. Dr. Paolo Solla gratefully acknowledges Sardinia Regional Government for the financial support (P.O.R. Sardegna F.S.E. Operational Programme of the Autonomous Region of Sardinia, European Social Fund 2007–2013—Axis IV Human Resources, Objective l.3, Line of Activity l.3.1 "Avviso di chiamata per il finanziamento di Assegni di Ricerca"). Dr. Paolo Solla gratefully acknowledges Fondazione Banco di Sardegna for the financial support.

Conflict of interest The authors declare that they have no conflict of interest. P. Solla has received institutional research funding from the University of Cagliari, received funding from the Fondazione Banco di Sardegna, and received research grant from the Dystonia Europe. Christian Cadeddu reports no disclosures relevant to the manuscript. Antonino Cannas reports no disclosures relevant to the manuscript. Martino Deidda reports no disclosures relevant to the manuscript. Nicola Mura reports no disclosures relevant to the manuscript. Giuseppe Mercuro reports no disclosures relevant to the manuscript. Francesco Marrosu reports no disclosures relevant to the manuscript.

Ethical standard All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

References

Cadeddu C, Deidda M, Mercuro G, Tuveri A, Muroni A, Nocco S et al (2010) Cardiovascular modulation during vagus nerve stimulation therapy in patients with refractory epilepsy. Epilepsy Res 92(2–3):145–152

Camm AJ, Malik M, Bigger JT et al (1996) Heart rate variability: standards of measurement, physiological interpretation and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing Electrophysiology. Circulation 93:1043–1065

Chaudhuri KR, Healy D, Schapira AHV (2006) The non-motor symptoms of Parkinson's disease. Diagnosis and management. Lancet Neurol 5:235–245

Eckberg DL (1997) Sympathovagal balance: a critical appraisal. Circulation 96(9):3224–3232

Eggers C, Kahraman D, Fink GR, Schmidt M, Timmermann L (2011) Akinetic-rigid and tremor-dominant Parkinson's disease patients show different patterns of FP-CIT single photon emission computed tomography. Mov Disord 26(3):416–423

Evans AH, Katzenschlager R, Paviour D, O'Sullivan JD, Appel S, Lawrence AD et al (2004) Punding in Parkinson's disease: its relation to the dopamine dysregulation syndrome. Mov Disord 19:397–405

Folstein MF, Folstein SE, McHugh PR (1975) Mini-mental state. A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 12(3):189–198

Friedrich C, Rudiger H, Schmidt C, Herting B, Prieur S et al (2008) Baroreflex sensitivity and power spectral analysis in different extrapyramidal syndromes. J Neural Transm 115:1527–1536

Goetz CC (2003) The unified Parkinson's disease rating scale (UPDRS): status and recommendations. Mov Disord 18(7): 738–750

Goldstein DS (2003) Dysautonomia in Parkinson's disease: neurocardiological abnormalities. Lancet Neurol 2(11):669–676

Goldstein DS, Bentho O, Park MY, Sharabi Y (2011) Low-frequency power of heart rate variability is not a measure of cardiac sympathetic tone but may be a measure of modulation of cardiac autonomic outflows by baroreflexes. Exp Physiol 96(12):1255–1261

Hoehn MM, Yahr MD (1967) Parkinsonism: onset. progression and mortality. Neurology 17(5):427–442

Hughes AJ, Daniel SE, Kilford L, Lees AJ (1992) Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases. J Neurol Neurosurg Psychiatry 55(3):181–184

Jankovic J, McDermott M, Carter J, Parkinson Study Group et al (1990) Variable expression of Parkinson's disease: a baseline analysis of the DATATOP cohort. Neurology 40(10):1529–1534

Jellinger KA (1999) Post-mortem studies in Parkinson's disease. Is it possible to detect brain areas for specific symptoms? J Neural Transm Suppl 56:1–29

Kay SM, Marple SLJ (1981) Spectrum analysis: a modern perspective. Proc IEEE 69:1380–1419

Langston JW (2006) The Parkinson's complex: parkinsonism is just the tip of the iceberg. Ann Neurol 59:591–596

Lewis SJG, Foltynie T, Blackwell AD, Robbins TW, Owen AM, Barker RA (2005) Heterogeneity of Parkinson's disease in the early clinical stages using a data driven approach. J Neurol Neurosurg Psychiatry 76:343–348

Lewis MM, Du G, Sen S et al (2011) Differential involvement of striato- and cerebello-thalamo-cortical pathways in tremor- and akinetic/rigid-predominant Parkinson's disease. Neuroscience 177:230–239

Maetzler W, Karam M, Berger MF, Heger T, Maetzler C, Ruediger H, Bronzova J, Lobo PP, Ferreira JJ, Ziemssen T, Berg D (2014) Time- and frequency-domain parameters of heart rate variability and sympathetic skin response in Parkinson's disease. J Neural Transm (Epub ahead of print)

Mathias CJ (1998) Cardiovascular autonomic dysfunction in parkinsonian patients. Clin Neurosci 5(2):153–166

Mitsui J, Saito Y, Momose T, Shimizu J, Arai N, Shibahara J et al (2006) Pathology of the sympathetic nervous system corresponding to the decreased cardiac uptake in 123I-metaiodobenzylguanidine (MIBG) scintigraphy in a patient with Parkinson disease. J Neurol Sci 243(1–2):101–104

Oh JY, Kim YS, Choi BH, Sohn EH, Lee AY (2009) Relationship between clinical phenotypes and cognitive impairment in Parkinsons disease. Arch Gerontol Geriatr 49:351–354

Pagani M, Montano A, Porta A, Malliani A, Abboud FM, Birkett C, Somers CK (1997) Relationship between spectral components of cardiovascular variabilities and direct measures of muscle sympathetic nerve activity in humans. Circulation 95:1441–1448

Rossi C, Frosini D, Volterrani D et al (2010) Differences in nigrostriatal impairment in clinical variants of early Parkinson's disease: evidence from a FP-CIT SPECT study. Eur J Neurol 17(4):626–630

Taki J, Yoshita M, Yamada M, Tonami N (2004) Significance of 123I-MIBG scintigraphy as a pathophysiological indicator in the assessment of Parkinson's disease and related disorders: it can be a specific marker for Lewy body disease. Ann Nucl Med 18(6):453–461

Valappil RA, Black JE, Broderick MJ, Carrillo O, Frenette E, Sullivan SS, Goldman SM, Tanner CM, Langston JW (2010) Exploring the electrocardiogram as a potential tool to screen for premotor Parkinson's disease. Mov Disord 25(14):2296–2303

Ziemssen T, Reichmann H (2010) Cardiovascular autonomic dysfunction in Parkinson's disease. J Neurol Sci 289(1–2):74–80