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Cardiac denervation occurs independent of orthostatic hypotension and impaired heart rate variability in Parkinson's disease

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Abstract

Patients with idiopathic Parkinson's disease (PD) have impaired sympathetically mediated neurocirculatory innervation. Here we analyzed the correlation between cardiac ^{123}I-metaiodobenzylguanidine (MIBG) uptake, orthostatic hypotension and heart rate variability in treated patients with PD. Orthostatic hypotension (OH) as a hallmark of sympathetic neurocirculatory failure was found with a high prevalence in PD. PD is known to affect cardiac innervation, resulting in a suppressed heart rate variability and a postganglionic noradrenergic lesion. We measured continuous arterial blood pressure in rest and 70° head-up tilt for at least 20 min, heart rate variability in the supine position, standing, deep respiration and Valsalva manoeuvre in 58 patients with PD (27 male, 31 female; mean age 71 years, mean PD duration 5.1 years, Hoehn and Yahr 3.1 ± 0.8). Sympathovagal balance was estimated by the low-frequency (LF: 0.04–0.15 Hz) and high-frequency bands (HF: 0.15–0.4 Hz) ratio in the analysis of heart rate variability in each condition. Myocardial adrenergic function was analyzed by imaging MIBG using the single-photon emission computed tomography technique. MIBG uptake expressed as heart-to-mediastinum ratio was reduced in all PD patients (H/M-ratio: 1.14 ± 0.16). We found no correlation between myocardial MIBG uptake and sympathovagal balance, blood pressure or other autonomic findings. The LF/HF ratio in tilt-table testing was significantly more reduced in PD with OH than without OH (2.18 vs. 1.49, $p = 0.022$). MIBG uptake did not differ.

It is concluded that scintigraphy with MIBG appears to be a highly sensitive and useful tool to demonstrate sympathetic postganglionic cardiac nerve disturbances. Loss of sympathetic innervation of the heart seems to occur early and independent of orthostatic hypotension, baroreflex failure and impaired heart rate variability in PD.

Keywords: Autonomic dysfunction; Cardiac denervation; Parkinson's disease; MIBG-SPECT

1. Introduction

Cardiovascular dysfunction is common in Parkinson's disease (PD). Orthostatic hypotension is the most frequent feature of autonomic dysfunction in PD. Symptoms resulting from orthostatic hypotension and impaired perfusion include dizziness, visual disturbances, loss of consciousness, impaired cognition, angina pectoris, oliguria, weakness, and falls [1]. In PD, orthostatic hypotension reflects sympathetic neurocirculatory failure from generalized sympathetic denervation [2]. Cardiac MIBG scintigraphy is a sensitive tool for the early detection of cardiac sympathetic denervation in Parkinson's disease [3,4]. Heart rate variability can buffer changes in blood pressure. Sympathetic and parasympathetic balance that control heart activity are impaired in Parkinson's disease and this dysfunction can be assessed by a frequency-domain analysis of heart rate (HR) changes [5]. Although prominent autonomic nervous system dysfunction is mostly associated with advanced PD, it may affect patients even in the early phase of the disease [6]. However, in the early stages of PD, these changes were not significant on an individual basis [7].

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Less data are available about the relationship between MIBG uptake, orthostatic hypotension and disturbed heart rate variability. If cardiac denervation follows a different pathophysiology than neurocirculatory dysfunction in PD, MIBG uptake would not be expected to correspond to neurocardiovascular function tests.

2. Patients and methods

2.1. Patients

All 58 PD patients were referred to our Department of Neurology and were consecutively included in this study. A clinical diagnosis of idiopathic definite PD was made according to the criteria set forth by the UK Parkinson's Disease Society Brain Bank [8]. The clinical stage of the patients was assessed using the Hoehn and Yahr scale and the Unified Parkinson's Disease Rating Scale motor score (UPDRS, part-III) during a practically defined "off" (at least after 12 h of the last levodopa intake) [9]. PD patients received a combination of levodopa and carbidopa or benserazide, amantadine, and dopamine agonists. Dopaminergic treatment was effective for parkinsonian symptoms in all patients. Patients were tested with their regular antiparkinsonian drugs. Midodrine and fludrocortisone were stopped 2 h before testing. The demographic data of the patients are given in Table 1. During the interview for admission to the study each patient was asked to date the probable onset of PD symptoms. With regard to MIBG scintigraphy no patient was treated with anticholinergics, reserpine, clonidine, amphetamines, phenylpropanolamine, amiodarone, or substances inducing any blockade of calcium channels [10]. Patients with any condition that might affect uptake of myocardial MIBG were excluded. The study was approved by the ethics committee of the University of Witten/Herdecke according to the revised Declaration of Helsinki. All subjects gave their written informed consent.

2.2. Autonomic testing

The cardiovascular autonomic function tests are based on blood pressure and heart rate at rest and after various stimulations under standardized environmental conditions at 20 °C. All tests were done in the morning. Finger arterial pressure was measured beat-to-beat continuously and non-invasively using the volume clamp method with the Portapres device (TNO TPD, Amsterdam, The Netherlands). The cuff was placed on the second phalanx of the third finger. Synchronous recording of a standard four-channel electrocardiograph and the respiratory effort measured by thoracic strain gauges and the Portapres signal were performed simultaneously with the fan device (Schwarzer GmbH, Munich, Germany). After the rest phase, head-up tilt-table testing with a 70° upright position within 20 s with an electrically driven tilt-table was performed. The Valsalva manoeuvre was performed by asking the subject to blow into a mouthpiece attached to an aneroid pressure gauge at a pressure of 40 mm Hg and to endure pressure for 15 s. In between each test, a return of the cardiovascular parameters to the baseline was awaited. The Valsalva ratio, diastolic blood pressure in phase II, and the latency between the minimum blood pressure in phase III of the Valsalva manoeuvre and the maximum in phase IV were evaluated. The response was considered to be normal if the diastolic pressure increased before the end of straining and if the systolic blood pressure during phase IV increased to a value exceeding the baseline within not more than 7 s. The Valsalva ratio of HR was calculated from the maxima of HR during or shortly after straining and the minimal depressed HR in the overshoot phase IV. Orthostatic hypotension was diagnosed based on the consensus statement on the definition of orthostatic hypotension using a decrease of at least 20 mm Hg in systolic blood pressure or at least 10 mm Hg within 3 min of standing [11].

Heart rate variability (HRV) analysis was performed according to the "Recommendations of the International Federation of Clinical Physiology for the Practice of Clinical Neurophysiology" in two main ways: by statistical operations on R–R intervals (time-domain analysis) and by the spectral analysis of a series of successive R–R intervals (frequency-domain analysis) [12]. In short, the ECG signal was digitized at a sample rate of 500 per second. Respiration was monitored by the registration of chest movements.

2.2.1. HRV in the time domain

Standard deviation (SD RRI), root mean square of successive differences of R–R intervals (RMSSD RRI) and the percentage of interval changes greater than 50 ms to normal sinus R–R intervals (PNN50) were calculated.

2.2.2. Spectral analysis

Fast Fourier transform (FFT)-based algorithm and autoregressive modelling were used for the spectral analysis of HRV. The R–R intervals were converted at 4 Hz and an exact Hamming window was applied for FFT. The power in the frequency range of low frequencies (LF: 0.04–0.15 Hz) and high frequencies (HF: 0.15–0.40 Hz) was calculated following Task Force recommendations. Spectral analysis allows a differentiation of the sympathetic and parasympathetic activation, which are related to a low-frequency (LF) and a high-frequency (HF) component of the HRV signal, respectively. The resulting LF/HF ratio as a quantitative index of the sympathovagal balance was calculated [11,12].

2.3. MIBG scintigraphy

Myocardial adrenergic function was analyzed by imaging with ^{123}I-metaiodobenzylguanidine (MIBG) using the single-photon emission computed tomography (SPECT) technique. MIBG is an analog of norepinephrine and a tracer for sympathetic neuron integrity and function. For imaging of the cardiac adrenergic innervation scintigraphy was performed by an injection of 180 MBq ^{123}I-MIBG (GE Healthcare Buchler, Braunschweig, Germany) after blocking iodine uptake in the thyroid gland with a total of 300 mg perchlorate. To allow for clearance of non-specific tissue uptake, data were acquired 4 h after injection. After obtaining a planar static image SPECT was performed using a dual-headed gamma camera (Hawkeye, GE Medical Systems, Solingen, Germany) equipped with low dose CT for image fusion and correction of attenuation. Thirty projections, 40 s each, were acquired over a 180° rotation. The data were stored into a 64 × 64 matrix and reconstructed iteratively. Cardiac MIBG uptake was assessed qualitatively for heart visualization on planar studies by nuclear medicine specialists, who were unaware of the autonomic function status. On the planar images, the regions of interest were drawn by three independent investigators over the heart and the mediastinum to calculate the heart/mediastinum (H/M) ratio. The mediastinum is used as a reference in our laboratory since it contains few sympathetic nerves. The H/M-ratio was compared to the normal range of >1.7 (4 h p.i.) as derived from earlier investigations [13]. Reproducibility of the region drawings by the three independent investigators is high with a maximum error of about 5%.

2.4. Statistical analysis

A two-sided *t* test was used for possible differences between subjects with different signs. A *p* value of less than 0.05 was considered statistically significant. Differences between the PD groups with and without OH were analyzed with the two-tailed Mann–Whitney U test. Correlations were performed with Spearman rank correlation. The analysis was executed with the help of S.

Table 1
Demographic and clinical data of the patients with PD

Number of patients	58
Age (years)	70.9 ± 9.7
Male/female (%)	56/42
Hoehn–Yahr scale	3.0 ± 0.9
Motor score of UPDRS	31.7 ± 7.5
Duration of disease (years)	5.1 ± 6.4
Mean dose of levodopa-equivalent medication (mg/day)	1128.3 ± 648.9

Levodopa-equivalent conversion factors were published previously as follows: 100 mg levodopa = 10 mg bromocriptine = 6 mg ropinirole = 1 mg pergolide = 1 mg lisuride = 1.3 mg cabergoline = 0.7 mg pramipexole.