

# Is there a correlation between urological and cardiovascular dysfunction in Parkinson's disease?

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## Summary

**It is well established that non-motor symptoms are a core feature of Parkinson's disease (PD). A dysregulation of the autonomic nervous system seems to be present in PD, supporting the coexistence of urological and cardiovascular non-motor features.**

**We evaluated whether bladder dysfunctions in patients with PD are linked to blood pressure dysregulation.**

**Twenty-eight mild PD patients, previously submitted to a urodynamic evaluation, underwent 24-hour ambulatory blood pressure and heart rate monitoring to allow assessment of their circadian blood pressure profile; the occurrence of postprandial hypotension and orthostatic hypotension was also investigated.**

**No significant differences in blood pressure control were detected between bladder hyperreflexic and normoreflexic subjects.**

**Our findings support different origins of urological and cardiovascular impairments in PD.**

**KEY WORDS:** bladder, cardiovascular, dysautonomia, Parkinson.

## Introduction

It is well known that urinary disturbances are present in two thirds of patients with Parkinson's disease (PD) and urodynamic studies in PD have shown detrusor overactivity. The urodynamic feature reported is commonly attributed to an autonomic dysfunction (Sakakibara et al., 2010). Previous studies reporting that repetitive transcranial magnetic stimulation applied over the prefrontal cortex (Brusa et al., 2009) and subthalamic nu-

cleus deep brain stimulation may improve bladder capacity and detrusor overactivity (Finazzi-Agrò et al., 2003) have led to the hypothesis that lower urinary tract (LUT) symptoms in PD patients may be due to central rather than peripheral autonomic dysregulation (Brusa et al., 2007). In particular, a lack of inhibitory control from the prefrontal cortex to the periaqueductal grey is hypothesised to be involved (Brusa et al., 2007). Indeed, in addition to the typical motor symptoms of the disease, PD patients show signs and symptoms of autonomic failure, mainly at gastrointestinal and cardiovascular level (Titova et al., 2017). Thus, a dysregulation of the autonomic nervous system seems to be present in PD patients.

At cardiovascular level, the main manifestation of sympathetic noradrenergic failure is orthostatic intolerance and orthostatic hypotension (OH) (Goldstein et al., 2014; Freeman et al., 2018). Whether urological dysfunction and autonomic cardiovascular dysregulation are two discrete entities in PD or share a single origin is still not defined.

The present investigation was undertaken to evaluate whether urological dysfunction in PD is linked to an impairment of blood pressure (BP) control.

## Materials and methods

Twenty-eight patients affected by idiopathic PD (Hohen and Yahr score  $\leq 2.5$ ) were enrolled (14 males and 14 females). Exclusion criteria were: hypertension, drugs acting on the LUT and on the central and/or autonomic nervous system, a history of urological disorders, diabetes or heart disease. The study was approved by the local ethics committee and was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. All the participants gave their informed consent to participate in the study.

The participants were submitted to a urodynamic evaluation and divided into hyperreflexic (HR)  $n=14$  (7 males and 7 females; mean age  $64 \pm 3$  years; mean disease duration:  $5 \pm 2$  years; l-dopa equivalent daily dose:  $600 \pm 150$  mg) and normoreflexic (NR)  $n=14$  (8 males and 6 females; mean age  $62 \pm 3$ ; mean disease duration:  $4 \pm 3$  years; l-dopa equivalent daily dose:  $750 \pm 150$  mg), according to international criteria (Garnett et al., 2002). The urodynamic evaluation was performed according to the International Continence Society guideline in off-treatment condition (Sakakibara et al., 2016).

All patients were monitored with an ambulatory BP monitor (model 90207, Spacelabs Medical, London); BP and heart rate (HR) measurements were obtained every 15 minutes over a 24-hour time period; patients were instructed to record, in a journal, the time of the following daily events: sleep and wake times, meal times, and any symptoms. "Daytime" BP values were defined as those

recorded between 6:00 a.m. and 10:00 p.m., while “night-time” values were those recorded between 10:00 p.m. and 6:00 a.m. The nocturnal fall in BP was calculated as follows: daytime mean BP minus night-time mean BP/daytime BP. Reversal of the circadian pattern (i.e., “non-dipper” pattern) was defined as a night-time BP reduction of less than 10% of the day-time blood pressure reading.

Postprandial hypotension (PPH) was defined as a systolic BP decrease of 20 mmHg within 75 minutes of eating meals (O’Mara et al., 2002). Postprandial changes in systolic BP (delta SBP) were calculated by subtracting the mean SBP within the 75 minutes following the meal from the mean SBP within the 75 minutes preceding the meal; this was done after the three main meals. PPH was defined by a delta SBP > or = 20 mm Hg (at least one episode).

Moreover, in each patient an active lying-to-standing test was performed while monitoring continuous beat-to-beat BP non-invasively (Finapres, Ohmeda, Englewood, USA) (Freeman et al., 2011). The measurements were performed in the morning – suspending BP

monitoring – between 8.00 a.m. and 1.00 p.m., in a room at controlled temperature (23°C). After instrument set-up and familiarisation with the apparatus, the subjects lay in the supine position for ten minutes, followed by five minutes of active, unaided, standing. OH was defined as a decrease of at least 20 mmHg in systolic BP recorded after three minutes of standing (Wieling et al., 2007).

Statistics: the results are expressed as mean ± SD. The significance of differences in BP and HR values recorded during the different time periods into which ABPM (ambulatory BP monitoring) was divided was compared between the two groups of patients by means of unpaired t-test. A significance level of P ≤ 0.05 was selected.

**Results**

No significant differences were detected between the two groups (HR and NR) in 24-hour systolic and diastolic BP, daytime and night-time HR, or daytime and

Table 1 - Cardiological and urological parameters explored in a pool of PD patients.

Cardiological results				
24-hour BP monitoring	Hyperreflexic pts	Normoreflexic pts	t-value	p-value
	Mean ± SD	Mean ± SD		
24-h systolic BP	131.00±13.02	134.8±19.49	-0.49	0.63
24-h diastolic BP	76.89±8.40	74.30±8.55	0.66	0.52
Mean 24-h BP	95.89±9.65	95.80±11.55	0.019	0.97
Mean 24-h heart rate	64.89±6.75	71.70±8.78	-1.88	0.07
Daytime systolic BP	133.11±11.37	135.00±19.74	-0.25	0.80
Daytime diastolic BP	78.78±8.47	76.30±9.72	0.59	0.56
Mean daytime BP	97.56±9.30	97.00±12.58	0.11	0.92
Mean daytime heart rate	67.89±7.47	75.50±9.56	-1.92	0.07
Night-time systolic BP	126.11±18.19	133.50±24.59	-0.73	0.47
Night-time diastolic BP	73.33±10.05	69.50±9.40	0.85	0.40
Mean night-time BP	92.22±12.61	92.80±14.64	-0.09	0.92
Mean night-time heart rate	58.33±6.28	64.80±7.05	-2.10	0.05*
Urological results				
Urodynamic variables	Hyperreflexic PD pts	Normoreflexic PD pts		
First sensation (ml) volume	131.3±36	210.8±38.4		
DNOC threshold (ml) volume	68.8±26	49.6±40.0		
Bladder control (ml) volume	245.40	410.10±18.4		
Residual urine (ml) volume	5.0±5.0	18.8±17.4		
DNOC amplitude (cmH <sub>2</sub> O) pressure	37.5±13.4	31.6±11.4		
Pdet@Qmax (cmH <sub>2</sub> O) pressure	24.1±7.7	29.0±6.2		
Max (ml/s) flow	13.6±3.3	12.6±1.6		

Abbreviations: BP=blood pressure; pts=patients; DNOC threshold/amplitude=neurogenic detrusor contraction threshold/amplitude; Pdet@Qmax=detrusor pressure at maximum flow

night-time BP (Table I). Fifteen patients (7 HR and 8 NR), representing 53.6% of the overall population, showed a non-dipping BP pattern. Orthostatic hypotension was found only in six patients (21.4%), three in the HR and three in the NR groups, while PPH was observed in seven patients (25%), 4 HR and 3 NR. All but one of the patients with PPH also had OH.

## Discussion

The main finding of this study is that urological and cardiovascular impairments in PD are discrete entities, although they may coexist in individual patients. Neuroendocrine mechanisms are the major determinants of the normal 24-h BP pattern. At central level, integration of the main factors driving this temporal variability is mediated by circadian rhythms of monoaminergic systems in combination with those of the hypothalamic-pituitary-adrenal axis, the hypothalamic-pituitary-thyroid, opioid, renin-angiotensin-aldosterone and endothelial systems, and specific vasoactive peptides (Fabbian et al., 2013). Our study confirms that PD patients present an abnormal circadian loss of nocturnal BP decrease (i.e., reverse dipping), and that those with a non-dipper pattern on 24-h ABPM exhibit a higher prevalence of OH (Sommer et al., 2011; Milazzo et al., 2018). However, the existence of a direct link between the non-dipper pattern and OH is still debated (Lanthier et al., 2011; Berganzo et al., 2013), also because a non-dipper BP pattern does not accompany the early stages of PD. The circadian pattern of BP seems to be present even in the early stages of the disease when OH is not present.

Postprandial hypotension was more frequent in patients showing OH, suggesting an underlying common dysautonomic mechanism. Food ingestion may cause a substantial fall in BP. This may occur within 10 to 15 minutes of eating meals, and reaches a nadir within about 60 minutes. It has been reported that this fall in BP is not accompanied by changes in blood flow in the forearm and skin vasculature, indicating that appropriate haemodynamic adjustments do not occur in response to falls in BP, likely because of a lack of reflex sympathetic activation (Goldstein et al., 2014).

Thus, in PD, OH and PPH both seem to be related to an impairment of sympathetic activation at the level of the peripheral vascular bed (Mathias et al., 1991), although this hypothesis was not directly investigated as part of our study.

On the basis of the observed results, it is plausible to hypothesize that bladder dysfunction and cardiovascular dysautonomia in PD patients may be due to partially different mechanisms. Autopsy studies in fact demonstrated that OH in Lewy Body disease may be primarily due to involvement of sympathetic ganglion neurons (Benarroch et al., 2005), while urological disorders may be more likely related to insufficient activation of D1 and/or coexisting activation of D1 and D2 receptors at central level, possibly located in the insula or prefrontal cortex where these receptors are largely found (Michels et al., 2015).

Limitations of the study: the main limitation is the relatively small sample size. Hence, this investigation should be regarded as a proof-of-concept study and its results cannot be generalized. However, the consistency

of the results makes our hypothesis tenable. A second limitation of our study is the lack of parasympathetic testing, which precludes any comment on the role of this branch of the autonomic nervous system in the observed results.

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