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Continuous non-invasive monitoring to detect covert autonomic dysfunction in Parkinson's disease

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ABSTRACT

Background: Lightheadedness on standing is a disabling symptom in Parkinson's disease associated with orthostatic hypotension and is thought to represent cardiovascular autonomic dysfunction. Traditional orthostatic blood pressures are normal in some patients with lightheadedness and other measures of cardiovascular dysautonomia can be insensitive. In this study, we used continuous non-invasive arterial pressure monitoring to measure beat-to-beat changes in blood pressure and heart rate on standing and during Valsalva as a potential marker of autonomic dysfunction.

Methods: Subjects had a diagnosis of Parkinson's disease with or without documented orthostatic hypotension. Each participant underwent traditional measurement of orthostatic blood pressure and heart rate as well as measurement of beat-to-beat blood pressure and heart rate using continuous non-invasive arterial pressure monitoring during Valsalva maneuver and in response to standing. Orthostatic change in blood pressure and heart rate, and frequencies of normal and abnormal blood pressure responses to Valsalva maneuver were analyzed.

Results: In subjects without documented orthostatic hypotension, there was a higher proportion of abnormal blood pressure responses to Valsalva in subjects with symptoms of lightheadedness or dizziness upon standing compared to those without symptoms ($p = 0.03$). Additionally, the proportion of abnormal blood pressure responses during Valsalva observed in symptomatic subjects without orthostatic hypotension was indistinguishable from those with documented orthostatic hypotension ($p = 0.7$).

Conclusions: Our findings suggest that continuous non-invasive arterial pressure monitoring may be more sensitive than traditional measurement of orthostatic blood pressure to detect subtle cardiac dysautonomia in Parkinson's disease and helpful in the diagnosis of unexplained lightheadedness.

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1. Introduction

Autonomic symptoms, including cardiovascular, gastrointestinal, urinary, and sexual symptoms, are commonly experienced by patients with PD [1]. Subtle dysautonomia may be an early unrecognized feature of PD that persists throughout the disease course and, therefore, is also of interest as a treatment-independent biomarker of disease progression. Orthostatic hypotension (OH), defined as a fall of >20 mmHg systolic blood pressure (SBP) or >10 mmHg diastolic blood pressure (DBP) within 3 min of standing [2], is a common autonomic non-motor symptom which may be exacerbated by the medications that treat PD [3]. Dysautonomia can cause cerebral hypoperfusion resulting in symptoms that may include dizziness, faintness, seeing black spots, and transient loss of consciousness [4]. OH has been associated with increased mortality in elderly men [5] as well as poor motor function [6], lower quality of life [7] and decreased survival in PD [8]. OH in PD is thought to represent cardiovascular autonomic dysfunction caused by a combination of cardiac and extracardiac noradrenergic denervation and failure of the arterial baroreflex [9]. Although it has long been believed to be present only late in the course of the disease [10], OH has more recently been shown to occur in early PD [11], and may even be present prior to onset of motor symptoms [12] as cardiac

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denervation has been detected by cardiac neuroimaging such as MIBG scintigraphy in pre-motor patients [13]. PD patients without OH or symptoms of OH have changes in autonomic response to standing such as blunted HR response, lower plasma norepinephrine, and decreased ability to modulate sympathetic efferent response [14].

Current methods of measuring cardiovascular dysautonomia can be problematic. Change in blood pressure from supine or sitting to standing can easily be measured at the bedside, but is less sensitive than using passive tilting [15]. However, passive tilting requires use of a tilt table in a specialized setting. Twenty-four hour ambulatory blood pressure monitoring is time-consuming and requires resources not readily available in many areas. Cardiac sympathetic imaging modalities using single photon emission computed tomography (SPECT) or positron emission tomography (PET) scanning can detect decreased cardiac uptake of radiolabled substrates such as [1–3] I-metaiodobenzylguanidine and 6-[18F] flurodopamine indicating loss of sympathetic innervation [11]. However, these tests require specialized machinery and injection of radiolabeled substrates. A reliable, inexpensive, non-invasive tool to measure cardiovascular dysautonomia represents an unmet need in PD research and therapy.

Continuous non-invasive arterial pressure (CNAP) monitors allow measurement of beat-to-beat changes in blood pressure and heart rate using the volume clamp method to translate blood flow in the finger arteries to arterial pressure [16]. This calculation of beat-to-beat systolic, diastolic, and mean blood pressure provides a real-time arterial pressure waveform without the placement of an invasive arterial line. One such device is the CNAP® Monitor 500 (CNSystems Medizintechnik AG, Graz, Austria (http://www.cnsystems.at/en/products/cnap-monitor-500).

The prevalence of objectively measured OH in PD has recently been estimated at 30% [17]. However, self-reported lightheadedness on standing was described in 56% of PD patients in one study [18], and low concordance has been reported between the presence of OH and subjective orthostatic symptoms [19]. Clinically, it is common for PD patients who complain of symptoms of dizziness with positional changes to have normal measured orthostatic vital signs. Therefore, traditional measurements of OH may lack sensitivity and specificity to detect clinically relevant autonomic dysfunction in PD. Blood pressure response to the Valsalva maneuver can be used to detect cardiac autonomic dysfunction [20], and CNAP has been shown to be reliable in detecting these changes [21]. In this study we aimed to evaluate whether CNAP can be used to detect cardiac autonomic dysfunction in those patients with orthostatic symptoms in the absence of OH assessed by traditional methods.

2. Methods

2.1. Subjects

Participants were recruited from the Philadelphia Veteran's Affairs Medical Center (PVAMC) Parkinson's Disease Research, Education, and Clinical Center (PADRECC). Subjects were age 18 years or older and had a clinical diagnosis of possible or probable Parkinson's disease according to the Gelb [22] criteria. Exclusion criteria included diagnosis of other degenerative parkinsonian syndromes, inability to stand independently and remain standing for 5 min, history of pacemaker placement, and cognitive impairment that was significant enough to affect their ability to provide informed consent or to reliably report orthostatic symptoms. Two subjects with OH were being treated with both fludrocortisone and midodrine. The protocol was approved by the Philadelphia VA Medical Center's Institutional Review Board, and each subject gave written informed consent prior to participation.

2.2. Procedures and data acquisition

Basic demographic data was collected from the medical record of each participant. For those participants on dopaminergic medications, a levodopa equivalent daily dose (LEDD) was calculated [23]. Participants were assessed on their normal medication regimen and were not withdrawn from dopaminergic therapy. Subjects were determined to be symptomatic by asking whether they experience symptoms of lightheadedness or dizziness when going from sitting or lying to standing. Traditional measurement of orthostatic blood pressure and heart rate was determined by measuring BP and HR change with a traditional blood pressure cuff within 3 min of standing from a sitting position. Beat-to-beat blood pressure and heart rate using CNAP during Valsalva maneuver and in response to standing for 3 min were also measured. CNAP was used as recommended by the manufacturer owners' manual. An appropriately sized finger cuff was applied to the index and middle fingers and the blood pressure cuff was applied to the upper arm. The Valsalva maneuver was performed by instructing subjects to bear down as if having a bowel movement while sitting. Study staff assessed success of the Valsalva by examining the CNAP output and observing subject effort during performance of the maneuver. Two subjects were eliminated from the analysis because of insufficient Valsalva.

2.3. Data analysis

Participants were classified into 3 groups for analysis: those with previously documented OH (with or without symptoms), those without measurable OH and without symptoms on position change, and those without measurable OH but with symptoms on position change (referred to hereafter as orthostatic intolerance).

In normal individuals performing the Valsalva maneuver, heart rate increases throughout phase II and blood pressure increases above baseline during the late portion of phase II (straining phase), blood pressure decreases in phase III, and blood pressure again increases and "overshoots" the baseline while heart rate decreases rapidly to baseline in phase IV (release phase). In individuals with autonomic failure, there is an exaggerated fall of blood pressure in early phase II, lack of increase in blood pressure in late phase II, attenuated increase in heart rate throughout phase II, and absence of blood pressure overshoot and compensatory drop in heart rate in phase IV [11,24]. In accordance with prior analysis performed by Goldstein and Tack [21], the response of beat-to-beat blood pressure during Valsalva maneuver was considered to be normal if the minimum value for mean arterial pressure (MAP) occurred approximately in the middle of phase II and increased by the end of phase II, and if the SBP increased progressively to a value exceeding the baseline during phase IV. If all 3 criteria were met, "Total BP response" (Table 3) was considered normal. If 1 or more were abnormal, "Total BP response" was abnormal [21]. The response of heart rate was considered normal if it increased during phase II and decreased to baseline in phase IV. All other responses were considered abnormal. The investigator was blinded to group designation at the time of this analysis. Numerical data with beat-to-beat BP and HR recordings that were time-registered with the CNAP curves were used to analyze changes in BP and HR.

Demographic and disease characteristics in addition to resting SBP, DBP, MAP, heart rate, orthostatic change in blood pressure and heart rate, and frequencies of normal and abnormal blood pressure responses to Valsalva maneuver were analyzed for significant differences between groups using ANOVA for continuous data or 2×3 χ^2 analysis for dichotomous data. Nonparametric tests were used for data that were not normally distributed. All statistical tests were two-sided.

3. Results

A total of 52 subjects aged 54–87 were enrolled in the study. Four subjects were excluded from the analysis because the blood pressure waveforms could not be interpreted due to excessive artifact (2 subjects) or insufficient Valsalva (2 subjects). Subject demographics and clinical characteristics are presented in Table 1. All subjects were male. There were no statistically significant differences between groups in age, race, disease duration, Hoehn and Yahr scale, levodopa equivalent dosage (LEDD), baseline blood pressures, or heart rate (Table 1).

3.1. Traditional blood pressure and CNAP responses to standing

There were 16 participants in the OH group, 11 of whom were symptomatic. Mean orthostatic change in SBP by traditional measurement was greater in subjects with OH than in those without OH, either with ($p = 0.005$) or without ($p = 0.001$) symptomatic lightheadedness (Table 2). There was no significant difference in orthostatic SBP change between the two symptomatic and asymptomatic groups without OH ($p = 1.00$). Mean change in DBP ($p = 0.06$) and heart rate ($p = 0.3$) were not significantly different between groups (Table 2). There was no correlation between the LEDD and traditional orthostatic blood pressure response to standing ($p = 0.47$). Mean orthostatic change in SBP by CNAP

Table 1
Subject demographics and clinical characteristics.

	No OH		OH	P value
	Symptomatic N = 16	Non-symptomatic N = 15		
Age, year, mean (SD)	69.7 (7.7)	69.5 (7.1)	71.1 (7.0)	0.80
Race, %, White	93.8	80	88	0.60
Sex, %, Male	100	100	100	1.00
Disease Duration, year, mean (SD)	5.2 (4.3)	6.5 (5.5)	6.6 (7.2)	0.76
Hoehn & Yahr, mean (SD)	2.4 (0.4)	2.2 (0.4)	2.2 (0.6)	0.62
Levodopa equivalent dosage (mg)	512 (479)	792 (560)	770 (569)	0.21
Systolic Blood Pressure, mmHg, mean (SD)	130 (18)	135 (23)	122 (20)	0.25
Diastolic Blood pressure, mmHg, mean (SD)	79 (16)	77 (11)	75 (12)	0.61
Heart Rate, beats per minute, mean (SD)	77 (12)	79 (13)	83 (18)	0.59

SD: standard deviation.

Table 2
Orthostatic blood pressure, and Valsalva response measured using traditional methods or CNAP.

		NO OH		OH	P
		Symptomatic	Non-symptomatic		
Traditional measurement	Orthostatic change in SBP, mmHg, mean (SD)	1.1 (11.9)	3.8 (8.4)	−14.7[a] (16.4)	0.001
	Orthostatic change in DBP, mmHg, mean (SD)	5.6 (13.5)	4.5 (5.7)	−3.3 (10.7)	0.06
	Orthostatic change in HR, beats per min, mean (SD)	4.0 (3.5)	5.8 (5.6)	6.5 (16.4)	0.30
CNAP measurement	Orthostatic change in SBP, mmHg, mean (SD)	5.6 (12.8)	8.2 (12.1)	−6.0 (15.2)	0.02
	Orthostatic change in DBP, mmHg, mean (SD)	3.9 (9)	2.8 (7.8)	−1.1 (10.5)	0.28
	Orthostatic change in HR, beats per min, mean (SD)	5.8 (12.3)	9.2 (11.2)	4.1 (8.3)	0.41
Valsalva Maneuver during CNAP measurement	Change in SBP, mmHg, mean (SD)	24.2 (27.8)	9.2 (35.0)	28.6 (36.34)	0.27
	Change in DBP, mmHg, mean (SD)	25.0 (17.4)	19.8 (21.9)	19.7 (18.5)	0.70
	Change in HR, beats per min, mean (SD)	39.8 (43.8)	47.0 (51.0)	34.6 (46.7)	0.17
	Change in SBP Phase II	26.0 (15.5)	28.9 (17.2)	44.7 (19.6)	0.009
	Change in SBP Phase IV	21.3 (10.6)	27.8 (28.0)	39.3 (25.5)	0.08
	BP recovery time (s)	20.8 (35.5)	15.3 (28.0)	17.1 (18.3)	0.86

SBP = systolic blood pressure, DBP = diastolic blood pressure, HR = heart rate, SD = standard deviation.
[a] An individual with OH may have a drop in either SBP or DBP. Therefore, the average drop in SBP for the entire group may not be greater than 20 mmHg SBP, which explains the observed mean decrease in SBP of only 14 mmHg in the OH group.

measurements between groups was significant (p = 0.02). There was no significant difference in mean change in DBP (p = 0.28) or HR (p = 0.41) (Table 2). Furthermore, there was no significant change in blood pressure and heart rate over 3 min with CNAP monitoring between groups (Table e-1). Comparison between the traditional method of orthostatic measurement of cuff BP at baseline and 3 min to CNAP values at baseline and 3 min revealed a similar proportion of subjects who were orthostatic among all subjects (18.9% vs 11.7%, p = 0.421).

3.2. Continuous blood pressure responses to valsalva maneuver

Sample blood pressure waveforms during Valsalva maneuver are illustrated in Fig. 1. The waveform in the subject without OH and without symptoms (Fig. 1A) demonstrates a normal response. Phase II is characterized by initial decrease in MAP which reaches its nadir by the middle of Phase II followed by a gradual increase throughout the end of Phase II. Phase IV is characterized by an overshoot of the SBP above baseline. The waveform in the subject with documented OH (Fig. 1B) demonstrates an abnormal response. The MAP does not reach its nadir until the end of Phase II and the SBP overshoot is missing in Phase IV. The waveform in the subject without OH but with orthostatic symptoms (Fig. 1C) demonstrates the same abnormalities as those observed in the subject with OH.

A summary of blood pressure responses to the Valsalva maneuver are presented in Table 3. Among subjects without OH, there was a higher proportion (75% vs 33%) of abnormal blood pressure responses in subjects with symptoms upon standing compared to those without symptoms (p = 0.03). Additionally, the proportion of abnormal blood pressure responses in those without OH but with orthostatic symptoms was indistinguishable from those with OH (p = 0.7) (Table 3). There was no difference in HR response between

Table 3
Blood pressure response to Valsalva maneuver.

	NO OH				OH		P	P	P
	Symptomatic		Non-symptomatic				All groups	Symptomatic vs non-symptomatic	Symptomatic vs OH
	Normal[a]	Abnormal	Normal	Abnormal	Normal	Abnormal			
Total BP response[b], n	4	12	10	5	6	10	0.06	0.03	0.7
MAP minimum mid-phase II, n	10	6	12	3	8	8	0.22	0.43	0.72
MAP increase end phase II, n	9	7	11	4	9	7	0.53	0.46	1.0
SBP overshoot phase IV, n	10	6	14	1	6	9	0.08	0.08	1.0

BP = blood pressure, MAP = mean arterial pressure, SBP = systolic blood pressure.
[a] A normal blood pressure response during Valsalva maneuver occurs if the minimum value for MAP occurred in the middle of phase II (strain phase) and increased by the end of phase II, and if the SBP increased progressively to a value exceeding the baseline during phase IV (release phase).
[b] Total BP response includes the 3 phases of Valsalva: MAP minimum by mid-phase II, MAP increasing by the end of phase II, and SBP overshoot in phase IV. If all 3 were normal, Total BP response was normal. If 1 or more were abnormal, Total BP response was abnormal.

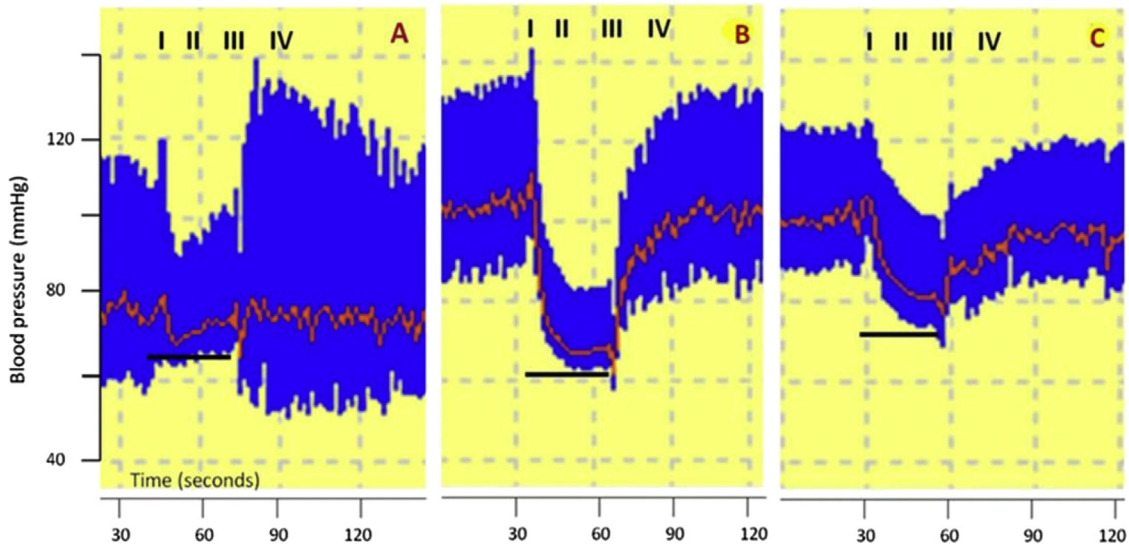

Fig. 1. Blood pressure response to Valsalva maneuver demonstrating a normal response in a subject without orthostatic hypotension and without symptoms (A), an abnormal response in a subject with orthostatic hypotension (B), and an abnormal response in a subject without orthostatic hypotension but with symptoms of lightheadedness or dizziness upon standing (C). Upper limit of the curve represents diastolic blood pressure, and the red line representation mean arterial pressure. Black bar represents the valsalva maneuver. Phases I–IV are labeled. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

those with a normal BP response to Valsalva [M:36.1(SD:43.5)] and those with an abnormal response [M:33.4(SD:50.1)] ($p = 0.85$). When excluding subjects treated with fludrocortisone and/or midodrine, the proportion of abnormal blood pressure responses in those without OH but with symptoms remained indistinguishable from those with OH ($p = 0.44$).

There was no statistically significant change in blood pressure and heart rate between groups during the Valsalva maneuver (Table 2) however, the size of SBP change in phase II between those with orthostatic intolerance, OH, and controls demonstrated a significant difference ($p = 0.009$) (Table 2) and there was a trend toward group differences in SBP change in phase IV ($p = 0.08$) (Table 2). A significant difference in blood pressure recovery time (time from bottom of phase III to return to baseline SBP) was not found between groups ($p = 0.86$) (Table 2). Even though subjects remained on dopaminergic therapy, there was no difference between mean LEDD of those with normal Valsalva response (M: 703) and those with abnormal Valsalva response (M:679) ($p = 0.88$).

4. Discussion

Cardiac dysautonomia causing orthostatic hypotension or other symptoms can have a dramatic impact on patients with PD [5,6]. Dopaminergic medications, the mainstay of symptomatic treatment in PD, can exacerbate OH, which can complicate management of motor features. A recent report describes that neurocirculatory abnormalities, even in early PD, are associated with white matter disease and cognitive dysfunction [25]. Additionally, lightheadedness in the absence of documented OH is common in PD and may reflect subtle dysautonomia. Traditional clinical measurements of OH at 3 min may miss some cases of delayed orthostatic hypotension due to early adrenergic failure as seen in PD patient without symptoms of OH [14]. Other more sensitive measures of autonomic function are often invasive, costly, and cumbersome. Therefore, a simple, sensitive, non-invasive method to measure autonomic dysfunction in PD is of substantial interest. In this study, we examined continuous non-invasive blood pressure monitoring in response to standing and Valsalva in association with orthostatic symptoms as a measure of dysautonomia in PD.

The usefulness of non-invasive beat-to-beat monitoring to characterize changes in heart rate, blood pressure, and Valsalva to detect autonomic dysfunction in PD has been established [26]. Blood pressure responses to Valsalva may act as a probe of autonomic function and abnormal Phase II and Phase IV blood pressure response have been reported in PD patients with OH and in a proportion but not all of PD patients without OH [27]. Furthermore, measures such as blood pressure recovery time following termination of Valsalva add to the utility of this maneuver by quantitatively detecting the degree of adrenergic failure [28,29]. Prior studies have demonstrated the ability of CNAP to detect these abnormal blood pressure responses in subjects with chronic primary autonomic failure, including those with PD-associated dysautonomia [20,21]. Our study confirms abnormal responses to the Valsalva maneuver are more common in PD patients with OH but also found an abnormal Valsalva response in a portion of those without OH but with orthostatic symptomology, which has not been previously studied. We further observed that the proportion of abnormal responses in subjects with orthostatic intolerance was significantly greater than in asymptomatic subjects and similar to subjects with documented OH, suggesting that a baroreflex abnormality may underlie their symptoms. Patients with orthostatic intolerance can be clinically challenging when it is unclear whether orthostatic symptoms reflect dysautonomia or other etiologies such as vertigo or sensory ataxia secondary to a peripheral neuropathy presenting as a sensation of dizziness. While not 100% sensitive, our results suggest that this method allows for the detection of autonomic dysfunction in many individuals that were not identified using traditional orthostatic vitals. Whether therapies to stabilize blood pressure in these patients might be effective in alleviating symptoms, remains to be seen.

Our findings must be interpreted in the context of several limitations. All subjects in our study were male which may limit generalizability of the findings. This pilot study was not powered to evaluate differences among subgroups, i.e. based on disease or treatment characteristics. While we monitored subject effort and success with Valsalva via examination of CNAP output and eliminated subjects with poor Valsalva from the analysis, we did not use a formal validation technique (i.e. having subjects blow into a sphygmomanometer). Inadequate validation of the Valsalva could result in an overall increase in the number of abnormal responses, but this

would not likely be differentially distributed among the groups. Additionally, the Valsalva maneuver was performed with participants sitting rather than lying supine which some studies [30,31] have suggested can diminish the baroreceptor response. Medications for the treatment of OH were not withdrawn due to the risk of worsening orthostatic hypotension, although our analysis suggests that this had no effect on the major findings of the study. Dopaminergic therapy was also not withheld during this study, in order to recapitulate conditions under which symptoms were normally experienced, but there was no relationship between LEDD and blood pressure response during standing or Valsalva. While asking participants if they experience lightheadedness on standing at the time orthostatic vitals are taken allows for the detection of a greater number of people with orthostatic symptoms in the setting of normal orthostatic vitals, it may also miss some patients that are asymptomatic at the time of presentation and does not allow for quantitation, as could be accomplished using other validated scales.

Finally, while we found abnormal blood pressure responses to Valsalva were significantly more common in symptomatic subjects without OH, we cannot be certain that the orthostatic symptoms were caused by the same mechanisms underlying the observed abnormalities. Further studies are needed to confirm this relationship, possibly expanding the role of CNAP monitoring as an non-invasive method to evaluate unexplained lightheadedness.

The lack of MAP increase in late Phase II and SBP overshoot in Phase IV indicate a loss of the sympathetically-mediated vasoconstriction reflex in response to decreasing stroke volume during Phase II. In patients who demonstrate these abnormalities, even without measurable OH, vasoconstricting medications, such as the alpha$_1$-agonist midodrine, could potentially be effective in treating the orthostatic symptoms. Further studies are needed to determine the effect of treatment on blood pressure responses to Valsalva maneuver measured by CNAP as well as on orthostatic symptoms in those patients with evidence of cardiac dysautonomia by CNAP assessment without clinically detectable OH.

Relevant conflicts of interest/financial disclosures

Nothing to report.

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Author roles

Amy Hellman contributed to the conception, organization, and execution of the research project and the design and execution of the statistical analysis. She wrote the first draft and contributed to review of the manuscript. Shital Shah contributed to execution the statistical analysis and review and critique of the manuscript. Stephanie Pawlowski contributed to organization and execution of the research project and review and critique of the statistical analysis and manuscript. John Duda and James Morley contributed to the conception and organization of the research project, design of the statistical analysis, and review and critique of the statistical analysis and manuscript.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.parkreldis.2015.04.016.

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