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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