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The footprint of orthostatic hypotension in parkinsonian syndromes

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Orthostatic hypotension (OH) is characterized by a sustained blood pressure (BP) fall within 3 minutes upon standing [1] and is associated with frequent falls, increased morbidity and mortality in the elderly population [2]. Being a common non-motor feature of parkinsonian disorders [3], OH may aggravate motor impairment and increase the risk of falls in these patients as well [4,5]. In this proof-of-concept study, we investigated the relationship between gait performance and OH in patients with Parkinson's disease (PD) and the parkinsonian variant of multiple system atrophy (MSA-P), by applying an instrumented gait analysis to a standardized walking test.

This study was approved by the local ethical committee (IRB-approval–No 0365, 344/4.25 378/5.3, 20.10.2017) and followed the principles of the Declaration of Helsinki. All participants gave written informed consent prior to participation. We performed an additional analysis of the baseline recordings of a previously published trial assessing the benefits of physiotherapy in patients with Parkinsonism (10 with probable MSA-P [6], 12 with clinically established PD [7]) recruited at the Movement Disorder Unit of the Medical University of Innsbruck [8]. For the purposes of the present study, the enrolled patients underwent oscillometric BP measurements with an arm-cuff after 5 minutes in the supine position and after 1, 3 and 5 minutes upon active standing [9]. OH and supine hypertension were diagnosed according to the current consensus criteria [1,10]. Afterwards, an instrumented gait analysis consisting of four consecutive tasks was performed (Fig. 1). The 2 minutes walking test was performed between minute 3 and 5 of testing. All investigations took place between 10 a.m. and 1 p.m., on regular medication, in a stable ON condition without motor fluctuations.

The distribution of quantitative variables was assessed with the Shapiro-Wilk test. Differences in qualitative variables were calculated using the Chi-square or Fisher's exact test. For continuous variables, the Mann-Whitney *U* test or *t*-test were used, depending on the distribution of the data. The Benjamini-Hochberg correction was applied to multiple testing. We used a Pearson's partial correlation analysis adjusted for the *short-walk* item of the Orthostatic Hypotension Questionnaire (indicating the degree of orthostatic intolerance during short walks) and the part III of the Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) to investigate the relationship between gait parameters and BP changes upon standing in the PD and in the MSA group separately. The statistical analysis was performed using SPSS version 25. Two-sided p-values < 0.05 were considered statistically significant.

Supplementary Table 1 (S1) shows the clinical demographic characteristics of the study population, the results of the standing test and of the instrumented gait analysis. PD and MSA-P patients were similar with respect to gender distribution, disease duration, L-dopa equivalent daily dose [11], Hoehn & Yahr stage, use of antihypertensives, cardiovascular comorbidities, presence of supine hypertension, OH and severity of orthostatic intolerance upon short walk. PD patients were significantly older, while the use of anti-hypotensive medication was more frequent in MSA-P patients. Despite not reaching statistical significance, the MDS-UPDRS motor score of MSA-P patients was twice as high compared to PD patients. PD and MSA-P patients showed no difference in spatiotemporal gait parameters after applying the Benjamini-Hochberg correction. In PD patients, we observed a moderate to strong correlation between reduced stride length during the 2 minutes walking test at self-preferred speed and lower systolic BP values after 3 and 5 minutes upon standing ($\rho = 0.840$ $P = 0.002$ and $\rho = 0.799$ $P = 0.006$, respectively), more severe systolic BP falls after 3 and 5 minutes upon standing ($\rho = 0.852$ $P = 0.002$ and $\rho = 0.826$ $P = 0.003$) and diastolic BP fall after 5 minutes upon standing ($\rho = 0.726$ $P = 0.018$). Reduced maximal toe-clearance during the 2 minutes walking test correlated with lower systolic BP values after 3 and 5 minutes upon standing in PD ($\rho = 0.720$ $P = 0.019$ and $\rho = 0.682$ $P = 0.03$), while reduced gait velocity both with lower absolute systolic BP values and more severe systolic BP falls at the 3rd minute upon standing ($\rho = 0.708$ $P = 0.022$ and $\rho = 0.919$ $P < 0.001$).

In MSA-P patients, we observed a moderate to strong correlation between lower gait velocity and lower systolic and diastolic BP values after 3 minutes upon standing ($\rho = 0.727$ $P = 0.041$ and $\rho = 0.861$ $P = 0.006$, respectively), but not between other gait and BP parameters.

Here we found that PD patients show a moderate to strong correlation of gait velocity, maximal toe-clearance and stride length during the 2 minutes walking test at self-preferred speed with orthostatic BP changes after 3–5 minutes upon standing. This suggests that OH indeed negatively impacts on gait performance in patients with PD. Interestingly, we observed that gait impairment correlated both with the amplitude of orthostatic BP fall and the absolute BP value reached

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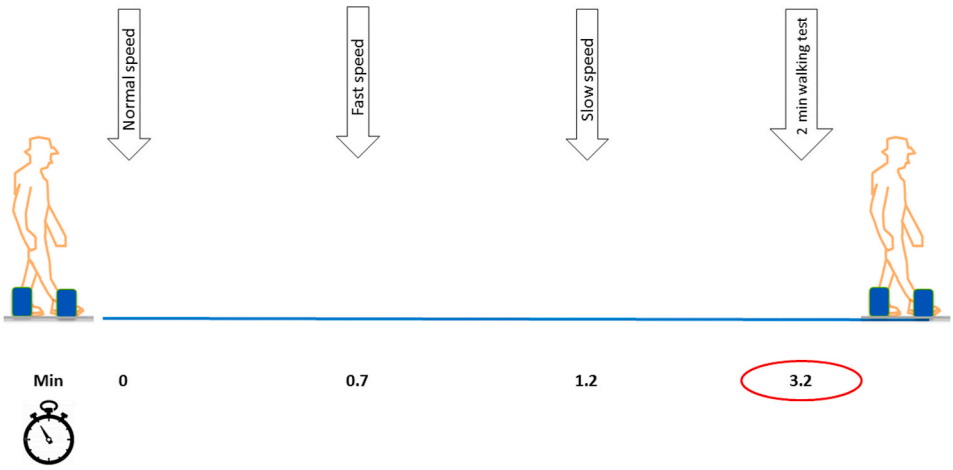

Fig. 1. Immediately after rising from a chair, patients were invited to walk back and forth a 10m-long corridor (= 20 mt) with self-selected comfortable speed first (2 × 10 m), then a self-selected fast (2 × 10 m) and slow speed (2 × 10 m). Afterwards, they were instructed to walk for 2 minutes at a comfortable speed. The gait tests were performed without interruptions. Numbers indicate the time points (in minutes) when the single segments of the gait test were performed. These were calculated by dividing the walking distance (2 × 10 m = 20 m) by the mean gait velocity during the tests (time = space/velocity).

upon standing and that systolic, rather than diastolic, BP changes may impact on gait performance.

In MSA-P, we observed only a positive correlation between gait velocity and higher systolic and diastolic BP values after 3 minutes upon standing. This suggests that in PD patients, where motor symptoms are well controlled by dopaminergic medications, OH may independently affect gait performance, while in MSA-P other factors (such as the greater motor impairment or fear of falling) may have a major impact on gait performance, masking the effect of OH. These preliminary observations should be validated with real-time BP measurements during gait analysis in the future. Portable beat-to-beat BP monitoring systems may also help clarify the effect of transient BP changes during the first minute upon standing on gait performance in parkinsonian syndromes.

Disclosure statement

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Cecilia Raccagni: Dr Raccagni reports one travel grant from MSA coalition.

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Authors roles

Cecilia Raccagni: Research project: conception, organization, execution; Statistical analysis: design, execution; Manuscript: writing of the first draft.

Victoria Sidoroff: Research project: execution; Manuscript: review and critique.

Georg Goebel: Statistical analysis: execution; Manuscript: review and critique.

Roberta Granata: Research project: execution.; Manuscript: review and critique.

Fabian Leys: Research project: execution.; Manuscript: review and critique.

Jochen Klucken: Manuscript: review and critique.

Bjoern M. Eskofier: Manuscript. review and critique.

Robert Richer: Manuscript: review and critique.

Klaus Seppi: Manuscript: review and critique.

Gregor Wenning: Research project: conception; Statistical analysis: review and critique; Manuscript: C. Review and Critique.

Alessandra Fanciulli: Research project: conception, organization. Statistical analysis: design, execution. Manuscript: review and critique.

Data availability statement

Any data not published within the article will be shared in an anonymized way upon reasonable request from any qualified investigator.

Declaration of competing interest

On behalf of all authors, the corresponding author states that there is no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.parkreldis.2020.06.029.

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