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# Influence of levodopa on orthostatic hypotension in Parkinson's Disease

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## ABSTRACT

**Aim of the study:** Orthostatic hypotension presents in all phases of Parkinson's Disease (PD) and occurs in about 80% of patients. There is some debate in the literature as to the relationship of orthostasis to the standard drug treatments. A distinct tendency towards hypotension has been found, especially for treatment with levodopa (LD). We therefore wanted to investigate the influence of LD on blood pressure response in PD patients.

**Methods:** We examined prospectively PD patients using lying-to-standing orthostatic tests (the modified Schellong test). The patients underwent measurements on two consecutive days, starting in the morning after a 12-hour period of restriction of food and medication. The second measurement ensued under the same condition of food restriction but consecutive to their usual LD dosage. Measurements were performed every minute for 10 minutes after rising. Measurements compared the maximum drop in blood pressure to the average resting blood pressure (after a 10-minute period of lying recumbent).

**Results:** We examined 99 PD patients (72 male, 27 female) with a mean age of 74 years (SD = 7.8; range 52-88). The duration of the disease (i.e. time from first diagnosis to date of examination) was on average seven years (SD = 4.4, range 0–19 years). The drop in blood pressure after orthostasis without levodopa medication reached on average 45.46 mmHg (SD = 23.76; SEM = 2.39), and the average drop after levodopa medication was 43.75 (SD = 17.88; SEM = 1.8). There was no significant statistical difference (t[98] = 0.91; p = 0.37). Subdivision into patient groups with (n = 32) or without (n = 67) antihypertensives revealed a similar result for these subgroups, i.e. no statistically significant difference in blood pressure drop in conditions with or without levodopa administration. There was no significant correlation of Hoehn & Yahr stage with drop in blood pressure.

**Conclusion:** Orthostatic hypotension frequently occurs in patients with PD, occasionally with serious consequences. LD has often been viewed as essentially causing this state. Our study did not confirm this supposition, but rather revealed merely a minor association in individual cases.

**Key words:** Parkinson's Disease, levodopa, orthostatic hypotension, lying-to-standing orthostatic test

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## Introduction

Cardiovascular symptoms present in all phases of Parkinson's Disease (PD), and thus even in *de novo* patients [1, 2]. The most frequent symptom identified is orthostatic hypotension, occurring in more than half of patients [3, 4]. A distinct fall in blood pressure is found in many PD patients with active orthostasis, and frequently becomes symptomatic. Such a pathological drop in pressure has been documented in all stages of the disease [1]. It is striking that the drop is not only distinct but that it also does not normalise within the first 10 minutes [3]. There is some debate in the literature as to the relationship of orthostasis to the severity and duration of PD. Orthostatic hypotension can present simultaneously with, or prior to, the emergence of motor symptoms [1, 5]. A recent publication demonstrated pathological hypotension in many *de novo* patients and found furthermore that there was no significant recovery over the course of the disease [1]. One explanation regularly advanced for the very frequent cardiovascular disturbances in PD entails the influence of the standard drug treatments themselves. A distinct tendency towards hypotension has been especially found for treatment with L-dopa (LD) and/or dopamine agonists [3, 6, 7]. We therefore wanted to

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investigate the influence of dopaminergic medication on blood pressure response in PD patients.

## Patients and methods

We examined prospectively PD patients (only definite idiopathic forms) using the lying-to-standing orthostatic test (the modified Schellong Test, otherwise known as the head up tilt test). All were inpatients. The patients were measured on two consecutive days. The first blood pressure measurement was carried out in the morning after 12 hours of food restriction and without medication (levodopa, dopamine agonists, and antihypertensives). The second measurement was carried out under the same conditions, but after taking the usual LD dose one hour before the examination (all other medications were administered after the second measurement). Firstly the resting blood pressure was determined after lying for 10 minutes. We measured the blood pressure every minute and the mean value was calculated from the three minute measurements at the end of the resting phase. After orthostasis, blood pressure and heart rate were measured every minute for 10 minutes. The maximum drop in systolic blood pressure to the mean at rest was statistically analysed.

Specifically, we compared the maximum drop in systolic blood pressure between treatment conditions (no LD and LD administration) employing a two-sided paired sample t-test.

To evaluate the possible influence of antihypertensive medication, we performed an additional analysis and separated patients into two groups: patients prescribed with antihypertensives and patients without. We then performed mixed analysis of variance (ANOVA) with a between-subject factor group (with or without hypertensives) and a repeated measure drug administration (with or without LD). The criterion for statistical significance was $\alpha = 0.05$. Correlations between Hoehn & Yahr stages and blood pressure drops were computed using Spearman's rho. Statistical significance was estimated with the AS89 algorithm implemented in the R software package (www.r-project.org).

## Results

99 patients were examined, comprising 72 men and 27 women, aged 52–88 years. 57 patients were in Hoehn & Yahr stage III (Hoehn & Yahr I–II: 1; II: 7; II–III: 3; III: 57; III–IV: 14; IV: 7; IV–V: 1; V: 3; stage not available: 6). The duration of illness (from first diagnosis to admission) was seven years on average (SD = 4.4, range: 0–19 years). All patients received levodopa, and 41 patients received dopamine agonists.

At the examination without LD administration before the examination, the mean blood pressure was 159/91 mmHg (SD 22.6/12.4), with a frequency of 69.1 bpm (SD = 10.6). The drop in blood pressure after orthostasis was 45.46 mmHg (SD = 23.76; SEM, standard error of the mean = 2.39).

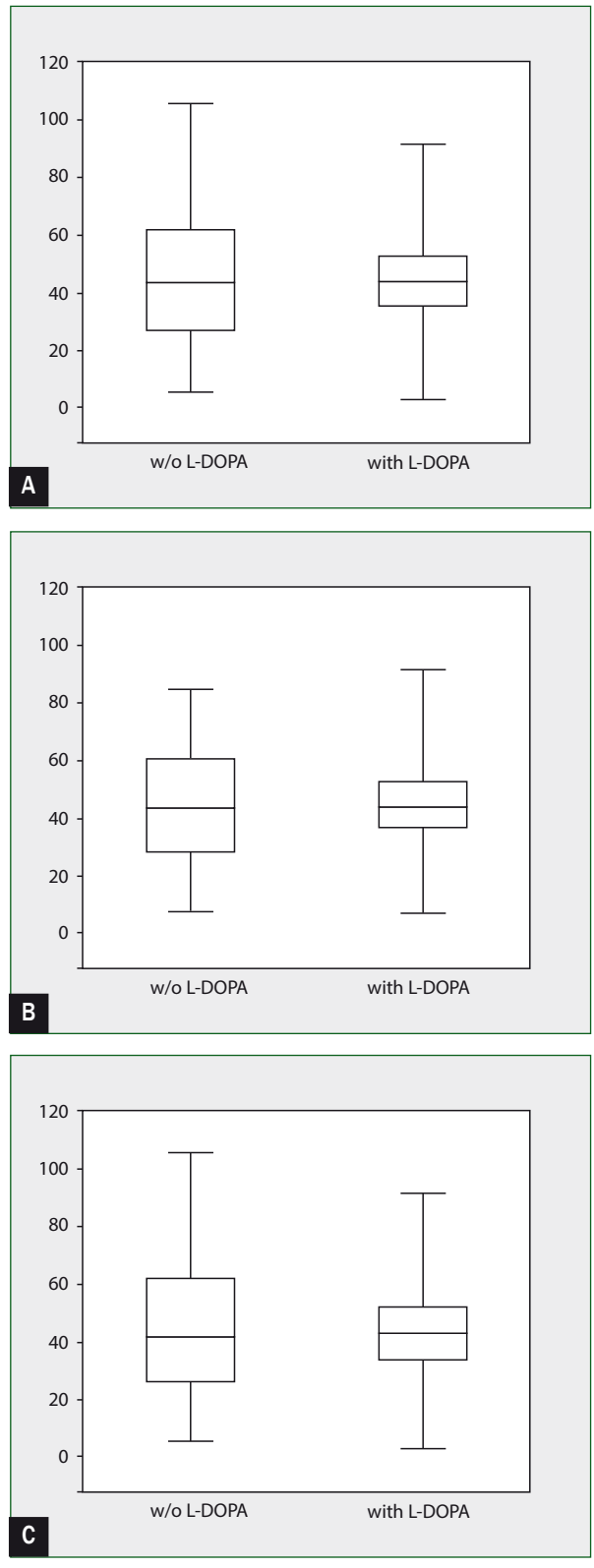


**Figure 1.** Drop in blood pressure after orthostasis, conditions without (w/o) and with L-DOPA medication depicted in box-plots. Central line indicates median, upper and lower boxes indicate 3rd and 1st quartiles, respectively. Whiskers show minimum and maximum values. 1A — all patients (N = 99); 1B — patients with antihypertensives (n = 32); 1C — patients without antihypertensives (n = 67)

When examined with regular LD administration, the blood pressure at rest was 137/81 mm Hg (SD 20/11.7) with a frequency of 68.8 bpm (SD = 11.1). The drop after orthostasis was 43.75 mmHg (SD = 17.88; SEM = 1.8). The two measurement (drop of blood pressure) series showed no statistically significant difference (t[98] = 0.91; p = 0.37).

We separated the patients into two subgroups i.e. patients with and patients without antihypertensive medication. The patients without antihypertensives (n = 67) showed, when no LD was administered, a blood pressure drop of 45.39 mmHg (SD = 25.02; SEM = 3.06). The patients with LD administration had a blood pressure drop of 43.52 mmHg (SD = 18.28; SEM = 2.23). This difference was not statistically significant (t[66] = 0.75; p = 0.46). The drop in blood pressure for patients with antihypertensives (n = 32) was, without LD, 45.63 mmHg (SD = 21.28; SEM = 3.76), and with LD 44.22 mmHg (SD = 17.30; SEM = 3.06). Again, there was no significant difference (t[31] = 0.53; p = 0.60). Nor did entering the blood pressure drop of both groups into a mixed ANOVA with the factor group (with or without antihypertensives) and the repeated measure of drug administration (with or without LD) reveal significant main effects (group: F[1.97] < 1; p = 0.99; drug administration: F[1.97] < 1; p = 0.46) nor an interaction effect (F[1.97] < 1; p = 0.99).

Correlations of Hoehn &Yahr stages with drop in blood pressure were small and statistically not significant (without levodopa: rho = -0.001, p > 0.99; with levodopa: rho = 0.089, p = 0.397).

## Discussion

In this prospective study, we investigated the influence of levodopa (LD) administration on orthostatic hypotension.

Our results do not suggest differences in blood pressure drop in the modified Schellong Test between conditions with or without LD administration. Taking into account treatment for hypertension did not change this result. We found no differential response in the groups with or without antihypertensive medication.

The cause of orthostatic hypotension (OH) is most probably multifactorial. A deficient adaptation in blood pressure occurs under strain. Frequently, blame is placed on a lack of activity, that is, insufficient circulatory training. An essential factor is also seen in the drug treatments themselves. But basically the OH in PD should be considered an intrinsic symptom of the primary disease itself [3], a symptom which is then reinforced by additional factors. The cardiovascular symptoms are most probably independent of the striatal deficiency in dopamine [8]. In PD, degeneration is of course found in the nigrostriatal system, but has also been found in the central and the peripheral autonomic nervous systems [3, 9]. The consequent influence on hormonal regulation can be viewed as an essential cause of the autonomic functional disturbances [3]. There is thus room to discuss whether damage also to the postganglionic sympathetic efferences is of significance.

As a result of the extensive degeneration in the noradrenergic system in PD patients, reduced norepinephrine concentrations can be seen in the corresponding brain regions. In the case of active orthostasis, there is a distinct reduction in the rise of serum norepinephrine [3]. It is now generally held that a systemic sympathetic denervation exists with varying degrees of severity and distribution [5].

One explanation regularly advanced for the very frequent cardiovascular disturbances in PD entails the influence of the standard drug treatments themselves. A distinct tendency towards hypotension has been especially found for treatment with LD and/or dopamine agonists [3]. This, however, disregards the observations that (1) hypotension tendencies in PD patients with orthostasis were described prior to the introduction of drug treatments, in particular LD (in the 1960s), and that (2) the same holds true for as yet untreated patients [1, 3, 10]. Furthermore, in early descriptions, in which a marked hypotensive effect of LD was described, there was either no additional application of a decarboxylase inhibitor, or else a very high dose was administered (up to a gram or even more).

Based on current information, the hypotonic effect manifests itself especially in the initial phase of LD therapy [3]. After longer treatment, blood pressure values regress to previous levels [3]. This is also confirmed by the data from our study. There was a significant drop in blood pressure in both groups, but this did not differ.

LD and all other Parkinson's medications can affect blood pressure and blood pressure regulation. In individual cases, this effect can also be relevant. However, we assume that LD is neither the trigger nor a decisive factor in orthostatic hypotension in PD patients.

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