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ORIGINAL ARTICLE

Levodopa-induced orthostatic hypotension in parkinsonism: A red flag of autonomic failure

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Abstract

Background and purpose: Levodopa (LD) is the main treatment for parkinsonism, but its use may be limited by a potential hypotensive effect.

Methods: We evaluated the cardiovascular effect of LD performing head-up tilt test (HUTT) before and 60 min after 100/25 mg LD/dopa-decarboxylase inhibitor (pre-LD vs. post-LD HUTT) in 164 patients with parkinsonism on chronic LD treatment. Features predictive of LD-induced orthostatic hypotension (OH) were assessed by logistic regression analysis.

Results: Basal supine blood pressure (BP) and heart rate (HR) decreased after LD. During post-LD HUTT, BP drop and HR increase were significantly greater than at pre-LD HUTT. Thirty-eight percent of patients had OH at post-LD HUTT compared to 22% of patients presenting OH at pre-LD HUTT ($p < 0.001$). Risk factors for LD-induced/worsened OH were pre-LD OH (odds ratio [OR] = 36, 95% confidence interval [CI] = 10–131), absence of overshoot at Valsalva maneuver (OR = 9, 95% CI = 4–20), and pathological Valsalva ratio (OR = 6, 95% CI = 2–15).

Conclusions: LD administration caused/worsened hypotension in both supine and orthostatic conditions. Patients with cardiovascular autonomic failure had a higher risk of developing LD-induced OH. In clinical practice, LD-induced OH could represent a red flag for cardiovascular autonomic failure.

KEYWORDS
atypical parkinsonism, autonomic dysfunction, cardiovascular reflex tests, dopaminergic drug, Parkinson disease

INTRODUCTION

Levodopa (LD) is the mainstay of treatment for parkinsonism [1, 2]; nonetheless, the improvement of motor symptoms can be accompanied by the occurrence or intensification of nonmotor symptoms, including orthostatic hypotension (OH) [1].

OH in patients with parkinsonism is frequently related to cardiovascular autonomic failure, but secondary causes could also contribute [3, 4]. Among the latter, LD administration could induce a hypotensive effect, with a decrease in blood pressure (BP) during supine position and orthostatic stress [5–11]. A recent review failed to show a conclusive relationship between LD and OH; however, in the selected studies OH was roughly recorded as an adverse event or derived from measurement of vital signs, without further specification [5].

Peripherally, LD causes vasodilatation in the renal vascular beds and inhibits the release of catecholamines from the postganglionic sympathetic nerves, lowering sympathetic activity on vascular

smooth muscle and peripheral vascular resistance [12–14]. A central hypotensive and bradycardic effect in brainstem region has also been reported in animals [15, 16].

The true mechanism leading to LD hypotensive effect in patients with parkinsonism remains controversial, and its predisposing factors are unknown, although in clinical practice this effect is well known and may cause disabling symptoms, limiting the treatment of parkinsonian features.

In the present study, we aim to evaluate whether the intake of LD induces or worsens OH [17] in patients with parkinsonism by performing the head-up tilt test (HUTT) twice, before and 60 min after the administration of a fixed oral dose of LD/dopa decarboxylase inhibitor (DCI). We also assessed the possible factors associated with the hypotensive effect, especially the presence of an underlying dysfunction of the autonomic nervous system.

METHODS AND MATERIALS

Study population

We recruited all patients with neurodegenerative parkinsonism chronically treated with LD/DCI (at least 6 months) from the prospective BoProPark cohort [18] and with the following inclusion criteria: absence of metabolic (i.e., complicated diabetes) and cardiovascular diseases that could have affected study results, a regular LD uptake and pharmacokinetics verified through a subacute challenge kinetic–dynamic test with an oral dose of 100/25 mg of LD/DCI (benserazide or carbidopa) [19], and written informed consent to participate in the study. The study was approved by the ethics committee of the Local Health Authority of Bologna (reference number 09070) and performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and subsequent amendments.

Study procedures

All patients underwent in two consecutive morning sessions:

(i) Cardiovascular reflex tests (CRTs): Valsalva maneuver (VM; forced expiratory pressure of 40 mmHg for 15 s), deep breathing (DB; 6 breaths/min), cold face (CF; cold stimulus on forehead for 1 min), and sustained handgrip tests (HG; 1/3 of maximal effort for 5 min) [20, 21]; and
(ii) HUTT (10 min at 65°) before (pre-LD HUTT) and 60 min after (post-LD HUTT) an oral dose of 100/25 mg LD/DCI.

The first 30 patients were reassessed on the third subsequent morning by means of two HUTTs (first HUTT and repeated HUTT [r-HUTT]) performed at 60-min intervals without LD administration to evaluate the effect of repeated HUTTs on cardiovascular parameters.

All tests were performed in the morning in a quiet, temperature-controlled clinical investigation room (23 ± 1°C). Subjects had a 12-h washout of any drugs including LD, and prolonged-release dopaminergic agents were discontinued for the necessary amount of time to achieve a proper washout. Subjects were allowed to have a light breakfast at least 2 h before the examination, avoiding coffee or tea and refraining from smoking. In the time between pre-LD and post-LD HUTT, as well as first and r-HUTT, patients were required to sit at rest.

CRTs were performed under audio- and video-polygraphic monitoring (ANScovery Modular System, SparkBio, Bologna, Italy). During the tests, beat-to-beat BP (Finometer Midi, Finapres Medical Systems, Amsterdam, the Netherlands), electrocardiogram, and oronasal and abdominal breathing were monitored continuously by means of a polygraph amplifier (Model 15LT, Grass Technologies, Quincy, MA, USA). All parameters were acquired and sampled at a rate of 500 Hz. Brachial BP was also systematically measured to confirm beat-to-beat BP finger values. ANScovery software was used to visualize, store, and analyze the data, providing a final report with the results. The correct execution of each test was checked automatically by an electronic device [22] and by a specialized technician who also monitored the subjects' level of vigilance and asked about any occurrence of symptoms of orthostatic intolerance during HUTT.

Data analysis

The following parameters were calculated: Valsalva ratio (VR) = heart rate (HR) phase II/HR phase IV of VM (pathological ≤1.21); overshoot = maximum BP phase IV − mean basal BP (pathological < 0 mmHg); sinus arrhythmia during DB (I/E) = average of the 10 shortest R-R intervals during inspiration/average of the 10 longest R-R intervals during expiration (pathological < 1.10); response to CF = difference between systolic BP (SBP), diastolic BP (DBP), and HR after 1 min of cold stimulus compared to basal values (pathological ΔSBP < 10 mmHg); response to HG = difference between SBP, DBP, and HR after 5 min of isometric effort compared to basal values (pathological ΔDBP < 10 mmHg); basal supine SBP, DBP, and HR values = mean value of the last 5 min of supine rest preceding HUTT; response to HUTT = difference between SBP, DBP, and HR values at the 3rd and 10th minute compared to basal supine; and post-HUTT SBP, DBP, and HR values = mean value of the last minute of supine rest after the 5 min following the end of HUTT.

OH was defined as a sustained reduction of at least 20 mmHg of SBP and/or 10 mmHg of DBP within 3 min of HUTT [17] and qualified as neurogenic (nOH) when associated with the absence of overshoot at the VM. Supine hypertension (SH) was established as SBP ≥ 140 mmHg and/or DBP ≥ 90 mmHg, measured after 5 min of supine rest preceding HUTT according to the definition of arterial hypertension [23] and neurogenic SH [24].

According to pre-LD HUTT and VM results, patients were divided into three subgroups: (i) nOH+, including patients with nOH; (ii) VM+, including patients without OH but with an abnormal

response at the VM defined by either a pathological overshoot or pathological VR; (iii) VM−, including patients without OH and normal response at the VM.

Disease diagnosis was performed by three neurologists expert in movement disorders on the basis of the clinical and instrumental data collected from the first to the last follow-up visit, according to consensus criteria for Parkinson disease (PD) [2], or atypical parkinsonism (AP) [25–28]. Patients not fulfilling any of such criteria were diagnosed with unspecified parkinsonism (uP). Age at disease onset, sex, and the following data related to the time of tests were also computed: patient's age, disease duration, disease severity (Unified Parkinson's Disease Rating Scale [UPDRS] part III, Hoehn and Yahr [H&Y] [29]), daily dosage of LD and of other parkinsonian treatment calculated as LD equivalent daily dose (LEDD) [30], the presence of concomitant diseases and treatments, and body mass index (BMI; kg/m^2). Finally, patients were asked about their history of symptoms of orthostatic intolerance during daily life [31] and the time lag between symptom occurrence and LD dose intake.

Statistical analysis

Because a deviation from a Gaussian distribution was found for all variables analyzed, data were expressed by median and interquartile range.

Cardiovascular changes were assessed by comparing variations in cardiovascular parameters (SBP, DBP, HR) at baseline and in Δ values calculated at the 3rd and 10th minute of HUTT between post-LD HUTT and pre-LD HUTT or between r-HUTT and first-HUTT by means of nonparametric test for paired samples (Wilcoxon signed-ranks test).

Comparisons between groups were performed by means of nonparametric tests for independent samples (Wilcoxon–Mann–Whitney test, chi-squared test).

Demographic data (age at study, sex, BMI), clinical features (age at disease onset, duration of disease, clinical diagnosis, UPDRS part III, H&Y, LEDD), and autonomic test results (pre-LD OH, VR, overshoot, DB, CF, HG) were evaluated as risk factors of post-LD OH by logistic regression analysis and expressed as odds ratio (OR) and 95% confidence interval (CI). Each feature was analyzed by simple logistic regression analysis. Only significant variables ($p \leq 0.05$) based on simple logistic regression analysis were analyzed using multivariable logistic regression analysis. Significance was set at $p \leq 0.05$.

RESULTS

Demographic, clinical, and autonomic features

A total of 164 patients were included (96 males; 137 PD, 20 AP, 7 uP; Table 1).

Of these, 87% of patients had an objective motor benefit from LD [32] and 13% a subjective benefit. Seventy-eight patients were also taking dopamine agonists. The most frequent comorbidities were arterial hypertension (30%) and uncomplicated type 2 diabetes treated with oral hypoglycemic agents (6%). Six of 164 patients reported a history suggestive of symptomatic OH not clearly related to LD intake; only one patient complained of orthostatic intolerance after each dose of LD/DCI.

CRTs documented a normal response at the VM in 94 patients, absence of overshoot and abnormal VR in 26 patients, absence of overshoot and normal VR in 30 patients, and abnormal VR in 7 patients. VM was not correctly performed in a further 7 patients. During DB, 60 patients presented a reduced sinus arrhythmia; responses to CF and HG were pathological in 34 and 52 patients, respectively. At pre-LD HUTT, 36 patients (22%) presented OH; all patients had a pathological VM indicating OH of neurogenic nature.

According to pre-LD HUTT and VM, 36 patients were then classified as nOH+, 27 patients as VM+, and 94 patients as VM− (Table 1).

Age at study and at disease onset was significantly lower in VM− ($p < 0.001$, $p = 0.003$) and BMI significantly higher in VM+ ($p = 0.005$). All other clinical and demographic features were similar among the groups.

Cardiovascular effects of a repeated HUTT

Cardiovascular effects of repeated HUTT without LD administration were assessed in 30 patients (first-HUTT vs. r-HUTT; Table 2, Figure 1a).

Patients did not differ in demographic features from those who did not undergo r-HUTT, although they were all diagnosed with PD and presented milder UPDRS part III scores (21 [16–25] vs. 27 [17–40]; Table S1).

The occurrence of OH at r-HUTT was similar to first HUTT, with 8 patients who showed OH at both first HUTT and r-HUTT and one extra patient who developed OH at r-HUTT (27% vs. 30%, $p = 0.157$; Table 2). SH was documented in 14 patients before first-HUTT and in 18 patients before r-HUTT (47% vs. 60%, $p = 0.102$).

Cardiovascular effects of LD at HUTT (pre-LD HUTT and post-LD HUTT)

Sixty-two patients (38%) showed OH at post-LD HUTT (52 PD, 8 AP, 2 uP) compared to 22% of patients with pre-LD OH ($p < 0.001$). A total of 35 of 62 patients showed OH also at pre-LD HUTT, but 27 patients presented OH only at post-LD.

Basal supine post-LD SBP, DBP, and HR were significantly lower compared to basal supine pre-LD (Figure 1b). A proportion of 28% of patients presented post-LD SH compared to 44% with pre-LD SH ($p < 0.001$).

TABLE 1 Demographic and clinical data of the study population.

Characteristic	Total	nOH+ group	VM+ group	VM− group
n	164	36	27	94
Age, years	67 (61–73)	71 (65–74)	71 (64–76)	64 (57–72)
Sex, M/F	96/68	23/13	15/12	55/39
BMI, kg/m^2	26 (24–29)	25 (23–28)	28 (26–32)	26 (24–29)
Comorbidity *n* (%)				
Arterial hypertension	49 (30%)	6 (17%)	13 (48%)	26 (28%)
Diabetes	10 (6%)	3 (8%)	1 (4%)	5 (5%)
Age at disease onset, years	60 (52–68)	65 (57–71)	63 (55–68)	58 (50–64)
Clinical diagnosis *n* (%)				
PD	137 (84%)	29 (81%)	19 (70%)	83 (88%)
MSA	9 (5%)	4 (11%)	4 (15%)	1 (1%)
DLB	3 (2%)	1 (3%)	1 (4%)	1 (1%)
PSP	5 (3%)	–	1 (4%)	3 (3%)
CBD	3 (2%)	–	–	3 (3%)
uP	7 (4%)	2 (5%)	2 (7%)	3 (3%)
Duration of disease, years	5.3 (3.3–8.3)	5.7 (3.3–8.0)	6.3 (3.7–10.6)	4.8 (3.0–8.3)
H&Y score	2.0 (2.0–2.5)	2.0 (2.0–3.0)	2.0 (2.0–3.0)	2.0 (2.0–2.0)
UPDRS part III score, OFF	27 (17–40)	29 (23–39)	30 (20–39)	25 (15–42)
LEDD, mg/day	400 (300–609)	389 (300–604)	530 (373–638)	343 (254–590)
LD pharmacokinetics				
LD dose, mg	100/25	100/25	100/25	100/25
LD C_{max}, μg/mL	2.0 (1.4–2.7)	1.6 (1.4–2.6)	2.0 (1.6–2.9)	2.0 (1.4–2.7)
LD T_{max}, min	30 (30–45)	30 (30–45)	30 (30–45)	30 (30–45)

Note: Data expressed as median (interquartile range).

Abbreviations: BMI, body mass index; CBD, corticobasal degeneration (CBD); C_{max}, maximum plasma drug concentration after a single-dose administration; DLB, dementia with Lewy bodies; F, female; H&Y, Hoehn and Yahr scale; LD, levodopa; LEDD, LD equivalent daily dose; M, male; MSA, multiple system atrophy; nOH, neurogenic orthostatic hypotension; PD, Parkinson disease; PSP, progressive supranuclear palsy; T_{max}, time to peak plasma LD concentration; uP, unspecified parkinsonism; UPDRS, Unified Parkinson's Disease Rating Scale; VM, Valsalva maneuver.

At pre-LD HUTT, 3rd- and 10th-minute values of SBP were decreased, whereas DBP and HR were increased compared to basal supine pre-LD (Table 2).

At post-LD HUTT, SBP decreased and HR increased significantly more at both the 3rd minute and the 10th minute of pre-LD HUTT, whereas DBP did not change (Table 2, Figure 1b).

Cardiovascular effects of LD in the three groups (nOH+, VM+, VM−)

Post-LD OH occurred in 97% of nOH+, 44% of VM+, and only 15% of VM− patients (Figure 1c–e).

At pre-LD HUTT, 3rd- and 10th-minute SBP and DBP values were lower compared to basal supine pre-LD values in the nOH+ and VM+ groups. In the VM− group at pre-LD HUTT, 3rd- and 10th-minute SBP values were unchanged and DBP values were increased compared to basal supine pre-LD. HR values at 3rd- and 10th-minute pre-LD HUTT were increased compared to basal supine pre-LD ones in all three groups, with ΔHR/ΔSBP <0.5 in the nOH+ group and ΔHR/ΔSBP >0.5 in the VM+ and VM− groups (Figure 1c–e, Table S2).

In all three groups, basal supine post-LD SBP and HR were significantly lower after LD administration, whereas basal supine post-LD DBP was reduced only in the nOH+ group. The occurrence of SH was significantly reduced after LD in the nOH+ (72% vs. 47%, $p=0.013$) and VM− groups (32% vs. 20%, $p=0.002$).

At post-LD HUTT, ΔSBP between basal supine post-LD and the 3rd minute was significantly increased in all three groups and ΔDBP was significantly higher in the VM+ and VM− groups. HR responses at 3rd-minute post-LD HUTT were unchanged in nOH+ compared to pre-LD-HUTT, whereas ΔHR was significantly higher in both the VM+ and VM− groups. At post-LD HUTT, the median of ΔHR/ΔSBP was <0.5 in the nOH+ and VM+ groups, whereas ΔHR/ΔSBP was >0.5 in VM−.

The cardiovascular effect of LD was similar among the groups, whereas LD-induced and LD-worsened OH was more frequent in the nOH+ and VM+ groups.

TABLE 2 Cardiovascular responses in patients at pre-LD HUTT versus post-LD HUTT and first HUTT versus r-HUTT.

	Pre-LD vs. post-LD HUTT			First vs. repeated HUTT		
Response	**Pre-LD HUTT**	**Post-LD HUTT**	***p***	**First HUTT**	**r-HUTT**	***p***
Basal supine SBP, mmHg	135 (121–155)	126 (116–142)	<0.001*	140 (130–149)	144 (133–156)	0.044*
Basal supine DBP, mmHg	74 (69–82)	71 (65–78)	<0.001*	68 (66–77)	73 (68–82)	0.011*
Basal supine HR, bpm	66 (58–73)	63 (57–69)	<0.001*	65 (60–70)	63 (57–67)	0.001*
SH, *n* (%)	72 (44%)	46 (28%)	<0.001*	14 (47%)	18 (60%)	0.102
3rd minute						
ΔSBP, mmHg	−2 (−16 to 6)	−11 (−26 to 0)	<0.001*	−8 (−23 to 5)	−10 (−22 to 2)	0.742
ΔDBP, mmHg	4 (−3 to 8)	0 (−7 to 7)	<0.001*	1 (−5 to 5)	3 (−3 to 8)	0.042*
ΔHR, bpm	9 (3–12)	10 (6–15)	<0.001*	7 (4–11)	10 (7–12)	0.001*
OH, *n* (%)	36 (22%)	62 (38%)	<0.001*	8 (27%)	9 (30%)	0.157
10th minute						
ΔSBP, mmHg	−5 (−21 to 5)	−12 (−30 to −2)	<0.001*	−10 (−29 to 2)	−10 (−22 to 4)	0.642
ΔDBP, mmHg	3 (−3 to 7)	0 (−7 to 5)	<0.001*	2 (−4 to 5)	2 (−3 to 8)	0.421
ΔHR, bpm	9 (4–15)	11 (6–17)	<0.001*	9 (5–13)	8 (6–16)	0.060
Delayed OH, *n* (%)	8 (5%)	12 (7%)	0.346	1 (3%)	0 (0%)	0.317
Post 5 min						
Supine SBP, mmHg	139 (123–160)	129 (117–145)	<0.001*	144 (133–155)	149 (136–166)	0.002*
Supine DBP, mmHg	76 (71–84)	71 (66–77)	<0.001*	70 (68–79)	75 (70–82)	0.003*
Supine HR, bpm	63 (57–71)	61 (55–68)	<0.001*	63 (55–69)	63 (56–70)	0.281

Note: Data are expressed as median (interquartile range).

Abbreviations: Δ, change compared to basal values; DBP, diastolic blood pressure; HR, heart rate; HUTT, head-up tilt test; LD, levodopa; OH, orthostatic hypotension; SBP, systolic blood pressure; SH, supine hypertension.

*p-values with statistical significance at Wilcoxon signed-ranks test ($p < 0.05$).

Risk factors related to LD-induced OH

The simple logistic regression analysis showed that post-LD OH was significantly associated with greater age at study (OR = 1.09, 95% CI = 1.04–1.14, $p < 0.001$), greater age at disease onset (OR = 1.05, 95% CI = 1.02–1.09, $p < 0.001$), OH at pre-LD HUTT (OR = 41, 95% CI = 12–144, $p < 0.001$), pathological values of VR (OR = 9, 95% CI = 3–12, $p < 0.001$), and absence of overshoot at the VM (OR = 11, 95% CI = 5–24, $p < 0.001$; Table 3). Older age at study and at disease onset did not determine a relevant increase in the risk of LD-induced/worsened OH, which stands at about 1.

The multivariable logistic regression analysis adjusting for age at study confirmed the association between OH at pre-LD HUTT, pathological values of VR, absence of overshoot, and high risk of developing post-LD OH.

A subanalysis of the logistic regression including only PD patients reported the same findings (Table 3).

DISCUSSION

In the present study, we confirmed on a large sample of 164 patients with PD and AP under chronic LD treatment the existing but weak observations derived from a few studies on small samples of PD patients, that subacute LD administration has a hypotensive effect [2–6].

LD administration determined a sustained decrease of basal supine SBP, DBP, and HR in all the patients irrespective of the presence of autonomic dysfunction (VM−, VM+, and nOH+ groups), a larger drop of SBP and DBP, and a greater increase in HR at the 3rd and 10th minutes of HUTT. Conversely, SBP and DBP changes were not different at r-HUTT compared to first HUTT, ruling out any bias related to repeat testing.

Furthermore, our study demonstrated that LD induced/worsened OH in a considerable number of patients (38%) in addition to reducing of the incidence of SH.

Features predictive of LD-induced/worsened OH are presence of OH before LD administration and a pathological response at the VM. Thus, patients with underlying autonomic dysfunction, encompassing both sympathetic (absence of overshoot) and parasympathetic (abnormal VR) impairment, had a considerably higher risk of developing LD-induced/worsened OH.

A single study, previously investigating the relation between cardiovascular autonomic functions and the LD effect in PD patients [33], reported that chronic LD treatment aggravated the pre-existing impairment of cardiovascular autonomic control. Accordingly, we outlined that although all patients experienced an LD hypotensive effect in the supine position, the clinical relevance in

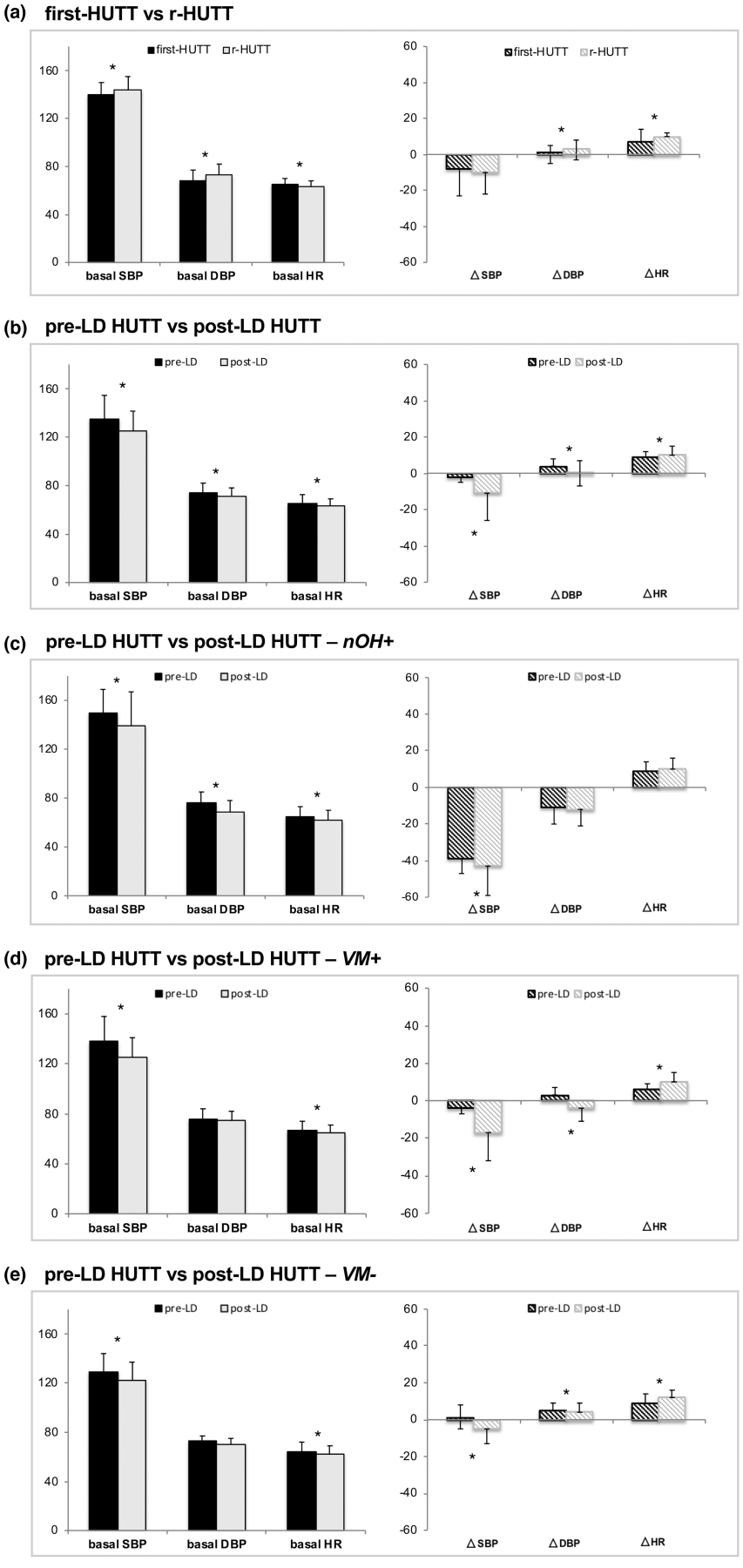

FIGURE 1 Comparison of cardiovascular parameters at first head-up tilt test (HUTT) versus repeated HUTT (r-HUTT) and at pre-levodopa (LD) versus post-LD HUTT. Basal supine values and 3rd-minute responses of systolic blood pressure (SBP), diastolic blood pressure (DBP), and heart rate (HR) at HUTT in all the patients (b), the neurogenic orthostatic hypotension (nOH)+ group (c), the Valsalva maneuver (VM)+ group (d), and the VM− group (e), and values of first-HUTT and r-HUTT are shown (a). Data are expressed as median (interquartile range). *$p < 0.05$ by Wilcoxon signed-ranks test between pre-LD and post-LD values.

TABLE 3 Likelihood of LD-induced/worsened OH at post-LD HUTT (logistic regression analysis).

Characteristic	Simple OR (95% CI)	*p*	Multivariable OR (95% CI)	*p*
Total population				
Age at study, years	1.09 (1.04–1.14)	<0.001*	–	–
Age at disease onset, years	1.05 (1.02–1.09)	0.004*	–	–
OH pre-LD, *n*	41 (12–144)	<0.001*	36 (10–131)	<0.001*
VR pathological	9 (3–21)	<0.001*	6 (2–15)	<0.001*
Overshoot pathological, *n*	11 (5–24)	<0.001*	9 (4–20)	<0.001*
PD population				
Age at study, years	1.11 (1.06–1.16)	<0.001*	–	–
Age at disease onset, years	1.07 (1.03–1.11)	0.001*	–	–
OH pre-LD, *n*	98 (13–758)	<0.001*	72 (9–580)	<0.001*
VR pathological	12 (4–37)	<0.001*	8 (2–27)	0.001*
Overshoot pathological, *n*	15 (6–38)	<0.001*	10 (4–27)	<0.001*

Note: Demographic data, clinical features, and autonomic test results were assessed by simple logistic regression analysis. Only significant variables are reported as OR and CI.

Abbreviations: CI, confidence interval; HUTT, head-up tilt test; LD, levodopa; OH, orthostatic hypotension; OR, odds ratio; VR, Valsalva ratio.

*p-values with statistical significance ($p < 0.05$).

terms of orthostatic intolerance and OH is observed only in patients with underlying autonomic dysfunction even if subtle (44% of VM+ patients). It is conceivable that the impairment of the cardiovascular autonomic responses, mostly a blunted vasopressor reaction, aggravates the hypotensive LD effect, leading to greater drop of BP and LD-induced/worsened OH.

This study was performed on a large sample of well clinically characterized patients with both PD and AP under chronic LD treatment who received a standard low dose of LD/DCI (100/25 mg) to minimize confounding factors related to irregular uptake or different LD doses.

We evaluated the hypotensive effect of LD after 60 min of the drug administration, at the time of peak plasma level and greater clinical improvement as documented in the subacute challenge kinetic–dynamic test. A prolonged effect of LD later than 60 min has been reported in a previous study [6], suggesting the possibility of an even greater hypotensive action of LD. The cardiovascular effect of LD was assessed through standardized CRTs in a specialized laboratory. Repeated HUTT allowed us to exclude possible cardiovascular effects related to the recurrence of HUTT, although the study was not designed as a randomized double-blind placebo-controlled trial and the absence of a placebo arm is a limitation.

The observation of relevant cardiovascular changes after the administration of a standard low dose of LD/DCI in this large population and with a rigorous methodology suggests that the hypotensive LD effect is consistent and possibly greater in clinical practice, when the use of higher doses is expected.

Furthermore, we demonstrated that patients at higher risk of developing OH and orthostatic symptoms after subacute LD administration are those presenting an underlying cardiovascular autonomic dysfunction. Therefore, LD-induced or worsened OH in patients with neurodegenerative parkinsonism should be considered a "red flag" for underlying autonomic dysfunction, and these patients should be investigated with gold standard evaluations to assess also mild autonomic dysfunction like impaired VM.

The results provided by our study have high relevance and enforceability in clinical practice, because cardiovascular autonomic failure is a key feature in the differential diagnosis of neurodegenerative parkinsonism and carries an important prognostic value, determining a negative impact on the quality of life and survival [34–36].

Certainly, our study constitutes only a frame of the landscape of neurodegenerative parkinsonism, and further longitudinal studies are required to evaluate whether the cardiovascular effect of LD represents such a relevant clinical feature. Especially, studies on early disease stage would be useful in defining the role of LD-induced or worsened OH in the differential diagnosis of PD and AP. It has already been demonstrated that the combination of HUTT and VM, which are the main risk factors of LD-induced/worsened OH in this study, is a highly accurate method to discriminate between the diagnosis of PD and multiple system atrophy–parkinsonian type in patients at an early stage of the disease [21].

In conclusion, the subacute administration of an oral dose of LD determined a diffuse hypotensive effect in both supine and orthostatic conditions. Patients at higher risk of developing LD-induced OH are those presenting a cardiovascular autonomic dysfunction. In

clinical practice, LD-induced OH should be considered a red flag for underlying autonomic failure.

AUTHOR CONTRIBUTIONS

Ilaria Cani, Pietro Cortelli, and Giovanna Calandra-Buonaura conceived and designed the study. Ilaria Cani, Giulia Giannini, Pietro Guaraldi, Luisa Sambati, and Giorgio Barletta acquired and analyzed data. Ilaria Cani, Pietro Cortelli, and Giovanna Calandra-Buonaura interpreted the data. Ilaria Cani wrote the first draft of the manuscript, and created the figure and tables. Pietro Cortelli and Giovanna Calandra-Buonaura contributed to revising the manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors report no relevant disclosures or conflicts of interests for this article.

DATA AVAILABILITY STATEMENT

The authors take full responsibility for the data, and the analysis and interpretation of the research, and they have full access to all of the data. Anonymized data that support the findings of the study are available from the corresponding author, upon reasonable request.

ETHICS STATEMENT

Written informed consent was collected from each patient for the inclusion of deidentified clinical data in a scientific publication, in accordance with the Declaration of Helsinki.

CONSENT FOR PUBLICATION

All authors agreed with this final version.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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