

Effects of mechanical stimulation of the feet on gait and cardiovascular autonomic control in Parkinson's disease

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THE NEURAL DEGENERATION OF the basal ganglia network is considered the critical mechanism inducing movement disorders in Parkinson's disease (PD). Furthermore, central (1, 23, 24) and peripheral (35) alterations of the sensory-motor system play a crucial role in influencing motor disability in this disorder. For example, sensory innervation of the soles of the

feet was found to be severely impaired in patients with PD, with an unequal deficit distribution at different sites such as a reduction in touch-pressure sensitivity at the hallux and first metatarsal joint (35). It has been reported that both electrical and mechanical stimulation (21), including the rhythmic vibratory stimulation of trunk muscles (11) or of the soles (28), ameliorated gait in PD.

Alterations in cardiovascular autonomic control resulting in orthostatic hypotension were recognized in 10–40% of patients with PD (2). Orthostatic hypotension may worsen motor disability by provoking falls and reducing a patient's self-sufficiency. In a previous study in patients with PD without a measurable orthostatic hypotension, we observed that cardiovascular autonomic control was impaired early in the upright position (3).

There is evidence of a functional interaction among neural somatosensory activation, and of motor and cardiovascular autonomic control both in health and disease. Indeed, the rhythmic perturbation of carotid baroreceptor afferents in healthy volunteers results in synchronous oscillations of postural sway (7). Also, the activation of plantar sensory afferents by electrical stimulation increases the arterial baroreflex sensitivity in patients with heart failure (17).

The present study was prompted by the serendipitous observation of both a remarkable motor improvement and a mild decrease in blood pressure values following the mechanical stimulation of both soles of the feet during rehabilitative physical therapy sessions in patients with PD. Surprisingly, most of these individuals showed a clinical improvement in performing both simple and complex motor tasks, and a reduction in systolic blood pressure at rest, not only within several hours from mechanical stimulation of the feet, but also for a few days after. This supports the hypothesis that motor and neural autonomic changes could be assessed after 24 h. This time frame is of great clinical interest given the well known short half-life of drugs for treating PD.

In the literature, step-synchronized vibratory stimulation of the soles (28) or plantar cutaneous sensory stimulation by facilitatory ribbed insole (21) resulted in significant facilitation of movement and gait in patients with PD. However, these studies were based on the use of rather complex devices, particularly when a vibratory stimulus was required (11).

In the present study we investigated whether or not the modulation of somatosensory afferents, obtained by using the simple technique of administering controlled pressure on specific skin sites of the feet, might affect motor and cardiovascular autonomic control 24 h later. Quantitative changes in computerized gait analysis parameters and spectral indices of cardiovascular autonomic function were measured both before and 24 h after mechanical stimulation of the feet to substantiate our previous qualitative clinical observations.

MATERIALS AND METHODS

All procedures were explained and carried out with an adequate understanding and written informed consent of the subjects. The Bolognini Hospital Institutional Review Board provided ethical approval for the investigation (approval R-156).

Population

We studied 18 consecutive patients with idiopathic PD characterized by a moderate motor impairment [Hoehn & Yhar (20) scale 2–3], who had been referred to the outpatient clinic of the Parkinson's Disease Center of Istituti Clinici di Perfezionamento in Milan. PD was diagnosed on the basis of clinical criteria (18, 30), dopamine transporter (DaT) scan, and/or magnetic resonance imaging. Patients were similar in terms of disease duration and were also free of peripheral sensory neuropathy and other disorders on the basis of their reported history, symptoms, physical examination, and routine tests. Patients with liver, kidney, lung, heart disease, diabetes or other causes of autonomic dysfunction were not included in the study.

Treatment for PD remained unchanged for the 30 days preceding and during the study procedures. Two patients showed short periods of atrial fibrillation during electrocardiographic monitoring and were excluded from the final analysis. Thus our study population consisted of 16 individuals. The characteristics of these patients are summarized in Table 1.

Definitions and Foot Stimulation Procedure

The term effective stimulation (ES) refers to pressure applied to two specific skin points of both forefeet. The sites of the stimulation corresponded to the tip of the hallux and the lower big toe first metatarsal joint plantar surface (Fig. 1). These stimulation sites were chosen as potentially the most effective on the basis of available evidence (35) that characterized these points as the greatest vibratory and touch pressure sensitivity thresholds in PD, and/or because their stimulation successfully improved gait parameters and modified cardiac autonomic profile in patients with PD according to observations from our laboratory obtained by previous feasibility studies.

Given that the sensitivity of the forefoot may be reduced to a certain extent in various patients with PD (35), the stimulation procedure was individualized to suit each patient. Progressively in-



● Points of Effective Stimulation
▲ Points of Sham Stimulation

Fig. 1. Sites of effective stimulation (ES) and sham stimulation (SS) on feet.

creasing mechanical pressure was administered at the selected stimulation sites of the foot skin until the onset of pain that induced reflex withdrawal of the stimulated leg. This mechanical pressure was made by using a steel stick with a smooth, 2-mm-diameter tip that was connected to a dynamometer for instantaneous pressure assessment. The magnitude of the mechanical pressure triggering the reflex withdrawal was then assumed to be the patient's individual pressure point and, indeed, it was subsequently used during the actual ES procedure.

The ES stimulation procedure consisted of the application, on the selected site, of a patient's individual pressure for 6 s by means of the steel stick of a dynamometer. Each of the two cutaneous sites of both feet was mechanically stimulated. The procedure was repeated four times in each subject so that the overall time period was ~2 min. The applied average pressure in the studied population was 0.58 ± 0.04 kg/mm².

The term sham stimulation (SS) refers to the application of an identical stimulation protocol to two skin sites different from those selected for ES. During SS, the same dynamometer with identical stimulus parameters were used. In particular, points located in the rear part of both plantar surfaces of the feet were chosen for stimulation. The time course of pressure administration and its magnitude were identical in each subject for both ES and SS. Similarly to ES, the applied amount of pressure during SS was reported as painful by the patients.

Study End Points and Protocols

The primary aim of the present study was to assess the motor and autonomic changes occurring in 16 patients 24 h after ES. The second goal of the study was to evaluate the site-specific efficacy of the mechanical stimulation. The working hypothesis was that no significant modifications in motor performance parameters or in spectral indices of cardiovascular autonomic control would be observed after

Table 1. Demographic and clinical features of the study population

Characteristic	Value*
Age, yr	66 ± 3
Male/Female	8/8
Body mass index, kg/m ²	23 ± 1
Hoehn-Yahr scale	2–3
UDPRS-III	22 ± 3
Disease duration, yr	13 ± 1
Levodopa mg/day (SD)	611 (185)
LEDD, mg/day (SD)	211 (94)

UDPRS III, Unified Parkinson's Disease Rating Scale, motor score; LEDD, Levodopa equivalent daily dosage; *n = 16.

SS. Toward this aim, a subgroup of 8 (*group B*, see below) out of the 16 patients was randomly assigned to an additional SS that was performed in a different study session.

Each patient was tested on the same day both at the Luigi Divieti Posture and Movement Analysis Laboratory - Politecnico di Milano, Milan, for gait and motion analysis and at the Syncope and Posture Disorders Unit, Bolognini Hospital, Seriate for Cardiovascular Autonomic Parameters. Subjects were studied after they had taken their routine medications and were at their best ON time, according to the protocol outlined below (Fig. 2).

Day 1: baseline assessment, randomization, and stimulation session. In the morning, each patient underwent baseline recording of the main parameters for gait and movement analysis. This study session lasted ~60 min starting at 9:00 a.m. Two hours later, the baseline cardiovascular autonomic evaluation took place. Thereafter, the 16 patients were randomized either to *group A* ($n = 8$) or *group B* ($n = 8$). *Group A* underwent bilateral ES; *group B* underwent bilateral SS and, 24 h later, ES.

Day 2: 24 h poststimulation assessment. Each patient in both *group A* and *group B* underwent the same protocol as described above to assess the 24-h motor and autonomic effects of ES and SS, respectively.

Twenty-four hours after the SS assessment, patients in *group B* crossed over and underwent ES. The SS procedure was hypothesized to be ineffective on gait and autonomic parameters on the basis of preliminary feasibility studies.

Day 3: (group B patients) 24 h post ES assessment. Twenty-four hours after ES, these individuals underwent a study protocol identical to that previously applied to assess 24-h gait and autonomic effects of ES. A total of 16 patients were therefore assessed 24 h after ES (Fig. 2).

Both pre- and poststimulation analyses of gait and autonomic parameters were performed off line by the bioengineers of the Politecnico (M.G. and V.C.) and Galeazzi Institute (A.P. and V.B.) who

were not aware of the site of mechanical stimulation (i.e., ES or SS) or the autonomic challenge (i.e., supine or 75° head-up tilt).

Gait Analysis

All patients with PD were evaluated by using an eight-camera optoelectronic system (ELITE2002; BTS, Milan, Italy) with a sampling rate of 100 Hz for kinematic movement evaluation, two force platforms (AMTI) for kinetic assessment, eight-channel surface electromyographic system (Pocket EMG; BTS) for muscle electromyographic signals monitoring, and two television camera video system (BTS) synchronized with the other equipment for video recording.

After collecting anthropometric measures (height, weight, tibia length, distance between femoral condyles or diameter of the knee, distance between malleoli or diameter of the ankle, distance between anterior iliac spines, and thickness of the pelvis), passive markers were placed at special reference points on a subject's skin as described by Davis et al. (10).

After each subject's preparation, acquisition sets of data were obtained during two tasks as follows: 1) gait: patients were asked to walk barefoot along a straight walkway 10 m long; and 2) rotation: in an upright position and barefoot, each patient was asked to turn clockwise.

At least three trials were recorded and elaborated for each task. For each biomechanical index the average of the three measures was calculated. The analysis was focused on the following parameters: 1) gait velocity: mean velocity of progression (m/s); 2) gait step length: longitudinal distance between the heel contact of one foot and the heel contact of the other (mm) normalized for individual height; 3) gait symmetry: the stance duration was assessed separately for the left and right steps and the right/left ratio was computed as gait symmetry index; 4) rotation velocity: this index was computed using the coordinates of the marker positioned on the sacrum (m/s); and 5) rotation steps: number of steps during the upright position rotation.

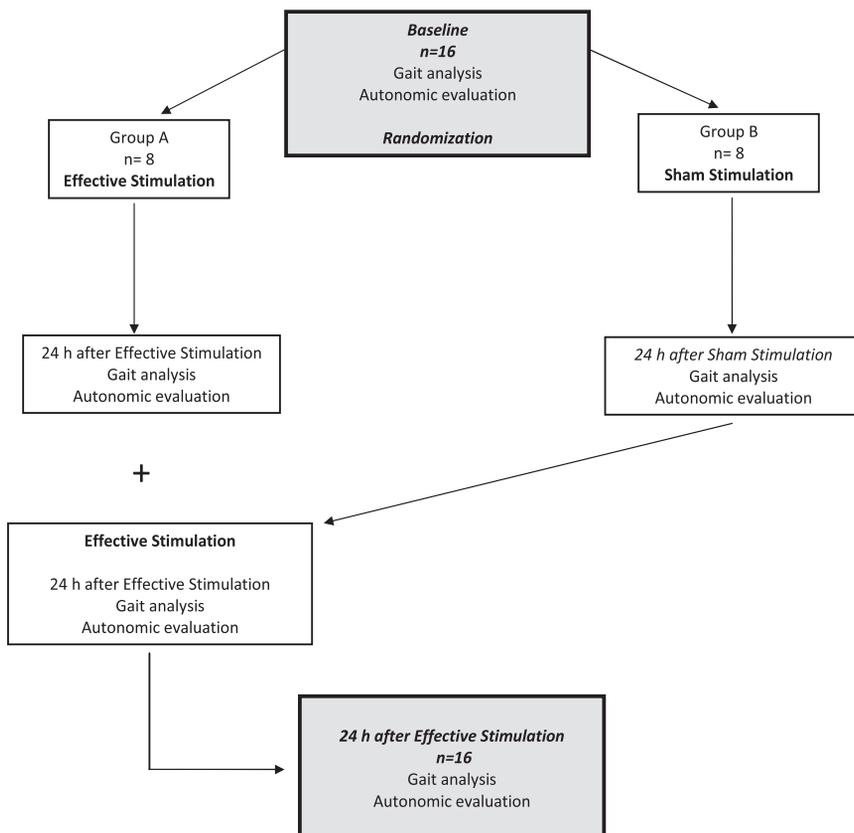


Fig. 2. Flow diagram of study protocol.

Cardiovascular Autonomic Profile Analysis

In each patient, we continuously recorded electrocardiography (ECG) and noninvasive beat-to-beat blood pressure by a volume-camp technique (Finometer, SEDA). Respiratory activity was simultaneously evaluated by a thoracic belt connected to a pressure transducer. ECG, arterial pressure, and respiratory activity were digitalized at 300 samples per second per signal by an analog-to-digital converter (AT-MIO 16E2; National Instruments) and stored on the hard disk of a personal computer.

Each patient was placed on a motorized tilt table with a footrest and underwent instrumentation as described above. Twenty minutes after instrumentation, baseline data acquisition was initiated in a recumbent position. Thereafter, each subject was tilted up to the 75° head-up position for 20 min.

Data Analysis

Software techniques for data acquisition, spectrum, and cross-spectrum analyses of RR interval, systolic arterial pressure (SAP) variability, and respiratory activity have been described in detail elsewhere (16, 40a). For RR spontaneous variability, there are two major spectral components, the amplitude of which are affected by changes in cardiac neural autonomic control (15, 16). One is the HF component ($HF_{RR} \approx 0.25$ Hz at rest), synchronous with respiratory activity, a recognized index of the vagal efferent modulation directed to the sinoatrial node (15, 16). The other spectral component is indicated as LF ($LF_{RR} \approx 0.1$ Hz), and when expressed in normalized units, has been proposed to primarily reflect the sympathetic efferent modulation to the sinoatrial node and its changes (15, 16, 31). Both spectral components of RR variability are provided in absolute units (ms^2) and normalized units (n.u.). Absolute values of each component were computed as the integral of the oscillatory components LF_{RR} and HF_{RR} . Normalization was achieved by dividing the absolute power of each component by total variance minus the power of the very-low-frequency component (<0.03 Hz) and subsequently multiplying by 100 (15, 31). The LF/HF ratio, a dimensionless index, was also calculated to assess the reciprocal changes of sympathetic and vagal modulation directed to the sinoatrial node discharge (15, 31). The LF oscillatory component of SAP variability ($LF_{SAP} \approx 0.1$ Hz) was expressed in absolute values and can be used as a marker of the sympathetic modulation of vasomotor activity (15, 31).

Arterial baroreflex function was assessed using three different methods as described in the following paragraphs.

1) A frequency-domain approach: this method is based on cross-spectral analysis of RR and SAP variability. After having obtained a squared coherence function (K^2) > 0.5 , the index alpha was computed as the square root of the ratio between the powers of the LF (0.1 Hz) spectral components of RR interval and SAP variability and used as an index of arterial baroreceptor activity (3, 32).

2) A time-domain approach: baroreflex sensitivity (BRS) was assessed according to the baroreflex sequence analysis (8). This technique relies on the search for sequences characterized by the contemporaneous increase (positive sequence) or decrease (negative sequence) of RR and SAP values. Both positive and negative sequences are referred to as baroreflex sequences. They are identified according to the following prerequisites: 1) the length of the sequences was four beats (three increases or decreases); 2) the lag between RR and SAP values was set to 0; 3) the total SAP variation was larger than 5 ms; 4) the total RR variation was larger than 1 mmHg; and 5) the correlation coefficient in the plane [SAP(i),RR(i)], where there is the cardiac beat number, was larger than 0.85. When a baroreflex sequence matched the above-mentioned prerequisites the slope of the regression line in the plane [SAP(i),RR(i)] was calculated and averaged over all baroreflex sequences. This average was indicated hereafter as BRS and expressed as $ms/mmHg$.

3) Baroreflex effectiveness index: the total number of BRS (see above) was retained and divided by the number of meaningful SAP

ramps, where an SAP ramp is identified as a sequence of four consecutive values of SAP leading to a total positive or negative SAP variation larger than 1 mmHg and a correlation coefficient in the plane [i,SAP(i)] larger than 0.85. This index was referred to as the baroreflex effectiveness index (BEI) (12) and is expressed as dimensionless units.

Statistics

Data are expressed as means \pm SE. A Kolmogorov-Smirnov test was used to verify normal distribution data. A Friedman's test was used to assess differences between the baseline measure and 24 h after ES and SS. A Friedman's test was also carried out over the variations of the cardiovascular control indexes in supine condition and during tilt to check the significance of the orthostatic response after ES and SS. Differences were considered significant at $P < 0.05$.

RESULTS

Demographic and clinical features of patients with PD are summarized in Table 1.

Gait and Movement Analysis

In all 16 patients there was a significant increase in mean step length ($+4.9 \pm 2.0\%$ from 529.9 ± 34.8 mm; $P < 0.05$) and in gait velocity ($+8.1 \pm 1.9\%$ from 0.89 ± 0.08 m/sec; $P < 0.05$) 24 h after effective plantar stimulus (ES) compared with baseline conditions (Table 2).

According to the baseline prestimulus analysis, the left step stance was longer than the right step stance in 9 out of 16 patients as assessed by the gait symmetry index (right/left ratio ≤ 1 , Fig. 3, *top*). For these nine subjects, the effective stimulation resulted in an increase of the right/left ratio suggesting a partial rebalancing of the gait (Fig. 3, *middle*). The opposite effect occurred in the remaining seven patients, characterized by a right/left ratio greater than 1 at baseline, who consistently reduced the right/left ratio 24 h after ES (Fig. 3, *bottom*).

Upright Rotation

Body rotation velocity, evaluated as the mean value of individual right and left foot rotation velocities, was significantly increased ($+35.7 \pm 13.5\%$ from 0.16 ± 0.01 m/sec; $P < 0.05$) 24 h after ES (Table 2). In addition, the number of steps during the rotation task significantly decreased ($-16.7 \pm 6.5\%$ from 9.8 ± 2.1 steps; $P < 0.05$) after ES (Table 2).

The overall motor response induced by ES can be summarized as follows: at least one of the motor parameters (i.e.,

Table 2. Gait and rotation parameters before (baseline) and 24 h post-ES in 16 subjects

Parameter	Baseline	24 h post-ES
Gait		
Velocity, m/s	0.89 ± 0.08	$0.96 \pm 0.08^*$
Left step length, mm	534.2 ± 37.3	$552.3 \pm 36.3^*$
Right step length, mm	525.6 ± 33.2	$554.6 \pm 34.1^*$
Mean step length, mm	529.9 ± 34.8	$553.4 \pm 34.8^*$
Rotation		
Velocity, m/s	0.16 ± 0.01	$0.21 \pm 0.02^*$
Mean steps, <i>n</i>	9.4 ± 1.9	$7.3 \pm 1.0^*$

* $P < 0.05$ 24 h post-ES versus baseline.

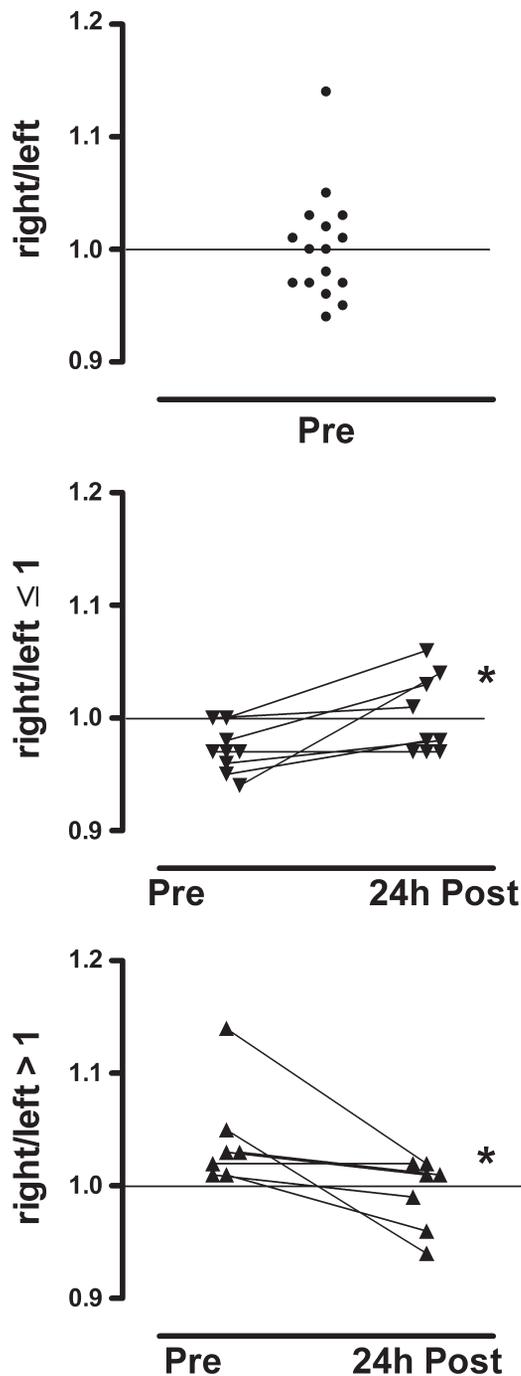


Fig. 3. Changes induced by ES on the index of gait symmetry. Foot ground touch duration (stance) was assessed separately for the left and right step, and the right/left ratio was computed as an index of gait symmetry (*top*). During walking preceding the feet stimulation, the left step stance was longer than the right one in 9 out of 16 patients (right/left ratio ≤ 1). For these 9 subjects, effective stimulation resulted in an increase in the right/left ratio, suggesting an asymmetrical change of gait possibly leading to a partial rebalancing of the gait itself (*middle*). The opposite effect occurred in the remaining 7 patients, characterized by a right/left ratio > 1 at baseline in whom the right/left ratio (*bottom*) was consistently reduced 24 h after ES. * $P < 0.05$.

mean step length, gait velocity, rotation step number, and velocity) was improved in 100% of subjects; two parameters were improved in 94% of subjects; three parameters were improved in 75% of subjects, and all four parameters were improved in 31% of subjects.

Cardiovascular Autonomic Profile

Table 3 summarizes the effects induced by the tilt maneuver on the hemodynamics and spectral indices of cardiovascular autonomic control before (baseline) and 24 h after ES.

In the recumbent position, systolic arterial pressure mean values and LF_{SAP} , an index of sympathetic vasomotor modulation (16, 31), were significantly decreased after ES compared with baseline.

Before ES, the spectral indices of cardiac (LF/HF ratio) and vascular (LF_{SAP}) sympathetic modulation did not increase during tilt, suggesting an impaired cardiovascular autonomic control in response to the gravitational stimulus in these patients (Table 3). Conversely, 24 h after ES, LF/HF and LF_{SAP} significantly increased during tilt, suggesting a greater enhancement of cardiac and vascular sympathetic modulation consistent with a more appropriate response to the orthostatic stimulus.

For baroreceptor sensitivity (Table 3), at rest, alpha and BRS indices were only slightly enhanced after ES. During tilt, alpha and BRS showed a mild decline before ES, whereas 24 h after ES there was a significant decrease in BRS, suggestive of a functional widening of baroreceptor sensitivity induced by the effective stimulation of the feet. The BEI index was unaffected by ES.

Motor and Autonomic Changes Induced by SS

In the eight patients who underwent mechanical stimulation of fictitious sites (SS), gait and rotation parameters were unchanged compared with baseline values (Table 4). Similarly, the spectral indices of cardiac and vascular autonomic control and of arterial baroreceptor gain were not affected by SS (Table 5).

DISCUSSION

The results of the present study suggest that in our cohort of patients with PD there was a significant improvement of gait parameters assessed 24 h after ES of the feet. In addition, 24 h after ES changes were also observed in the cardiovascular autonomic profile; namely, a reduced vascular sympathetic modulation at rest and a greater increase in both cardiac and vascular sympathetic modulation together with a functional widening of arterial baroreceptor mechanisms in the upright position. These latter autonomic changes are consistent with a more appropriate baroreceptor and autonomic regulatory response to the orthostatic stimulus. Finally, after SS, no significant motor or autonomic changes were observed, suggesting that a site specificity is required for mechanical sensory stimulation to achieve significant motor and autonomic effects.

Motor Changes After Mechanical Stimulation of the Feet

After sensory stimulation of the feet, we observed a significant increase in step length and gait velocity in our patients with PD, together with a very interesting interlimb change of left/right ratio in the ground touch duration. These findings indicate that in most cases there was a remarkable modification of the support phase of gait and, in some cases, a gait rebalancing. In addition, a complex motor task such as the upright rotation, was accomplished faster and with a reduction in the number of steps. Notably, in all patients, at least one of the

Table 3. *Indexes of cardiac and vascular autonomic regulation at rest and during 75° head-up tilt before (baseline) and 24 h post-ES in 16 subjects*

Parameter	Baseline		24 h post-ES	
	Rest	Tilt	Rest	Tilt
RR, ms	835.1 ± 31.7	695.0 ± 26.2*	838.7 ± 31.6	726.5 ± 27.3†
RR var, ms ²	779 ± 342	287 ± 98	799 ± 163	403 ± 118
LF _{RR} , ms ²	136.5 ± 47.4	54.3 ± 19.1	126.7 ± 47.3	156.8 ± 53.4§
n.u.	42.9 ± 5.0	41.2 ± 6.1	33.4 ± 4.7	67.9 ± 6.5†§
HF _{RR} , ms ²	222.0 ± 125.2	75.2 ± 46.1*	204.6 ± 76.0	60.9 ± 24.1†
n.u.	45.1 ± 4.7	38.3 ± 5.2	56.3 ± 6.0	21.6 ± 4.1†
LF/HF	1.3 ± 0.2	3.5 ± 1.8	0.8 ± 0.2	7.5 ± 2.2†§
SAP, mmHg	130.6 ± 5.4	126.4 ± 4.9	121.8 ± 3.3‡	115.3 ± 4.2
SAP var, mmHg ²	17.1 ± 2.3	27.7 ± 4.1*	18.5 ± 3.7	30.4 ± 7.3†
DAP, mmHg	76.9 ± 2.6	78.8 ± 2.7	72.8 ± 1.8	73.8 ± 2.26
LF _{SAP} , mmHg ²	1.9 ± 0.4	2.0 ± 0.5	0.8 ± 0.1‡	6.4 ± 1.9†§
Resp, cycles/min	21.2 ± 0.6	20.3 ± 0.9	20.1 ± 0.6	19.6 ± 0.7
αLF ms/mmHg	10.0 ± 2.7	5.2 ± 1.0	12.7 ± 2.8	6.2 ± 1.2
BRS ms/mmHg	8.2 ± 2.8	3.1 ± 0.4	15.6 ± 6.3	4.8 ± 1.1†
BEI	0.13 ± 0.02	0.14 ± 0.03	0.13 ± 0.04	0.14 ± 0.02

RR indicates R-R interval; var, variance; LF_{RR}, low frequency power of RR variability; HF_{RR}, high frequency power of RR variability; n.u., normalized units; SAP, systolic arterial pressure; DAP, diastolic arterial pressure; LF_{SAP}, low frequency power of SAP variability; Resp, respiration; αLF, index of arterial baroreceptor sensitivity assessed by bivariate power spectrum analysis; BRS, baroreflex sensitivity; BEI, baroreflex effectiveness index. BRS and BEI, *n* = 10 subjects. **P* < 0.05 baseline tilt vs. rest. †*P* < 0.05 24 h post-ES tilt vs. rest. ‡*P* < 0.05 24 h post-ES rest vs. baseline rest. §*P* < 0.05 24 h post-ES tilt vs. baseline tilt.

indices assessing the motor changes improved after ES. In 31% of the participants, all of the considered motor parameters improved.

These findings as a whole indicate that ES significantly improved the control of gait in patients with PD, and that this effect could be assessed 24 h after the stimulation.

The calibration of the stimulus intensity that was used in the present study and the following implications deserve a short discussion. As stated in MATERIALS AND METHODS, the intensity of the pressure applied to skin sites during the stimulation procedure was precalibrated in every subject to reach the threshold that would trigger the reflex withdrawal of the leg (tibialis anterior twitch). Although the precise definition of the sensory receptors activated by mechanical stimulation of the feet was not the scope of the present study, it is possible to hypothesize that different populations of fibers were involved in different ways during the mechanical stimulus. The leg reflex withdrawal response is likely mediated by nociceptive afferents (Aδ fibers) discharging at high frequencies (13, 27, 44, 45). However, it is possible an additional contribution of other nonnociceptive sensory afferents that are known to converge in the motor spinal reflex arc. These include touch fibers, proprioceptors, and other receptors characterized by an activation threshold lower than that characterizing nociceptors. By

Table 4. *Gait and rotation parameters before (baseline) and 24 h post-SS in 8 subjects*

Parameter	Baseline	24 h post-SS
Gait		
Velocity, m/s	0.82 ± 0.09	0.86 ± 0.10 n.s.
Left step length, mm	486.9 ± 39.2	486.0 ± 45.6 n.s.
Right step length, mm	481.3 ± 41.4	505.3 ± 46.0 n.s.
Mean step length, mm	484.1 ± 39.5	495.6 ± 44.5 n.s.
Rotation		
Velocity, m/s	0.16 ± 0.02	0.17 ± 0.03 n.s.
Mean steps, <i>n</i>	12.4 ± 4.1	10.6 ± 4.0 n.s.

n.s., not significant (*P* > 0.05).

the spino-thalamic ascendant pathway, activation of sensory afferents may reach higher centers, including the basal ganglia and the nucleus subthalamicus. It is just a reminder that nucleus subthalamicus bilateral structures have long been recognized as being functionally impaired in PD (5, 6, 25) and are indeed targeted by a therapeutic technique known as deep brain stimulation (22, 26). We hypothesize that in our patients, the sensory afferent activation by mechanical stimulation of the feet might eventually disrupt the exaggerated excitatory modulation exerted by the subthalamic nuclei (5, 6, 25), similarly to what has been hypothesized to underlie the motor benefits exerted by the chronic electrical stimulation of the subthalamic nuclei by deep brain stimulation (22, 26).

An increase in dopamine availability in the substantia nigra might also underlie the gait improvement in our patients. However, in the present study we could not measure dopamine plasma levels to substantiate the above hypothesis, nor did we assess potential changes in dopamine pharmacodynamics.

Notably, in physiological conditions, a very high sensitivity for mechanical stimulation (touch and vibratory separately) of the hallux, metatarsal, and lateral arches regions while walking and running has been described (29). There is the suggestion that the body moves the center of pressure to these areas of greater sensitivity both on stance (19) and during gait (29). The plantar sensory system (touch-pressure and vibration) has been found to be severely impaired in patients with PD, with a remarkable deficit corresponding to the first metatarsal site and a significant correlation between motor impairment and sensory alteration (35).

In keeping with these findings is the observation that epidural stimulation of the dorsal column of the spinal cord could restore locomotor ability in rodent models of hypokinetic PD (14). Moreover, the vibratory (28) or plantar cutaneous sensory stimulation by facilitatory ribbed insole (21), both likely to induce foot cutaneous mechanoreceptor activation, resulted in a significant facilitation of movement and gait in patients with PD. Accordingly, in our patients the mechanical stimulation of

Table 5. Indexes of cardiac and vascular autonomic regulation at rest and during 75° head-up tilt, before (baseline) and 24 h post-SS in 8 subjects

Parameter	Baseline		24 h post-SS	
	Rest	Tilt	Rest	Tilt
RR, ms	860.3 ± 31.8	702.8 ± 28.5*	876.2 ± 37.9	749.7 ± 34.7†
RR var, ms ²	1073 ± 677	371 ± 1201*	1148 ± 568	782 ± 520#
LF _{RR} , ms ²	143.6 ± 64.3	66.2 ± 36.2	241.6 ± 121.0	31.8 ± 15.9†
n.u.	39.2 ± 8.5	36.1 ± 8.9	35.1 ± 6.3	18.25 ± 5.9
HF _{RR} , ms ²	296.7 ± 224.2	111.8 ± 83.3	251.2 ± 92.1	109.2 ± 50.2
n.u.	48.3 ± 6.5	42.1 ± 6.6	51.1 ± 6.2	44.2 ± 6.4
LF/HF	1.1 ± 0.3	1.7 ± 0.7	1.04 ± 0.4	1.4 ± 1.0
SAP, mmHg	131.5 ± 7.6	130.1 ± 8.1	132.6 ± 7.4	128.2 ± 8.3
SAP var, mmHg ²	16.8 ± 2.9	31.6 ± 6.5	15.3 ± 3.8	23.2 ± 5.4
DAP, mmHg	78.0 ± 3.9	81.5 ± 4.4	78.6 ± 3.9	82.5 ± 4.2
LF _{SAP} , mmHg ²	2.5 ± 0.6	1.6 ± 0.5	2.6 ± 1.0	3.0 ± 1.2
Resp, cycles/min	21.3 ± 0.7	21.7 ± 1.4	19.1 ± 1.5	22.5 ± 1.5
αLF, ms/mmHg	6.9 ± 1.8	5.3 ± 1.2	10.0 ± 2.0	5.0 ± 1.7
BRS, ms/mmHg	10.3 ± 4.4	2.6 ± 0.9	9.5 ± 2.8	3.5 ± 1.1
BEI	0.12 ± 0.02	0.13 ± 0.04	0.16 ± 0.05	0.14 ± 0.04

See Table 3 for abbreviations. BRS and BEI, $n = 5$ subjects. * $P < 0.05$ baseline tilt vs. rest. † $P < 0.05$ 24 h post-SS Tilt vs. Rest

specific sites on the feet resulted in an overall improvement of motor parameters measured at 24 h after the stimulus was delivered.

Cardiovascular Autonomic Changes After Mechanical Stimulation of the Feet

The patients with PD involved in the present study were characterized by remarkable alterations in cardiovascular autonomic control, namely, by a blunted capability to increase the spectral markers of sympathetic modulation of the heart and arterial vessels during the upright position. This finding is in keeping with previous observations (3) reporting that in patients with PD and mild-moderate motor impairment, there is a reduced capability of properly activating the cardiac and vascular sympathetic activity during a gravitational stimulus, in the absence of other signs and symptoms of orthostatic intolerance.

Twenty-four hours after effective mechanical stimulation of the feet, we observed a significant increase in the spectral indices of cardiac (LF/HF ratio) and vascular (LF_{SAP}) sympathetic modulation during tilt, a pattern of sympathetic activation similar to the one previously described in healthy individuals (3, 16). This observation suggests that in our patients, sensory input arising from specific areas of the feet were involved in neural control of the autonomic response to the gravitational stimulus.

An important finding of our study is the reduction in LF_{SAP}, a spectral index of vascular sympathetic modulation 24 h after mechanical stimulation of the feet. Accordingly, blood pressure values were lower than those observed at baseline. In addition, a concomitant slight reduction in both the RR interval and the LF/HF index, together with a weak increase in the gain of arterial baroreceptor mechanisms (BRS and alpha indices) observed at rest after the effective stimulus, suggest a mild although nonsignificant enhancement of tonic and phasic cardiac parasympathetic modulation, possibly mediated by increased baroreceptor functioning.

The reduced cardiovascular sympathetic modulation while supine and the greater capability to enhance the vascular sympathetic modulation and reduce arterial baroreceptor gain

during the upright position indicate that the effective mechanical stimulation of the feet may promote a functional widening of the phasic control of the cardiovascular system exerted by neural sympathetic activity. This effect is likely achieved by a concomitant enhancement of the efficiency of arterial baroreflex mechanisms as inferred by their functional broadening (i.e., a larger gain decrease in response to the upright position).

Altogether, these findings bear potential important clinical implications. Given that PD is often characterized by remarkable clinostatic and nocturnal hypertension (38, 40), mechanical stimulation of the feet might be added to drug therapy to lower blood pressure and optimize its control in the supine position. In addition, the greater capability to decrease baroreflex gain and increase vascular sympathetic modulation during tilt might improve blood pressure control in the head-up position, thus reducing intensity and number of orthostatic intolerance episodes in these patients.

Notably, in a previous study (17), feet somatosensory activation by transcutaneous electrical nerve stimulation proved to affect the cardiovascular autonomic control by increasing arterial baroreceptor sensitivity in patients with heart failure. A proper long-term follow-up is needed to clarify whether these poststimulation autonomic modifications may play a role in delaying the progression of the autonomic impairment leading to orthostatic hypotension and upright position intolerance described in more than 40% of patients with PD (2).

Previous studies have shown that changes in cardiovascular autonomic control by arterial baroreceptor function manipulation may affect stance (7) and motor function by inhibiting spinal reflexes (36). On the other hand, activation of ergoreceptor associated fibers by the working muscle during gait results in profound changes in cardiovascular neural control, namely, an overall increase in cardiovascular sympathetic outflow (37).

Taken together, these observations support the concept of a complex functional neural network underlying motor and cardiovascular autonomic modifications observed 24 h after effective mechanical stimulation of the feet in our patients with PD.

This study was not designed to disclose the neural circuits mediating the observed autonomic changes following mechan-

ical stimulation of the feet. However, it could be reasonably suggested that the effect on cardiovascular autonomic control might be due to the activation of a tactile and/or nociceptive afferent pathway projecting to the medulla oblongata. These neural afferents were previously reported to influence both the sympathetic and parasympathetic branches with distinguishable features when activating the different groups of fibers (41). Evidence from different laboratories (9, 43) points to the nucleus tractus solitarius as a potential site where both nociceptive and homeostatic afferents regulating the cardiovascular system, including baroreceptor afferents, converge and are processed.

Study Remarks

In the present study, the magnitude of the modifications in the motor parameters following mechanical stimulation of the feet was mild, although statistically significant. However, an improvement involving at least one of the movement indices could be observed in 100% of the patients, suggesting that such a procedure may be beneficial in a large majority of patients.

In this investigation we used a quantitative methodology, such as computerized gait analysis, in an attempt to assess the extent of the patients' motor improvement following mechanical stimulation of the feet. Notably, such modifications in motor capability were previously described by the patients themselves when they consistently reported a remarkable increase in their ability to perform motor tasks during physical rehabilitation sessions. In addition, reduced stiffness and increased speed during walking were qualitatively evident by simple clinical examination in most of the patients attending our outpatient clinic after stimulation of the feet. Both our observations and patient reports taken together prompted us to design and carry out the present study.

It must be pointed out that we did not systematically address the problem of the effectiveness of the stimulus in relation to the magnitude of pressure used (i.e., whether pain onset was essential to obtain both the motor and autonomic effects 24 h after stimulation in our patients). Previous anecdotal observations from our laboratory suggested that mild skin pressures were ineffective in producing motor changes in these patients. In the present study we chose to address only the problem of site specificity efficacy of mechanical stimulation, and indeed found that stimulation of fictitious sites was ineffective in producing motor improvements and neural autonomic changes. We, however, acknowledge the importance of the problem of the intensity of the stimulus that future ad hoc designed studies should address.

Conclusions and Perspectives

Despite the small number of patients with PD, the data obtained in the present study highlight the strict functional relationships between lower limb somatosensory afferents and the neural control of gait on one side, and cardiovascular autonomic regulation on the other side. This complex neural network may be set in motion by the mechanical stimulation of specific points on the feet eventually resulting in the functional improvement of both gait and upright position cardiovascular autonomic control.

Thus according to a possible unifying hypothesis, effective stimulation of the feet by lowering the noradrenergic/adrener-

gic central network baseline activity and increasing the reactivity of this network projecting on the spinal cord during the upright position may eventually allow the spinal motor network to function more appropriately. Indeed, catecholamine release proved to modulate cell responsiveness to excitatory and inhibitory inputs as suggested in a neural network model by Servan-Schreiber and colleagues (39). In this context, we speculate that the repetition of mechanical stimulation of the feet every 48–72 h, combined with a pharmacological strategy aimed at further reducing vascular sympathetic drive at rest by increasing parasympathetic activity and baroreceptor gain with clonidine, pirenzepine, or scopolamine (33), may over time stabilize the gait and (34, 42) cardiovascular autonomic improvements in patients with PD.

From a clinical standpoint, gait improvement following sensory stimulation of the feet might allow PD drug dosage reduction, thus diminishing treatment side effects, thereby facilitating physical rehabilitation and, ultimately, reducing falls and disability.

After stimulation of the feet, the autonomic changes resulting in diminished resting blood pressure values may help in controlling clinostatic hypertension, which often is present in these patients. In addition, effective stimulation reestablished the capacity to increase cardiac and vascular sympathetic modulation in response to the gravity stimulus and widened the functionality of arterial baroreceptor mechanisms. We hypothesize that this autonomic change might contribute to delaying the onset of late orthostatic intolerance in patients with PD.

Finally, on the basis of results of the present study, devices may be engineered to perform controlled and automatic mechanical stimulations using the feet sites described in the present study. Additional investigations are obviously required to properly evaluate the effectiveness of such an automatic stimulation.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS

Author contributions: F.B., M.G., M.C., A.P., G.C., and R.F. conception and design of research; F.B., M.C., V.C., and F.D. performed experiments; F.B., M.G., L.D.V., V.C., A.P., V.B., F.D., T.B., and R.F. analyzed data; F.B., M.G., L.D.V., M.C., V.C., A.P., V.B., G.C., F.D., T.B., D.C., G.P., and R.F. interpreted results of experiments; F.B. and F.D. prepared figures; F.B., M.G., V.C., A.P., G.C., F.D., and R.F. drafted manuscript; F.B., L.D.V., M.C., A.P., G.C., T.B., D.C., G.P., and R.F. edited and revised manuscript; F.B., M.G., L.D.V., M.C., V.C., A.P., V.B., G.C., F.D., T.B., D.C., G.P., and R.F. approved final version of manuscript.

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