Original Article

Mechanical somatosensory stimulation decreases blood pressure in patients with Parkinson's disease

Antonio R. Zamunér[a], Dana Shiffer[b], Franca Barbic[b,c], Maura Minonzio[b], Carolina P. Andrade[d], Manuel Corato[e], Stefania Lalli[e], Franca Dipaola[b,c], Beatrice Cairo[f], Alberto Albanese[e], Alberto Porta[f,g], and Raffaello Furlan[b,c]

Objective: The current study aimed to assess the effects of five cycles of automated mechanical somatosensory stimulation (AMSS) of the fore-feet on blood pressure (BP) and cardiovascular autonomic control in Parkinson's Disease patients.

Methods: Out of 23 patients, 16 underwent an AMSS session every 72 h, for a total of five sessions per patient. Electrocardiogram, noninvasive beat-to-beat blood pressure and respiratory activity were recorded for 20 min in supine position at baseline and after the AMSS sessions. Main outcomes were the changes in SBP and DBP, in the spectral indices of cardiac sympathetic ($LF_{RR\ n.u.}$) and vagal (HF_{RR}) modulatory activities, cardiac sympathovagal relationship (LF/HF), vascular sympathetic modulation (LF_{SAP}) and arterial baroreflex sensitivity (sequence technique). Symbolic analysis of heart rate variability provided additional indices of cardiac sympathetic (0V%) and vagal (2UV%) modulation to the sinoatrial node.

Results: After five AMSS trials a reduction in SBP (baseline: 131.2 ± 15.5 mmHg; post-AMSS: 122.4 ± 16.2 mmHg; $P = 0.0004$) and DBP (baseline: 73.2 ± 6.1 mmHg; post-AMSS: 68.9 ± 6.2 mmHg; $P = 0.008$) was observed. Post-AMSS, spectral and symbolic indices of cardiovascular sympathetic control decreased and arterial baroreflex sensitivity increased (baseline: 5.7 ± 1.3 ms/mmHg; post-AMSS: 11.27 ± 2.7 ms/mmHg).

Conclusion: AMSS sessions were effective in reducing BP, increasing baroreflex sensitivity and decreasing cardiovascular sympathetic modulation in Parkinson's disease patients. AMSS might be useful to control supine hypertension in Parkinson's disease.

Keywords: cardiovascular autonomic control, heart rate and blood pressure variability, hypotension, Parkinson's disease, somatosensory stimulation, symbolic analysis of heart rate variability, sympathetic nervous system

Abbreviations: 0V, pattern with no variation derived from symbolic analysis; 1V, patterns with one variation derived from symbolic analysis; 2LV, patterns with two like variations derived from symbolic analysis; 2UV, patterns with two unlike variations derived from symbolic analysis; AMSS, automated mechanical somatosensory stimulation; ANS, autonomic nervous system; BP, blood pressure; CO, cardiac output; ECG, electrocardiogram; HFRR, high frequency derived from RR interval variability; HRV, heart rate variability; LFRR, low frequency derived from RR interval variability; LFSAP, low frequency derived from systolic arterial pressure variability; PD, Parkinson's disease; SAP, systolic arterial pressure; SD, standard deviation; SEM, standard error of the mean; TPR, total peripheral resistance

INTRODUCTION

Parkinson's disease is a neurodegenerative disorder mainly characterized by gait abnormalities. However, a variety of additional symptoms may occur, such as depression, sleep disorders, cognitive impairment as well as signs and symptoms of neural autonomic dysfunction, including supine hypertension and orthostatic hypotension [1–3].

Several studies have shown reduced cardiac sympathetic innervation or function in Parkinson's disease [1,4,5] based on cardiac norepinephrine up-take MIBG scan [6], norepinephrine spillover [5], Fluordopamine PET scan [7] and heart rate variability methodology [4]. In addition, initial alterations in both cardiac and vascular sympathetic modulation were revealed in Parkinson's disease patients by means of heart rate and arterial pressure variability analyses, particularly, whenever the gravitational stimulus was used [1].

Neurogenic supine hypertension [7] has been reported in almost 50% of Parkinson's disease patients [1], especially in advanced disease stages [8–13]. This is possibly related to a remaining sympathetic function in a setting of autonomic and baroreceptor abnormalities [14]. Notably, supine hypertension represents a potential risk factor for adverse

Journal of Hypertension 2019, 37:1714–1721

[a]Universidad Católica del Maule, Departamento de Kinesiología, Talca, Maule, Chile, [b]Internal Medicine, Syncope Unit, Humanitas Clinical and Research Center- IRCCS, [c]Department of Biomedical Sciences, Humanitas University, Rozzano, Milan, Italy, [d]Secretaria municipal de Saúde, Guarí, SP, Brazil, [e]Department of Neurology, Humanitas Research Hospital, Rozzano, [f]Department of Biomedical Sciences for Health, University of Milan and [g]Department of Cardiothoracic, Vascular Anesthesia and Intensive Care, IRCCS Policlinico San Donato, San Donato Milanese, Milan, Italy

Correspondence to Raffaello Furlan, MD, Humanitas University, Humanitas Clinical and Research Center, Via A. Manzoni, 56, 20089 Rozzano, Italy. Tel: +39 282247228; e-mail: raffaello.furlan@hunimed.eu

Received 27 October 2018 **Revised** 5 February 2019 **Accepted** 17 February 2019

DOI:10.1097/HJH.0000000000002084

cardiovascular events [8,12,13]. This requires appropriate antihypertensive treatment [1] that at present is only partially effective because medications may adversely result in daily orthostatic hypotension.

Of interest, a mild decrease in BP was found 24 h after manual mechanical stimulation of both fore-feet, in patients with Parkinson's disease, along with gait improvement [15]. Similar motor enhancement was described [16] 72 h after applying mechanical stimuli using a standardized foot pressure stimulation by an ad hoc developed boot (Gondola; Ecker Technologies, Lugano, Switzerland). However, the possible associated cardiovascular autonomic or hemodynamic changes were not addressed.

The current study aimed to assess the after effects induced by five cycles of automated mechanical somatosensory stimulation (AMSS) of the forefeet on the cardiovascular autonomic control and hemodynamics in a group of patients with Parkinson's disease. The hypothesis being that following somatosensory stimulation, a decrease in sympathetic vasomotor control and an increase of arterial baroreflex mechanisms were likely to occur which, in turn, would result in a possible decline in systemic blood pressure (BP).

METHODS

Study population

Twenty-three patients with idiopathic Parkinson's disease, characterized by moderate-to-severe motor impairment (Hoehn & Yhar stage 2–4) [17], were consecutively enrolled in the study. The patients had been referred to the neurology outpatient clinic of the Humanitas Research Hospital. Parkinson's disease diagnosis was made based on clinical criteria (complete medical evaluation, symptoms, physical examination and routine laboratory tests) [18,19] and a dopamine transporter scan. Exclusion criteria were: peripheral sensory neuropathy, liver, kidney, lung or heart diseases, diabetes or any disease possibly related to autonomic dysfunction. Five patients were excluded from the study based on these criteria.

In two patients, short periods of atrial fibrillation were detected during electrocardiographic monitoring and were, therefore, excluded from the final analysis. Hence, the final study population consisted of 16 individuals.

This clinical evaluation was performed at enrollment, 7 days before baseline recordings, in order to get patients familiarized with both the mechanical stimulator device (Gondola) and the clinical laboratory environment.

Parkinson's disease treatment remained unchanged for the preceding 30 days and throughout the study duration. The levodopa-equivalent daily dose (LEDD) was calculated [20]. Six out of the 16 patients had a previous diagnosis of essential hypertension and were treated with one or two antihypertensive medications (ace-inhibitors, calcium channel blockers and angiotensin receptor blockers), which remained unchanged throughout the duration of the study. Of those six patients, two were also found to have asymptomatic orthostatic hypotension during daytime; notably, they were taking their antihypertensive therapy late in the evening. In this subset of patients, AMSS was, therefore, added 'on-top' of the antihypertensive therapy.

The study protocol was approved by the institution's ethics committee and was registered on clinicalTrials.gov (#NCT02608424). We hereby present part of the results, specifically those dealing with the hemodynamic changes following automatic somatosensory stimulation. Following a thorough and detailed explanation of the study, scope and the procedures involved, all patients signed a written informed consent.

Experimental procedures

The AMSS was delivered over two specific points on each fore-foot using the Gondola medical device (Ecker Technologies). Detailed description of the device and the adjustments required before each session are provided elsewhere [16]. Briefly, Gondola is a shoe-shaped device supporting both feet. It consists of battery-supplied electrical motors, which activate two steel rods (smooth rounded tips) that deliver mechanical pressure over two specific areas of each fore-foot: the tip of the hallux and the plantar surface of the first metatarsal joint [16]. These specific sites were determined based on previous studies showing significant changes in the cardiovascular autonomic profile consistent with a decreased sympathetic modulatory activity and improvement of gait in Parkinson's disease patients [1,16].

Calibration procedure: during initial calibration, for each participant, the physician in charge gently increased the stimulation pressure, in a stepwise manner, until the nociceptive reflex appeared, seen as contraction of the tibialis anterior muscle. That pressure was set as the pressure value to be used for that specific patient. The reflex was identified by an experienced researcher.

Every participant underwent an AMSS session every 72 h for a total of five AMSS sessions in each patient.

Cardiovascular autonomic profile analysis

For each participant, an ECG, noninvasive beat-to-beat BP, cardiac output (CO), total peripheral resistance (TPR; Nexfin monitor, BMEYE B.V., Amsterdam, the Netherlands) and the respiratory activity (thoracic bellow) were continuously recorded for 15 min in the supine position.

The Nexfin device measures CO and TPR continuously by combining beat-by-beat blood pressure monitoring at the finger level, a transfer function approach to refer the recorded blood pressure waveform to the heart level, and a Windkessel model-based approach accounting for the decay of the blood pressure and the systolic pressure area [21].

All the signals were digitalized at 300 Hz/signal by an analog-to-digital converter (ADInstruments, Powerlab, PL3516/P, Oxford, United Kingdom) and stored on the hard disk of a personal computer for off-line analysis.

The Valsalva maneuver [22] and the sinus arrhythmia [23] test were also performed during the 15-min recording in order to complete the patients' autonomic assessment and to exclude the presence of a significant attending dysautonomia that might have impaired the AMSS effectiveness. Indeed, Valsalva maneuver addresses the integrity and efficiency of the blood pressure and heart rate changes relationship, as controlled by arterial baroreceptor mechanisms [22]. It is based on the evaluation of the reflex changes in heart rate in response to the perturbation of blood

pressure obtained by exhaling forcibly into a manometer to reach a pressure of 40 mmHg for 20 s and then releasing [22]. Sinus arrhythmia assesses the cyclic variation in heart rate that are coupled with respiration and is considered to reflect mainly the cardiac vagal modulation [23]. Valsalva and sinus arrhythmia ratios were computed by dividing the maximum heart rate value by the minimum heart rate value assessed during each of the tests.

SBP and DBP were also recorded by an automated device (Philips M3046A M3, Boebingen, Germany) and were determined as the average of four consecutive measurements obtained over 15 min in a supine position, and at 1, 3 and 5 min following active standing.

All participants were assessed twice during the study: baseline, that is, before intervention and 72 h after the last AMSS session.

Data analysis

Spectral analysis

Software techniques for data acquisition, spectral and cross-spectral analyses of RR interval, systolic arterial pressure (SAP) variability, and respiratory activity have been described in detail elsewhere [24,25]. Briefly, the heart rate spontaneously fluctuates because of the instantaneous influences of the excitatory sympathetic modulation and inhibitory vagal influence on the sinus node activity [25]. These fluctuations give rise to the so-called heart rate variability [25]. Spectral analysis techniques may assess both the amplitude and the frequency of these oscillations [25,26].

There are two major oscillatory components obtained from RR interval variability. The high frequency (HF) component has a central frequency ranging from 0.15 to 0.4 Hz and its power, termed HF_{RR}, is taken as an index of the vagal efferent modulation directed to the sinoatrial node [24,25]. The low frequency (LF) component has a central frequency ranging from 0.04 to 0.15 Hz and its power is indicated as LF_{RR}. When LF_{RR} is expressed in normalized units may be considered as an index of the sympathetic modulation of the sinoatrial node activity and of its changes [25], although its physiological meaning is still debated [26,27], because of its possibly sympathetic and vagal mixed origin [28]. If LF is obtained from systolic arterial pressure variability (LF_{SAP}), it is a noninvasive marker of the sympathetic vasomotor control [24,25,29]. The LF_{RR}/HF_{RR} ratio, a dimensionless index, assesses the sympathovagal instantaneous modulation to the cardiac sinoatrial node [24,29].

Symbolic analysis

Symbolic analysis was used as an additional method to estimate cardiac autonomic control. A full description of symbolic analysis is provided elsewhere [30]. Briefly, it is a nonlinear method used to analyze heart rate variability (HRV) allowing the characterization and quantification of the prevalence of sympathetic and parasympathetic modulations to the heart. It is based on a process, which transforms the RR intervals series into short patterns of three beat sequences, classifies them and quantifies their occurrence rate and distribution in the RR series. As it considers and recognizes short patterns occurring in the RR interval series, it is deemed more suitable for the study of short nonlinear heart rate variability instabilities, which may occur in disorders associated with major HRV alteration [31].

Initially, a segment of RR interval sequences was selected and was uniformly spread on six levels. Each RR value was substituted with an integer coding the level it belonged to. Then, corresponding three-symbol length patterns were constructed. Quantification of the complexity of the pattern distribution was achieved by calculating the Shannon Entropy of the distribution of the patterns [30]. All the resulting possible patterns were grouped into one of several possible categories: 0V, flat symbolic pattern with no variation (all three symbols are equal); 1V, patterns with one variation (two equal consecutive symbols and one different); 2LV, patterns with two like variations (the three symbols form an increasing line or decreasing ramp) and 2UV, patterns with two unlike variations (the symbols form a peak or a valley).

Each pattern occurrence rate is given in percentage over the total amount of patterns (i.e. 0V, 1V, 2LV and 2UV%). Previous studies have shown that the occurrence rate of 0V patterns (i.e. prevalence of no variations) reflects cardiac sympathetic modulation whereas 2UV patterns are linked to parasympathetic modulation of the heart [32–34].

Baroreflex analysis

Baroreflex sensitivity was assessed using the baroreflex sequence analysis technique [35–37] as implemented in the study by Porta *et al.* [38,39]. This relies on the identification of sequences characterized by the contemporary increase (positive sequence) or decrease (negative sequence) of four RR and SAP values (i.e. three variations). Both positive and negative sequences are referred to as baroreflex sequences. They were identified according to the following prerequisites: the length of the sequences was four beats (three increases or decreases); the time-lag between RR and SAP values was set at 0 s; the total SAP variation was greater than 1 mmHg; the total RR variation was longer than 5 ms; the correlation coefficient in the plane [SAP(i),RR(i)], where i is the cardiac beat number, was greater 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. Hereafter, this average is indicated as BRS and expressed in ms/mmHg.

Statistical analysis

The Wilcoxon Signed Rank Paired Test was used to assess the differences between the cardiovascular autonomic profile at baseline (pre-AMSS procedures) and after the last AMSS procedure in the same group of patients. Significance level was set at 5% for all analyses. Data are expressed as mean ± standard deviation (SD) in tables and as mean ± standard error (SEM) in Fig. 1 in order to optimize spaces. The statistical analyses were performed using the BioStat software.

RESULTS

Demographic and clinical features of the patients with Parkinson's disease are summarized in Table 1. The

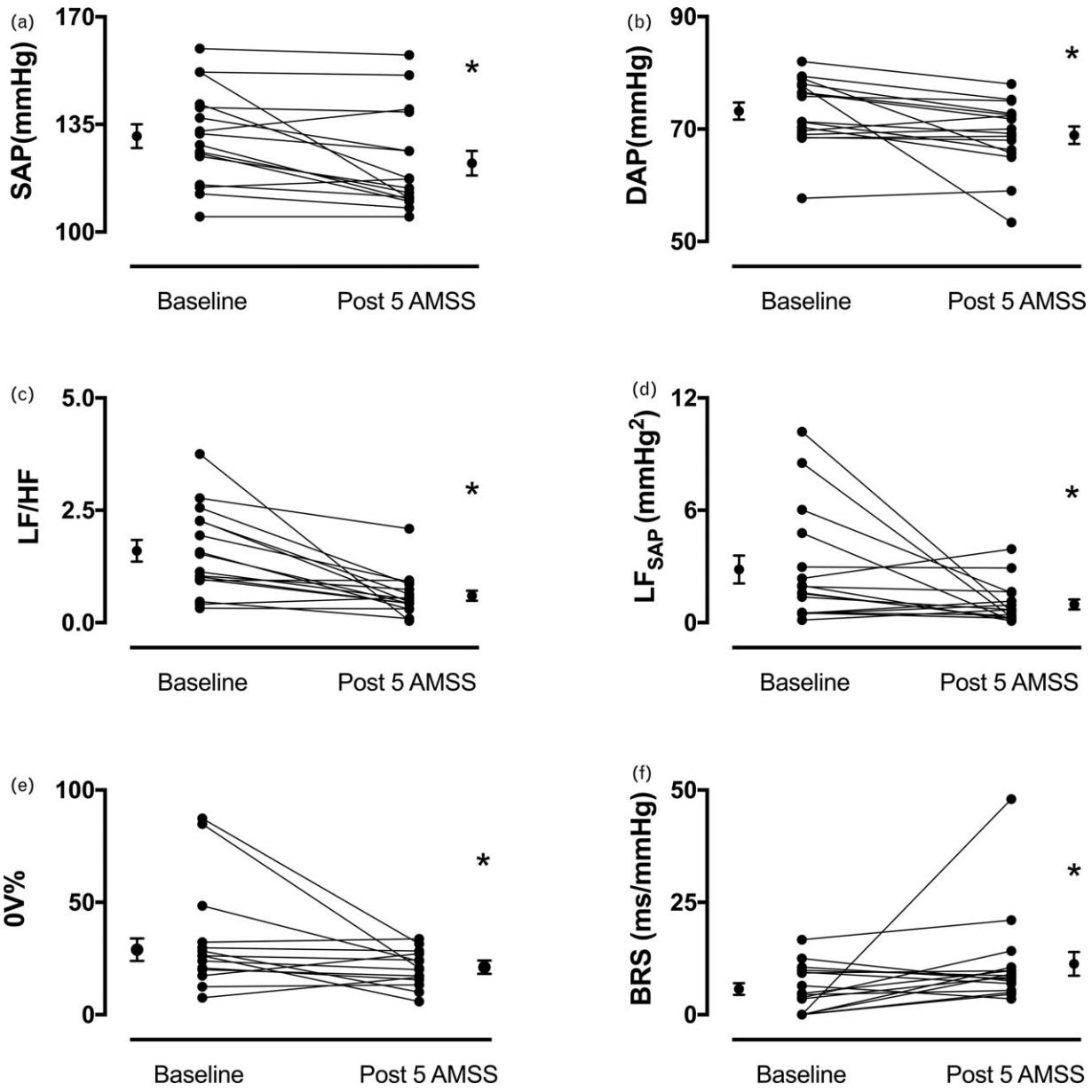

FIGURE 1 Changes observed in each Parkinson's disease patient and groups mean values ± SEM of the hemodynamics, spectral and symbolic analysis indices and arterial baroreceptor sensitivity, induced by five automated mechanical somatosensory stimulation. Notice that a decrease in both systolic and diastolic arterial pressure was consistently observed in 14 out of 16 of patients (panels a and b). Blood pressure values were automatically and intermittently assessed by the Phillips Comfort Care Adult device. Panels c and d highlight the decrease in the markers of cardiac and vascular sympathetic modulation after AMSS. The greater the markers values at baseline the greater their decline after AMSS. The 0V%, a symbolic index of cardiac sympathetic modulation (panel e), decreased after AMSS in keeping with panels c and d markers pattern. Finally, BRS sensitivity increased after AMSS (panel f). AMSS, automated mechanical somatosensory stimulation; BRS, arterial baroreflex sensitivity index; DAP, diastolic arterial pressure; LF/HF, ratio between the low-frequency and the high-frequency components of RR variability; LF_{SAP}, low-frequency component of SAP variability; 0V(%), occurrence rate of flat symbolic pattern because of no variation; SAP, systolic arterial pressure.*$P < 0.05$.

TABLE 1. Demographic and clinical features of the patients with Parkinson's disease

Characteristics	Value
Age (years)	66.2 ± 9.4
Male/female	6/10
BMI (kg/m^2)	24.2 ± 2.8
Hoehn–Yahr stage	2–4
UDPRS-III score	25.3 ± 16.6
Disease duration (years)	7 ± 3.5
Levodopa (mg/day)	249.5 ± 351.6
LEDD (mg/day)	249.5 ± 351.7

Data expressed as mean ± SD. LEDD, Levodopa equivalent daily dosage (mg/day); UDPRS-III, Unified Parkinson's Disease Rating Scale, motor score.

mean ± SD values of the hemodynamics and respiratory activity observed in the patients in resting condition at baseline and post five AMSS sessions are presented in Table 2. At rest, there were no significant differences between baseline and post five AMSS sessions in heart rate (HR) and respiratory rate. In contrast, systolic and diastolic arterial BPs decreased significantly ($P = 0.0004$ and $P = 0.008$, respectively).

During active standing, no changes were observed in both HR and blood pressure values compared with the supine position. In addition, no modifications were seen in arterial pressure after AMSS sessions upon active standing (Table 2).

TABLE 2. Hemodynamic and respiratory profile of Parkinson's disease patients at baseline and post five automated mechanical somatosensory stimulation sessions, assessed in supine position (rest) and upon active standing during out-patient clinic evaluation

Parameter	Baseline	Post five AMSS	*P* value
Rest			
HR (bpm)	66.4 ± 9.3	67.9 ± 7.9	0.13
SAP (mmHg)	131.2 ± 15.5	122.4 ± 16.2	0.0004
DAP (mmHg)	73.2 ± 6.1	68.9 ± 6.2	0.008
Resp (cycles/min)	18.6 ± 3.2	18.0 ± 2.9	0.50
Active standing			
HR (bpm)	74.5 ± 10.7	74.9 ± 12.0	0.90
SAP (mmHg)	124.6 ± 17.7	122.3 ± 17.8	0.18
DAP (mmHg)	75.1 ± 8.3	73.3 ± 6.6	0.11
Resp (cycles/min)	19.4 ± 4.7	18.1 ± 3.2	0.51

AMSS, automatic mechanical somatosensory stimulation; DAP: diastolic arterial pressure; HR, heart rate; Resp, respiratory activity; SAP, systolic arterial pressure. Data expressed as mean ± SD. *P* value less than 0.05 was considered significant.

Individual changes in systolic and diastolic arterial pressures induced by five AMSS sessions are exhibited in panels (a) and (b) of Fig. 1. Note that a decrease in BP values after AMSS sessions was observed in the large majority of Parkinson's disease patients (14 out of 16), although of different magnitudes.

Table 3 summarizes the autonomic changes induced by the AMSS sessions in supine position as well as the attending modifications in CO and TPR. No changes were observed in Valsalva ratio and sinus arrhythmia ratio values. There was a significant decrease in the LF/HF ratio suggestive of a diminished cardiac sympathetic modulation and/or increased cardiac vagal drive. Additionally, a decrease in the marker of sympathetic vasomotor modulation (LF_{SAP}) and a concomitant increase in the vagal related spectral component (HF_{RR} nu) were observed, compared with baseline ($P < 0.05$). The decrease in the indices of vascular sympathetic modulation after AMSS sessions were associated with a significant decrease in TPR and an expected increase in CO. Figure 2 depicts the power spectra of the RR interval, systolic arterial pressure variability and respiration at baseline and after five AMSS sessions in a representative Parkinson's disease patient. Following AMSS sessions, the low-frequency oscillatory components of RR and SAP variability markedly declined compared with baseline. This suggests a reduction in the overall cardiovascular sympathetic modulation after AMSS. Furthermore, the cardiac vagal-related oscillatory component, HF_{RR}, was slightly enhanced after AMSS, pointing to a shift in the sympathovagal relationship towards a reduced sympathetic prevalence.

TABLE 3. Autonomic and hemodynamic changes induced by the automatic mechanical somatosensory stimulation sessions, as obtained by RR interval and systolic arterial pressure variability analysis

Parameters	Baseline	Post five AMSS	*P* value
VM ratio	1.34 ± 0.18	1.35 ± 0.17	0.93
SA ratio	1.25 ± 0.12	1.25. ± 0.13	0.86
R-R interval (ms)	897.6 ± 183.9	867.4 ± 162.4	0.16
σ^2_{RR} (ms^2)	563.4 ± 507.3	591.0 ± 802.0	0.38
HF_{RR} (ms^2)	123.5 ± 136.8	110.4 ± 104.1	0.67
HF_{RR} (nu)	50.2 ± 13.7	66.0 ± 17.0	0.002
LF_{RR} (ms^2)	138.4 ± 113.7	76.4 ± 149.1	0.02
LF_{RR} (nu)	49.8 ± 13.7	34.0 ± 17.0	0.002
LF/HF	1.56 ± 0.96	0.60 ± 0.48	0.0007
SAP (mmHg)	130.3 ± 19.1	115.00 ± 18.9	0.003
σ^2_{SAP} ($mmHg^2$)	14.9 ± 12.5	13.85 ± 9.1	0.71
LF_{SAP} ($mmHg^2$)	2.84 ± 3.02	0.97 ± 1.09	0.038
0V (%)	33.27 ± 24.37	21.14 ± 8.09	0.049
2ULV (%)	18.08 ± 8.15	21.58 ± 1.99	0.09
BRS (ms/mmHg)	5.7 ± 1.3	11.27 ± 2.66	0.04
CO (L/min)	6.37 ± 0.85	6.95 ± 0.80	0.001
TPR (mmHg s/ml)	2951.06 ± 586.51	2422.83 ± 688.80	0.002

Data expressed as mean ± SD. σ^2_{RR}, variance of R-R interval; σ^2_{SAP}, variance of systolic arterial pressure; 0V(%), occurrence rate of flat symbolic pattern because of no variation; 2ULV (%) occurrence rate of patterns with two unlike variations (the three symbols form increasing or decreasing lines); BRS, arterial baroreflex sensitivity; CO, cardiac output; HF, high-frequency component; LF, low-frequency component; LF/HF, ratio between the low frequency and the high frequency components of RR variability; nu, normalized units; SA, sinus arrhythmia, ratio between the highest and the lowest heart rate values during a 2-min long controlled respiration at six breaths per minute; SAP, systolic arterial pressure; TPR, total peripheral resistance; VM ratio, ratio between the highest and the lowest heart rate values during the Valsalva maneuver.

In Fig. 1, panels (c) and (d) illustrate the individual changes in the spectral indices of the cardiac sympathovagal relationship (LF/HF) and sympathetic vasomotor control (LF_{SAP}), respectively, before and after AMSS. Please notice the significant decrease of both indices after AMSS. In addition, the greater the LF/HF and LF_{SAP} were at baseline the greater was their decrease after five AMSS. Panels (e) and (f) show the modifications of the symbolic analysis index of cardiac sympathetic modulation (0V%) and of the arterial baroreflex gain (BRS), respectively, after AMSS. The decrease of 0V% after AMSS is in keeping with the LF/HF changes, corroborating the hypothesis of a decline in the sympathetic modulation to the heart. Likewise, AMSS induced a significant enhancement in the cardiac baroreflex sensitivity, as indicated by the increase ($P = 0.04$) of BRS compared with baseline.

DISCUSSION

The main findings of the present study were a decline in supine arterial BP, a concomitant decrease in the overall cardiovascular sympathetic control and increase in arterial baroreflex sensitivity after five AMSS cycles in Parkinson's disease patients. Importantly, AMSS did not induce any additional decrease in blood pressure upon active standing and did not lead to orthostatic hypotension [7] in Parkinson's disease patients.

The results of the current investigation are in agreement with those reported in a previous study showing a reduction of vascular sympathetic modulation in Parkinson's disease patients in the supine position, 24 h after a single session of mechanical somatosensory stimulation of the feet [15]. In the current study, the use of symbolic analysis of RR variability, which assesses the separate contribution of the sympathetic and vagal modulation to the sinoatrial node activity by a nonlinear methodology, corroborated the finding obtained by the autoregressive spectral approach. Indeed, the markers of cardiac sympathetic modulation (i.e. 0V%, LF_{RR} nu and the LF/HF ratio) were reduced after repetitive AMSS had been applied to the fore-feet, compared with baseline. As to the vagal cardiac modulation, the results of the current study are less consistent. Despite the significant increase of the HF_{RR} in nu, suggestive for an

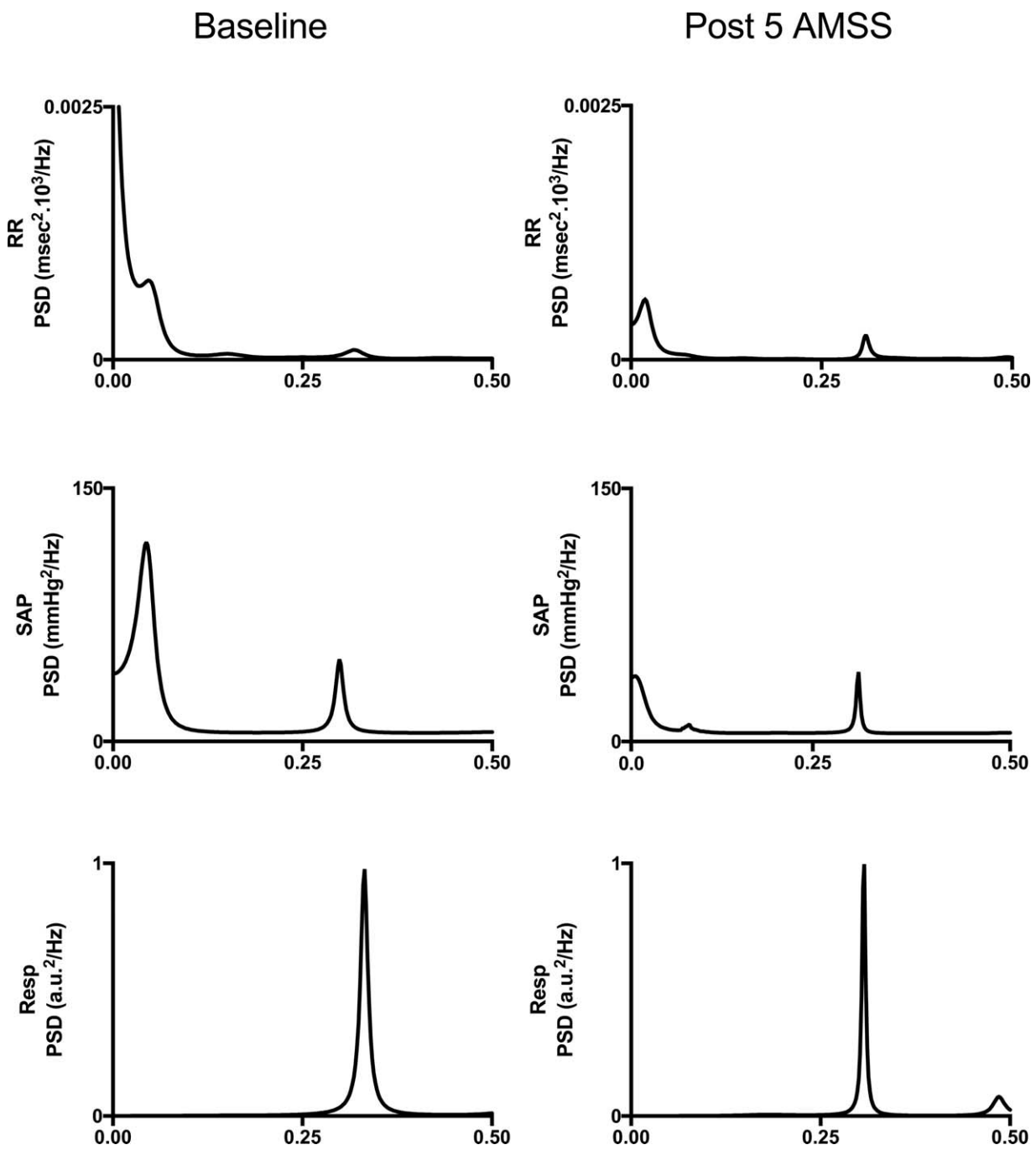

FIGURE 2 Power spectral analysis of a single Parkinson's disease patient in the supine position, obtained at baseline and post five automated mechanical somatosensory stimulation. Please notice that after the AMSS sessions, there was a clear reduction of the low-frequency component of both RR interval and SAP variability suggesting an overall reduction in cardiovascular sympathetic modulation. AMSS, automated mechanical somatosensory stimulation; PSD, power spectrum density; Resp, respiratory activity; RR, RR interval; SAP, systolic arterial pressure.

increased vagal modulation of the sinoatrial node activity, definitive conclusions cannot be drawn as the values in both HF and 2UV% indices remained unchanged.

This modified autonomic pattern was associated with a decrease in total peripheral resistance and in both systolic and diastolic arterial pressure while recumbent. This last finding is in keeping with preliminary results observed 24 h following a single manual somatosensory stimulation, in a study performed by our group [15]. Valsalva maneuver and sinus arrhythmia tests were unmodified after AMSS. That finding is not surprising, given that results of these tests shift to abnormality in the presence of a clear dysautonomia, which is not the case of our Parkinson's disease population.

A significant increase in baroreceptor sensitivity was also observed after AMSS. HR did not change compared with baseline in spite of the presence of lower blood pressure values after AMSS, possibly because of the reduced cardiac sympathetic modulation and/or increased vagal activity to the heart that might have blunted the expected increase of heart rate in response to reduced blood pressure values.

The decline in arterial pressure after repetitive AMSS may be relevant for the clinical control of supine hypertension and 'nondipping' BP often occurring in these patients. Nondipping BP is defined as the absence of nocturnal BP fall [9,40]. In fact, six out of the 16 patients in the present study had a previous diagnosis of essential hypertension. It is important to mention that the use of antihypertensive medications can promote or exacerbate orthostatic hypotension during the day in Parkinson's disease patients with autonomic dysfunction. This along with the postural instability characterizing Parkinson's disease could increase the risk of falls and injury, thus adversely impacting patients' autonomy and quality of life. Notably, AMSS did not induce a fall in blood pressure in the upright position. AMSS, therefore, could be considered as a potential therapeutic tool for BP control strategy in Parkinson's disease patients with supine hypertension and orthostatic hypotension. However, ad hoc studies should address this issue in the future.

The mechanisms underlying the effects of AMSS on cardiovascular autonomic control and BP are still unknown. However, a possible interaction between sensory inputs from specific areas of the plantar surface of the foot and neural control of the ANS might play a role [15]. This hypothesis arises from the fact that the mechanical somatosensory stimulation pressure, used during this procedure, was set as the pressure, which elicited a pain withdraw reflex response. This implies that the nociceptive somatosensory pathway is stimulated during an entire stimulation procedure (lasting about 2 min). It is known that the ANS and nociceptive somatosensory system interact at several levels, including the periphery and brainstem, among others [41]. In the brainstem, the nucleus tractus solitarius has an important linking role between the autonomic and sensory systems and may receive and process afferents from both nociceptive and cardiovascular regulating homeostatic pathways [41,42]. Thus, it is reasonable to hypothesize that AMSS applied to the fore-feet could elicit cardiovascular adaptation by the peripheral nociceptive and/or tactile afferent pathways. In turn, these afferent pathways project to the medulla oblongata that contains the cardiovascular autonomic control centers [41].

Hemodynamic results similar to those seen in the present study, that is, a decrease in SBP and DBP values without changes in heart rate, were observed in seven hypertensive patients after painless somatosensory stimulation by neuromuscular taping [43]. Moreover, a study conducted by Gademan *et al.* [44] showed that periodic electrical somatosensory stimulation of the feet increased BRS in chronic heart failure patients. As for the possible underlying mechanisms, the authors suggested that periodic application of electrical stimulus may excite mainly A-δ nerve fibers [44,45], responsible for carrying somatosensitive afferent information and mediate cold, touch and sharp pain perception. Hence, somatosensory stimulation could lead to hypothalamic endorphynergic system activation, which in turn activate serotonergic descending inhibitory fibers to the rostral ventral lateral medulla (RVLM). This ultimately may inhibit sympathetic outflow and possibly contribute to a decrease in arterial BP [41,46]. Although the type of stimulus and the stimulated points were different from those in the present study, it is reasonable to assume that a similar mechanism might underlie the autonomic and hemodynamic modifications observed in the current study.

Limitations

Two limitations of the present study should be acknowledged: a control group of patients was not included and no sham stimulation was performed.

As to the first issue, the current protocol was very demanding for our Parkinson's patients who had to undergo five sessions of somatosensory stimulation, in the hospital, over the 3-week duration of the study. Because of that, we hypothesized that a patient control group would be excessively fatigued by this protocol without any potentially useful intervention. Thus, we deemed such an approach unfeasible.

Regarding the sham stimulation issue, as the present investigation lacked a control group of patients, a possible placebo effect promoting the current findings could not be excluded. However, in a previous study on Parkinson's disease patients, conducted by our group [15], a somatosensory sham stimulation had been used in clinically similar patients and resulted in nonsignificant modifications of both the autonomic profile indices and hemodynamic parameters, compared with the effective stimulation. Taking this group as reference may help us to indirectly rule out a placebo influence affecting the results of the current investigation. This is because of the likely presence of site-specific efficacy of the mechanical somatosensory stimulation [15].

Perspectives

Five repetitive sessions of AMSS by mechanical pressure applied for a short time-period on the fore-feet, were effective in reducing BP at rest, increasing baroreflex sensitivity and decreasing cardiovascular sympathetic modulation. This approach might be considered in future studies as a therapeutic strategy for promoting a reduction in resting BP in patients with Parkinson's disease characterized by supine hypertension.

ACKNOWLEDGEMENTS

We thank Parkinson's disease patients who volunteered to participate in the study.

Source of funding: The present study was supported by Fondazione Humanitas per la Ricerca.

Conflicts of interest

There are no conflicts of interest.

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