**Difference in cardiovascular response during orthostatic stress in Parkinson's disease and multiple system atrophy**

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Total word count: 3852, Number of references: 38, Number of tables: 4, Number of figures: 1

**Keywords**: Parkinson's disease; multiple system atrophy; cardiac response; cardiac denervation; total peripheral resistance; orthostatic hypotension

**Acknowledgements**

We are grateful to Dr. Akira Takahashi, former Professor of Nagoya University, for his kind suggestions and advice.

**Abstract**

**Background and purpose**

Although orthostatic hypotension is more prominent in multiple system atrophy (MSA) than in Parkinson's disease (PD), there is no study comparing the degree of decrease in total peripheral resistance and cardiac response during orthostatic stress between both diseases. In this study, we examined whether there is a difference in cardiovascular response between MSA and PD.

**Methods**

We examined the results of the head-up tilt test in 68 patients with MSA, 28 patients with cardiac non-denervated PD, and 70 patients with cardiac denervated PD whose total peripheral resistance after 60° tilting was lower than the value at 0°. Differences in cardiac output and blood pressure changes were compared against the decrease in total peripheral resistance.

**Results**

There was no difference in the degree of decrease in total peripheral resistance among the three groups. However, the slope of the regression line revealed that the increase in cardiac output against the change in total peripheral resistance was significantly lower in the MSA group than in the cardiac non-denervated and denervated PD groups, and that the decrease in systolic blood pressure against the change in total peripheral resistance was significantly greater in the MSA group than in the cardiac non-denervated and denervated PD groups.

**Conclusions**

In MSA, the cardiac response during orthostatic stress is lower than that in PD, possibly underlying the fact that orthostatic hypotension is more prominent in MSA than in PD.

**Introduction**

Multiple system atrophy (MSA) is an adult-onset neurodegenerative disease clinically characterized by parkinsonism, cerebellar dysfunction, pyramidal tract involvement, and autonomic dysfunction (Gilman et al. 2008). Almost all patients with MSA develop autonomic dysfunction at some point during the course of the disease. This usually manifests as urinary disturbance and orthostatic hypotension (OH), which are important symptoms used in the diagnosis of MSA. OH is defined as a reduction in systolic blood pressure (SBP) ≥ 20 mmHg or diastolic blood pressure (DBP) ≥ 10 mmHg within 3 minutes of standing or head-up tilt to an angle of at least 60°. A more pronounced reduction ( ≥ 30 mmHg for SBP and/or ≥ 15 mmHg for DBP) is often reported in MSA and is one of the criteria for probable MSA (Sun et al. 2016; Pavy-Le Traon et al. 2016). The frequency of occurrence of OH in MSA is reported to be 41 - 88% (Suzuki et al. 2015). A recent large study involving 349 patients with MSA revealed that 187 patients (54%) had moderate (≥ 20 mm Hg for SBP and/or ≥ 10 mm Hg for DBP) or severe ( ≥ 30 mmHg for SBP and/or ≥ 15 mmHg for DBP) OH(Pavy-Le Traon et al. 2016).

OH is also one of the commonly occurring non-motor symptoms in patients with Parkinson's disease (PD) and its prevalence in PD varies between 9.6% and 58% (Fereshtehnejad and Lokk 2014). Central lesions in the upper brainstem affecting postural control of BP through baroreflex failure, and loss of sympathetic innervation, e.g., postganglionic impairment, most noticeably in the heart, are suggested to be the main causes of OH in PD (Jain and Goldstein 2012; Nakamura et al. 2014; Iodice et al. 2011). On the other hand, in MSA, the loss of sympathetic preganglionic neurons in the intermediolateral spinal cord and supraspinal lesions of areas involved in central autonomic control (notably in the brainstem) contribute to autonomic failure (Pavy-Le Traon et al. 2016). Regardless of the actual mechanisms, they will ultimately contribute to the inability to increase vascular resistance and/or cardiac output during orthostasis in these patients (Iodice et al. 2011). Differences in such pathological conditions may cause

differences in cardiovascular responses and in the degree of OH.

Previously, we found that there is a difference in cardiac response at the same degree of total peripheral resistance reduction during the head-up tilt test between patients with cardiac non-denervated and cardiac denervated PD. Patients with cardiac non-denervated PD showed a higher cardiac response than those with cardiac denervated PD, which leads to the difference in BP change during orthostatic stress, whereby patients with cardiac non-denervated PD are less likely to demonstrate OH (Nakamura et al. 2014). However, there is no report on the difference in cardiac response to the decrease in total peripheral resistance between MSA and PD.

In this study, we investigated changes in total peripheral resistance and cardiac output, the major autonomic factors associated with SBP reduction during the head-up tilt test, in patients with MSA and PD, and whether an intergroup difference exists in the cardiac response to the decrease in total peripheral resistance, and if so, whether it leads to the difference in the degree of BP reduction during the head-up tilt test between patients with MSA, cardiac non-denervated PD, and denervated PD.

**Methods**

Subjects

We retrospectively investigated the results of patients with PD and MSA who underwent the head-up tilt test at Nagoya University Hospital. PD and MSA were diagnosed according to the diagnostic criteria (Gibb and Lees 1988; Gilman et al. 2008). Disease onset was defined as the time the patient first experienced motor symptoms.

The head-up tilt test was performed in the morning in a temperature-controlled clinical laboratory (average temperature 25 ± 2°C) after an overnight fast. Any drugs that might

influence the cardiovascular system, such as antiparkinsonian drugs, were discontinued at least 12 h before the examination. After resting for at least 5 min in a supine position, patients were gradually tilted up to 60° in 20° increments (20°, 40°, and 60° for 5 min each), as described in previous reports (Nakamura et al. 2011; Nakamura et al. 2014). Continuous non-invasive cardiovascular monitoring was performed using an impedance cardiography device (Task Force Monitor, CNSystems, Medizintechnik, Graz, Austria). Electrocardiograms (ECG) were recorded continuously using four spot electrodes. Beat-to-beat BP measurements were obtained via finger plethysmography of the index finger on one side of the hand and continuously corrected to the BP of the brachial artery on the opposite side of the arm obtained by oscillometric measurements. Cardiac parameters such as total peripheral resistance and cardiac output were obtained at every beat from the impedance cardiography, and the averages of the last 30 s at the 0° and 60° tilt were used for the analysis. The bioimpedance technique may not accurately measure absolute values (Cybulski et al. 2012; Tang and Tong 2009). However, this technique accurately determines relative changes over a wide range of conditions (Boer et al. 1979). Thus, in this study, we focused on these relative changes in the analysis. We evaluated patients who showed a decrease in total peripheral resistance at 60° as compared with that at 0°. Decreased total peripheral resistance was indicated when the total peripheral resistance of the position at 60° was lower than that at 0° in the head-up tilt test. Individuals with diabetes mellitus, any known heart disease, or other neurological disorders were excluded. Patients who were taking an ergot dopamine agonist, had been diagnosed with a valvular disorder, or were taking selegiline were also excluded.

Because OH may be observed after 3 min of orthostatic stress in autonomic failure, such as PD (Jamnadas-Khoda et al. 2009; Freeman et al. 2011), OH was diagnosed as a reduction in SBP of at least 20 mmHg and/or DBP of at least 10 mmHg at the 5 min mark in the 60° position compared to baseline (Goldstein et al. 2015; Nakamura et al. 2016). However, when the test was

stopped in the middle of the protocol, owing to severe hypotension or any patient complaint that required test interruption, the data obtained just before discontinuation of the tilt test were still used. Supine hypertension was defined as SBP ≥ 140 mmHg and/or DBP ≥ 90 mmHg, measured after at least 5 min of rest in the supine position (Fanciulli et al. 2018).

Cardiac $^{123}$I-metaiodobenzylguanidine (MIBG) scintigraphy

All participants underwent cardiac MIBG scintigraphy. MIBG (111 mBq) was injected intravenously, and delayed images were obtained after 3 h. Regions of interest included the whole heart and the mediastinum in the anterior projection, and the MIBG heart-to-mediastinum (H/M) ratio was calculated and evaluated. We defined H/M ratios <1.7 as cardiac denervation and those ≥ 1.7 as no cardiac denervation. The delayed image reflects the functional status and displays the neuronal uptake more explicitly than the early image, and an H/M ratio <1.7 is the value that we previously determined to represent cardiac denervation (Nakamura et al. 2010)

Olfactory testing

The odor-identification performance of each patient with PD was measured using the Odor Stick Identification Test for Japanese (OSIT-J, Daiichi Yakuhin, Co., Ltd., Tokyo, Japan), which consists of 12 odorants familiar to Japanese people (normal = 8–12 points) (Baba et al. 2011). This test has been successfully applied for the assessment of odor-identification ability in Japanese patients with PD and the precise protocol used has been described previously (Oka et al. 2010; Mizutani et al. 2014; Hara et al. 2013).

Statistical analyses

SPSS software version 27 (SPSS, Chicago, IL) was used for statistical analyses. Significant differences were defined as $p < 0.05$. Data are expressed as mean ± standard deviations. Categorical variables were analyzed by chi-square statistics. The Mann-Whitney U test was

performed for the comparisons of two groups. For comparisons of more than two groups, data were analyzed by nonparametric analysis of variance (ANOVA), and statistical significance was further examined by Kruskal-Wallis test for multiple comparison. The Spearman rank correlation was calculated to assess the correlation between the data. A multivariate analysis was performed to estimate the predictors of SBP changes during the head-up tilt test by using the following factors: age, disease duration, body mass index (BMI), levodopa equivalent daily dose, H/M ratio of cardiac MIBG, SBP at 0°, change in cardiac output, and change in total peripheral resistance in MSA. Factors such as Hoehn and Yahr scale score and OSIT-J score were also analyzed in addition to these factors in PD. Differences in the correlation coefficients of the regression lines obtained from the groups were analyzed. A linear mixed model analysis was also conducted while analyzing the regression lines to determine whether various background factors also affected the covariates of the dependent variables.

## Results

### *Clinical characteristics*

We identified 68 patients with MSA, 70 patients with cardiac denervated PD, and 28 patients with cardiac non-denervated PD. The characteristics of the three groups are shown in Table 1. Among the patients with MSA, 35 had predominant parkinsonian features (MSA-P) (20 probable and 15 possible) and 33 had predominant cerebellar ataxia (MSA-C) (23 probable and 10 possible). Brain magnetic resonance imaging (MRI) revealed abnormalities in the putamen that were considered to be MSA in 18 cases, cerebellar or brainstem abnormalities that were consistent with MSA in 33 cases, and abnormalities in both areas in 12 cases. There were 5 cases without obvious brain MRI abnormalities: 4 of these were diagnosed as probable MSA, while 1 case had pyramidal lesions diagnosed as possible MSA. Dysuria was observed during the head-up tilt test in 59 out of 68 patients with MSA, but not in any of the patients with

cardiac non-denervated PD. There were 18 cases with MSA wherein levodopa was used, but none of the patients had a good responsiveness to this. On the other hand, all patients with cardiac non-denervated PD were diagnosed with clinically established PD according to the diagnostic criteria of the Movement Disorder Society in 2015 (Postuma et al. 2015), due to the presence of favorable levodopa reactivity and resting tremor with no red flags after the head-up tilt test. Cardiac MIBG showed no abnormalities in all patients with MSA. Body weight and BMI were significantly different in multiple comparisons but not in the post hoc comparison. There were no differences in the use of pressor agents or antihypertensive medications that affect the cardiovascular system among the groups. Rasagiline was used in only 1 patient from the cardiac denervated PD group (H/M ratio = 1.19).

OSIT-J showed olfactory dysfunction with a score of 7 or less in 62 cases from the cardiac denervated PD group and in 15 cases from the cardiac non-denervated PD group.

*Result of the head-up tilt test*

Supine hypertension was observed in about 30% of patients, but there was no difference in its frequency among the groups (Table 2). The 60° head-up tilt test was discontinued in the middle of the protocol in 3 patients with MSA (one with dizziness at 1 minute and another at 2 minutes, and one with a complaint of difficulty in standing) and 3 patients with PD (one with poor physical condition at 1 minute, one with a decreased SBP of <60 mmHg at 1 minute, and one who felt unwell at 2 minutes). The frequency of OH was significantly higher in the MSA group than in the cardiac non-denervated PD group. In the comparison between the MSA and cardiac denervated PD groups, the frequency of OH was also significantly higher in the MSA group ($p = 0.042$). There was no difference in the change in total peripheral resistance among the three groups. However, there was a significant difference in the changes in cardiac output and SBP: the change in cardiac output in the cardiac non-denervated PD group was significantly higher than that in the cardiac denervated PD and MSA groups; the decrease in SBP was significantly

higher in the cardiac denervated PD and MSA groups than in the cardiac non-denervated PD group. In one patient taking rasagiline, the SBP decreased by 41 mmHg, total peripheral resistance decreased by 51%, and cardiac output increased by 64%.

*Factors related to SBP reduction during the head-up tilt test*

Table 3 shows the correlation between the SBP changes and the various parameters. Change in cardiac output showed a correlation with SBP changes in all the groups, and SBP at 0° and change in total peripheral resistance showed a correlation in the MSA and cardiac denervated PD groups. The multiple stepwise regression analysis confirmed that SBP at 0°, change in cardiac output, and change in total peripheral resistance were independently related to the SBP changes during the head-up tilt test in the MSA and cardiac denervated PD groups. The changes in cardiac output and total peripheral resistance were independently related to the SBP changes during the head-up tilt test in the cardiac non-denervated PD group (Table 4).

*Changes in cardiac output and SBP change against decrease in total peripheral resistance*

Change in cardiac output correlated with change in total peripheral resistance in the cardiac non-denervated ($\rho = 0.61$, $p < 0.001$) and cardiac denervated ($\rho = 0.66$, $p < 0.001$) PD groups but not in the MSA group ($\rho = -0.15$, $p = 0.23$). By analyzing the regression line, we examined differences in slope or *y*-intercept between the changes in cardiac output and SBP and the change in total peripheral resistance during the head-up tilt test between the three groups. The results showed that the cardiac denervated PD group had a lower response to cardiac output and greater SBP decrease against the decrease in total peripheral resistance than the non-denervated PD group. Furthermore, the MSA group had poorer response to cardiac output and greater decrease in SBP against the decrease in total peripheral resistance than both PD groups (Fig 1). In the linear mixed model analysis, the disease severity in PD patients, disease duration, body weight, BMI, and levodopa-equivalent dose had no influence as background factors on the

change in SBP and change in cardiac output against the change in total peripheral resistance. However, age had a background effect on SBP changes against the change in total peripheral resistance between the MSA and cardiac denervated PD groups ($p = 0.004$).

**Discussion**

In this study, we showed that changes in total peripheral resistance and cardiac output were both determinants of SBP change during the head-up tilt test, but the involvement of cardiac response differs depending on the disease and cardiac condition. The cardiac response during orthostatic stress is more impaired in MSA than in PD with and without cardiac denervation, with similar changes in total peripheral resistance providing a possible reason for the prominence of OH in MSA compared to PD.

Generally, OH results from autonomic failure that reduces the capacity to increase vascular resistance on standing, resulting in venous pooling in the lower extremities, thereby reducing the stroke volume and cardiac output (Jamnadas-Khoda et al. 2009; Smit et al. 1999). Our results showed that the abovementioned mechanism was more frequent in patients with MSA, despite their younger age and shorter disease duration, than in those with cardiac denervated PD. The precise mechanism of the difference in cardiovascular response on standing between PD and MSA is unclear. In MSA, the intermediolateral nucleus of the spinal cord is mainly involved in BP regulation such as increased peripheral vascular resistance and increased cardiac output. Once affected, both the peripheral blood vessels and the heart are affected simultaneously; hence, BP may decrease easily during standing. Conversely, PD is a slowly progressing disease as compared with MSA, and the damage of the sympathetic nerves of the peripheral blood vessels and the heart progresses independently and slowly. Thus, cardiac response may not be as impaired as that in MSA, even when peripheral blood vessels are impaired, which results in peripheral vasoconstriction failure. This may more likely occur in

cardiac non-denervated PD. Although the pathological background of the cardiac non-denervated PD group is unclear, it is reported that not all components of the autonomic nervous system are uniformly affected at the same time in the course of PD and that the cardiovascular autonomic control and reactivity system may be impaired in different ways at multiple sites (Haensch et al. 2009)

Decreased uptake of cardiac MIBG scintigraphy may be observed in patients with MSA (Skowronek et al. 2019), and a previous study reported that 30% of patients with MSA show decreased cardiac uptake of MIBG (Nagayama et al. 2010). The precise mechanisms underlying low cardiac MIBG uptake in patients with MSA remain unclear. However, pathological changes within the sympathetic ganglia with a concomitant Lewy body pathology may be a suitable explanation for the low myocardial MIBG uptake in patients with MSA (Nagayama et al. 2010). In addition, other studies reported almost abolished norepinephrine content in the myocardial tissue of autopsied patients with MSA having alpha-synuclein deposits limited to the glial cells, excluding the neurons or sympathetic ganglia, which suggests that cardiac sympathetic denervation can occur even without Lewy bodies or alpha-synuclein deposition in neurons in patients with MSA (Cook et al. 2014). In this study, all patients with MSA had normal cardiac MIBG values, so poor cardiac response due to cardiac denervation unlikely caused a greater SBP decrease. In the future, if some cases with MSA have decreased cardiac MIBG uptake, investigating whether such patients will demonstrate greater decreases in BP than the participants in this study may be useful.

A recent large-scale study of MSA revealed that OH magnitude is strongly associated with disease severity (UMSARS I, II and IV), orthostatic symptoms (UMSARS I), and supine hypertension (Pavy-Le Traon et al. 2016). However, we did not evaluate UMSARS or orthostatic symptoms. Thus, the association of such index with total peripheral

resistance/cardiac output should be studied in the future. If this point is clarified, the clinical features of patients who are likely to exhibit OH in patients with MSA could be predicted. The correlation between resting SBP at 0° and the SBP change in the cardiac denervated PD and MSA groups supports a previous report claiming that supine hypertension could influence SBP change. Some patients with supine hypertension were taking hypertensive or antihypertensive agents, and such agents can also affect hemodynamic responses during the tilt test. However, as shown in Table 2, the number of supine hypertension patients taking hypertensive or antihypertensive drugs was small, and the frequency was not different among the groups. Therefore, we considered that the use of hypertensive and antihypertensive agents had little effect on the difference in cardiac response and BP changes among the groups.

As for PD, higher levels of fasting blood glucose, higher levels of hemoglobin A1c (HbA1c), higher levodopa-equivalent daily doses (Li et al. 2019), and disease severity (Kotagal et al. 2016) are all associated with OH. Fasting blood glucose and HbA1c were not analyzed in the present study, thus the possibility that these factors affect hemodynamic changes needs further investigation. With regard to levodopa-equivalent daily dose and disease severity, multiple regression analysis and linear mixed model analysis did not find any association with SBP changes. However, as the cardiac denervated PD group had higher Hoehn and Yahr score and larger amount of levodopa-equivalent daily dose than the cardiac non-denervated PD group, these factors may also be important for hemodynamic responses.

BMI in the cardiac denervated PD group was lower than that in the cardiac non-denervated PD group, although without statistical significance; thus, BMI may also be a factor of cardiac response during orthostatic stress in PD. However, in our previous report on the relationship between BMI and OH in PD (Nakamura et al. 2017), we divided patients by sex and age, so further cases are needed to clarify this.

Distribution of the SBP changes in PD in the present study is different from that in our previous study (Nakamura et al. 2014). In our previous report, 45 out of 95 patients with PD had a reduction in total peripheral resistance during the tilt test, whereas the remaining patients had an increase in total peripheral resistance and were unlikely to have OH. In the present study, we focused on the cardiac response against decrease in total peripheral resistance and the resulting SBP change. Therefore, patients with an increased total peripheral resistance were not included in this study. This may underlie the different patient distribution between studies. Regarding MSA, in our previous report, 69.5% of 82 patients with MSA had decreased total peripheral resistance during the tilt test (Suzuki et al. 2015). This is also different from the frequency of OH in MSA in the present study.

When using the linear mixed model to analyze the differences between the regression lines of the MSA and cardiac denervated PD groups, age was found to affect the results of SBP change. However, the patients with MSA were younger than those with cardiac denervated PD. Therefore, we arrived at these results because of the fact that patients with MSA tends to have lower BP despite being younger.

Rasagiline was used in one patient with cardiac denervated PD. Rasagiline is a MAO-B inhibitor that carries a risk of OH (Tolosa and Stern 2012) and may reduce the H/M ratio on cardiac MIBG scintigraphy (Chung and Kim 2015; Nakamura and Sobue 2016). Severe hypotension during the head-up tilt test and the reduced H/M ratio in this patient may be due to this drug. If this patient is excluded, the regression line for change in cardiac output in Fig. 1 changes to $y = -0.896x-9.4918$, and the regression line for SBP change changes to $y = 0.4316x-9.5044$. However, there would be no difference in the overall results of group comparisons (not shown in the results), and the overall conclusion would not change.

We did not include a control group in the present study. This is because normal subjects present an increase in peripheral vascular resistance in response to orthostatic stress (Suzuki et al. 2015). In this study, we analyzed patients with a decrease in total peripheral resistance, so there was no need to set up a control group.

There are several limitations in this study. First, impedance cardiography is affected by body weight: the higher the weight, the lower actual cardiac output is measured (Woltjer et al. 1996; van der Meer et al. 1997). It is generally believed that weight loss more likely progresses in PD than in MSA, and other factors such as age and duration of the disease may also influence the weight (Ma et al. 2018). There was no significant difference in body weight or BMI among the groups on post hoc test; however, patients in the cardiac denervated PD group tended to be lighter; this may have had some influence on the measurements. Second, although we confirmed that all patients in the cardiac non-denervated PD had good levodopa responsiveness, absence of clear abnormalities suggesting MSA on brain imaging, and absence of dysuria, some patients with MSA may have been included in the cardiac non-denervated PD group, because patients in both groups do not have reduced MIBG uptake and their olfactory function is usually normal.

## Conclusion

The cardiac response against similar reduction in peripheral resistance during head-up tilt appears to be lower in patients with MSA than in those with PD, which may be one of the reasons for the high frequency and severity of OH in patients with MSA.

## Compliance with ethical standards

Conflicts of interest

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

Ethical standards

This study was conducted in accordance with the 1964 Declaration of Helsinki and its later amendments. The study was approved by the Ethics Review Committee of Nagoya University. Written informed consent was waived because the study involved only a retrospective review of routine clinical tests and medical records. Instead, the study protocol was open to the public to assure the patients' right to withdraw.

**Funding**

This work was supported by a grant from the Ministry of Health, Labor, and Welfare of Japan.

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**Figure captions**

**Fig. 1** Comparison of the regression line between the groups. a, The regression line of the changes in cardiac output (*y*) and total peripheral resistance (*x*). The *y*-intercept of the regression line of the cardiac non-denervated PD group was significantly higher than that of the cardiac denervated PD group ($p < 0.001$). The slope regression line was significantly less steep in the MSA group than in the cardiac non-denervated ($p = 0.017$) and denervated PD groups ($p < 0.001$). b, Regression line of the changes in SBP (*y*) and total peripheral resistance (*x*). The *y*-intercept of the regression line of the cardiac non-denervated PD group was significantly higher than that of the cardiac denervated PD group ($p < 0.001$), and the regression line slope was significantly steeper in the MSA group than in the cardiac non-denervated ($p = 0.022$) and denervated PD groups ($p = 0.007$). PD: Parkinson's disease; MSA: multiple system atrophy; SBP: systolic blood pressure

Table 1. Clinical characteristics of the subjects

| | PD | | MSA | *p* |
|---|---|---|---|---|
| | Cardiac denervated group (n = 70) | Cardiac non-denervated group (n = 28) | MSA-P (n = 35) MSA-C (n = 33) | |
| Sex (M/F) | 37/33 | 13/15 | 38/30 | 0.70 |
| Age (y) | 66.7 ± 8.7[a] | 62.4 ± 9.8 | 61.6 ± 7.6 | 0.001 |
| Disease duration (y) | 6.7 ± 5.0[b, c] | 2.2 ± 1.9 | 2.5 ± 1.5 | < 0.001 |
| Hoehn and Yahr scale | 2.6 ± 1.1 | 2.1 ± 0.8 | - | 0.031 |
| OSIT-J score | 3.9 ± 2.6 | 6.5 ± 3.4 | - | 0.001 |
| Cardiac MIBG H/M ratio | 1.30 ± 0.16[b, c] | 2.76 ± 0.59 | 3.33 ± 0.79 | < 0.001 |
| Body weight (kg) | 52.5 ± 12.1 | 57.7 ± 10.6 | 57.3 ± 14.7 | 0.042* |
| Body mass index (kg/m$^2$) | 20.3 ± 3.4 | 21.9 ± 3.2 | 21.9 ± 4.3 | 0.028* |
| L-dopa equivalent dose (mg/day) | 346.3 ± 368.4[c, d] | 130.8 ± 283.9 | 97.2 ± 192.6 | <0.001 |
| Pressor agents | n = 7 (10%) | n = 0 (0%) | n= 8 (12%) | 0.176 |
| Antihypertensive drugs | n = 3 (4%) | n = 5 (18%) | n = 4 (6%) | 0.070 |

[a] vs MSA, p = 0.001, [b] vs Cardiac non-denervated PD, p < 0.001, [c] vs MSA, p < 0.001, [d] vs Cardiac non-denervated PD, p = 0.002, *no significant differences between the two groups in the post hoc comparison.

PD; Parkinson's disease, MSA; multiple system atrophy, P, parkinsonian form of MSA, C, cerebellar form of MSA, OSIT-J; Odor Stick Identification Test for Japanese, MIBG; $^{123}$I-metaiodobenzylguanidine, H/M; heart to mediastinum

Table 2. Head-up tilt test

| | PD | | MSA | *p* |
|---|---|---|---|---|
| | Cardiac denervated group | Cardiac non-denervated group | | |
| SBP at 0° (mmHg) | 123.9 ± 20.5 | 123.0 ± 20.7 | 123.1 ± 19.9 | 0.93 |
| DBP at 0°(mmHg) | 75.9 ± 12.7 | 76.3 ± 13.3 | 78.9 ± 14.5 | 0.45 |
| HR at 0°(bpm) | 67.0 ± 11.6 | 65.7 ± 11.7 | 68.6 ± 9.9 | 0.28 |
| ⩘SBP (mmHg) | -17.8 ± 15.0 [a] | 1.3 ± 11.1 [b] | -23.5 ± 25.7 | <0.001 |
| ⩘DBP (mmHg) | -6.8 ± 8.7 [c] | 3.7 ± 9.9 [b] | -11.4 ± 15.9 | <0.001 |
| ⩘HR (/min) | 12.0 ± 7.2 | 11.4 ± 7.8 | 12.4 ± 9.3 | 0.89 |
| Supine hypertension | n = 19 (27%) | n = 7 (25%) | n = 22 (32%) | 0.74 |
| Pressor agents | n = 1 (5%) | n = 0 (0%) | n = 5 (23%) | 0.180 |
| Antihypertensive drugs | n = 1 (5%) | n = 2 (29%) | n = 1 (5%) | 0.188 |
| Orthostatic hypotension | n = 33 (47%) | n = 1 (4%) | n = 44 (65%) | <0.001 |
| Pressor agents | n = 4 (9%) | n = 0 (0%) | n = 8 (18%) | 0.67 |
| Antihypertensive drugs | n = 1(2%) | n = 0 (0%) | n = 2 (5%) | 0.91 |
| Change in total peripheral resistance (%) | -19.0 ± 11.8 | -19.3 ± 11.0 | -21.4 ± 13.9 | 0.75 |
| Change in cardiac output (%) | 7.9 ± 16.4 [a] | 26.1 ± 16.9 [b] | 6.4 ± 17.8 | < 0.001 |

[a] vs Cardiac non-denervated PD, $p < 0.001$, [b] vs MSA, $p < 0.001$, [c] vs Cardiac non-denervated PD, $p = 0.001$.

PD; Parkinson's disease, MSA; multiple system atrophy, SBP; systolic blood pressure, DBP; diastolic blood pressure, HR; heart rate

Table 3. Correlation with SBP change during the head-up tilt test

| | PD | | | | MSA | |
|---|---|---|---|---|---|---|
| | Cardiac denervated group | | Cardiac non-denervated group | | | |
| Clinical parameters | ρ | p | ρ | p | ρ | p |
| Age | -0.20 | 0.102 | 0.17 | 0.40 | -0.06 | 0.61 |
| Disease duration | 0.03 | 0.83 | 0.06 | 0.78 | 0.02 | 0.99 |
| Hoehn and Yahr scale | -0.21 | 0.87 | -0.49 | 0.009 | | |
| OSIT-J score | -0.10 | 0.94 | -0.16 | 0.44 | | |
| Cardiac MIBG H/M ratio | 0.24 | 0.045 | 0.06 | 0.76 | 0.02 | 0.85 |
| Body mass index | -0.06 | 0.61 | 0.38 | 0.047 | -0.12 | 0.34 |
| L-dopa equivalent dose | -0.14 | 0.25 | -0.26 | 0.185 | 0.43 | < 0.001 |
| SBP at 0° | -0.46 | < 0.001 | -0.05 | 0.80 | -0.63 | < 0.001 |
| Change in total peripheral resistance | 0.35 | 0.003 | 0.06 | 0.76 | 0.47 | < 0.001 |
| Change in cardiac output | 0.33 | 0.005 | 0.47 | 0.011 | 0.62 | < 0.001 |

PD; Parkinson's disease, MSA; multiple system atrophy, OSIT-J; Odor Stick Identification Test for Japanese, MIBG; $^{123}$I-metaiodobenzylguanidine, H/M; heart to mediastinum, SBP; systolic blood pressure,

Table 4. Stepwise multiple regression analysis for SBP change

| | B | SE | β | p |
|---|---|---|---|---|
| Cardiac denervated PD[a] | | | | |
| Constant | 31.724 | 54.848 | | < 0.001 |
| SBP at 0° | -0.273 | 0.038 | -0.381 | < 0.001 |
| Change in total peripheral resistance | 1.301 | 0.094 | 1.046 | < 0.001 |
| Change in cardiac output | 0.840 | 0.067 | 0.952 | < 0.001 |
| Cardiac non-denervated PD[b] | | | | |
| Constant | -4.775 | 3.316 | | 0.164 |
| Change in total peripheral resistance | 0.537 | 0.161 | 0.574 | 0.003 |
| Change in cardiac output | 0.620 | 0.123 | 0.870 | < 0.001 |
| MSA[c] | | | | |
| Constant | 43.875 | 8.697 | | < 0.001 |
| SBP at 0° | -0.419 | 0.073 | -0.357 | < 0.001 |
| Change in total peripheral resistance | 0.993 | 0.107 | 0.532 | < 0.001 |
| Change in cardiac output | 0.683 | 0.076 | 0.556 | 0.001 |

SBP; systolic blood pressure, PD; Parkinson's disease, MSA; multiple system atrophy.

[a]Adjusted $R^2 = 0.814$, $F = 97.136$, $p < 0.001$, [b]Adjusted $R^2 = 0.500$, $F = 12.940$, $p < 0.001$, [c]Adjusted $R^2 = 0.800$, $F = 86.562$, $p < 0.001$.

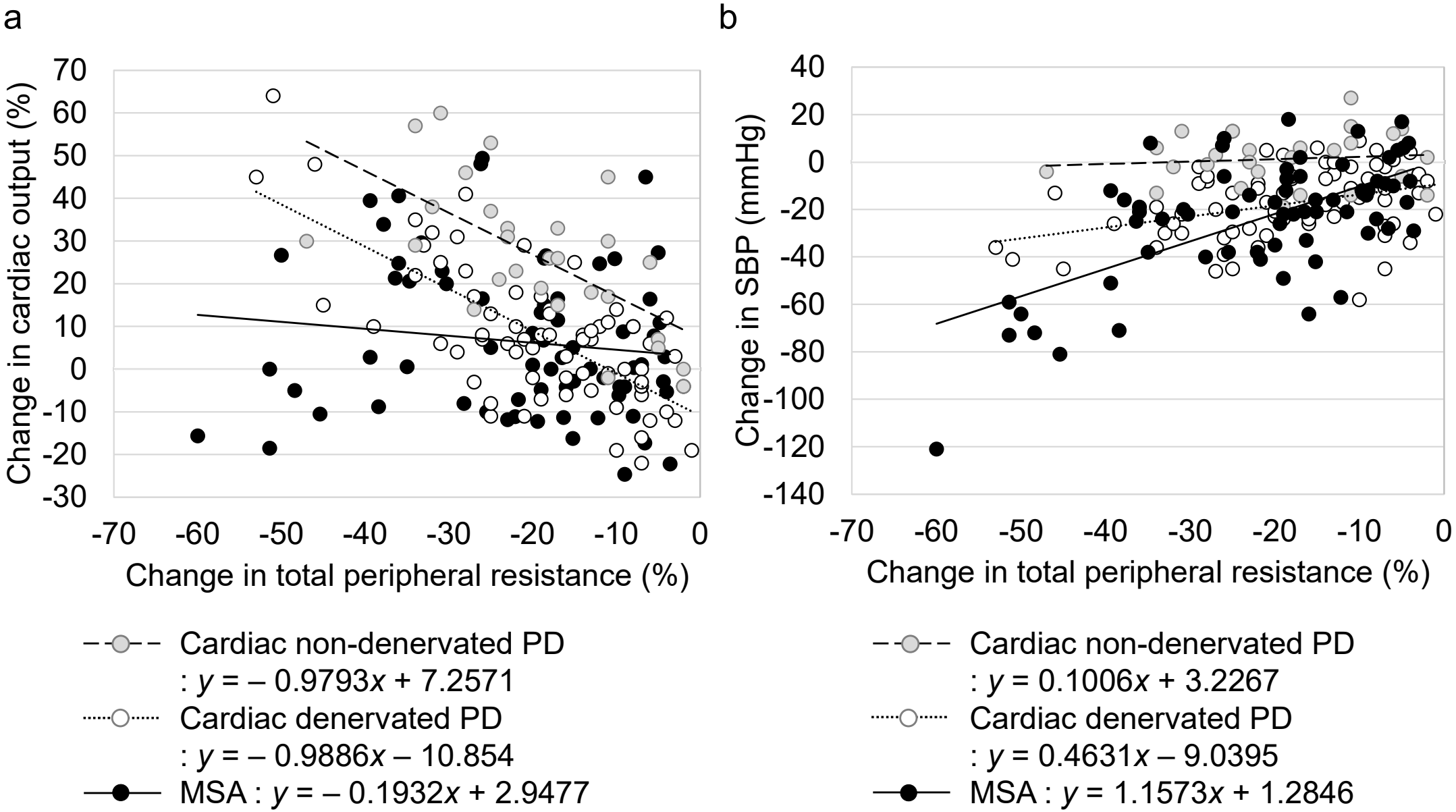
a
b
Change in cardiac output (%)
70
60
50
40
30
20
10
0
-10
-20
-30
-70
-60
-50
-40
-30
-20
-10
0
Change in total peripheral resistance (%)
Change in SBP (mmHg)
40
20
0
-20
-40
-60
-80
-100
-120
-140
Change in total peripheral resistance (%)
Cardiac non-denervated PD
: y = – 0.9793x + 7.2571
Cardiac denervated PD
: y = – 0.9886x – 10.854
MSA : y = – 0.1932x + 2.9477
Cardiac non-denervated PD
: y = 0.1006x + 3.2267
Cardiac denervated PD
: y = 0.4631x – 9.0395
MSA : y = 1.1573x + 1.2846

Fig. 1