*Neurology Asia 2012; 17(4) : 311 – 318*

# Exploring orthostatic hypotension in patients with multiple system atrophy by a non-invasive cardiac output system

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### *Abstract*

*Objective:* To detect early subclinical signs of autonomic dysfunction in the cardiovascular system and explore the mechanism of orthostatic hypotension (OH) in patients with multiple system atrophy (MSA). *Methods:* Eighteen male patients with possible MSA and 10 healthy men were recruited. The hemodynamic responses to head-up tilt and tilt-reversal were studied by an electrically-powered tilt table and a non-invasive cardiac output measurement (NICOM) system. *Results:* At supine, there was no significant difference in blood pressure, heart rate (HR), stroke volume, cardiac output and total peripheral resistance between MSA patients and healthy controls. During tilting upright, OH developed in 5 MSA patients, with a 23.7±4.8 mmHg drop in systolic blood pressure. Patients with OH were older and exhibited higher scores in unified Multiple System Atrophy Rating Scale part I than patients without OH. The stroke volume, cardiac output and total peripheral resistance did not differ between groups. The controls had the most significant HR elevation (6.5±2.5 bpm) during tilt-up, followed by patients without OH (2.8±1.6 bpm) and those with OH (-0.2±2.2 bpm). A similar trend of HR decrease was observed during return to supine posture. The process of tilt-reversal altered HR more significantly than head-up tilt in controls (8.0±2.9 vs 6.5±2.5 bpm; P=0.031) and patients without OH (4.2±2.1 vs 2.8±1.6 bpm; P=0.032), but not in patients with OH (1.2±1.5 vs -0.2±2.2 bpm; P=0.380).
*Conclusions:* The HR change during postural challenge showed significant difference between MSA patients and healthy controls. Impaired HR responsiveness contributed to OH in MSA. Monitoring HR during the tilt table test may be a practical and useful method to detect early autonomic dysfunction in patients with MSA.

## INTRODUCTION

Multiple system atrophy (MSA), ranking the third of extrapyramidal syndromes[1], should be suspected when seeing patients with cerebellar ataxia or Parkinsonism, poor responsiveness to levodopa and autonomic dysfunction.[2] Urological complaints appear to be the first symptom of autonomic disturbance followed by orthostatic hypotension (OH).[3] Disordered regulation of blood pressure against orthostatic stress indicated disease progression and shortened survival in MSA patients[4], but may not be identified until it becomes symptomatic. Since sudden blood pressure drop while standing upright leads to cerebral hypoperfusion, patients can present with syncope that hampers their safety and daily activities. Thus detection of autonomic failure in cardiovascular systems at the subclinical stage helps in preventing falls due to OH.

Maintaining homeostasis during postural challenge requires immediate withdrawal of parasympathetic output and subsequent activation of sympathetic outflow. Patients with MSA are known to have impairment in central sympathetic neuronal transmission[5] and cardiovagal responsiveness.[6] Therefore, reduced peripheral vasoconstriction, failure of reflex tachycardia and inability to augment cardiac

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contractility can probably be responsible for the development of OH in MSA patients. Understanding the underlying mechanisms contributes to successful treatments, although current strategies mainly rely on medication, lifestyle changes, physical measures or wearing stockings to enhance fluid retention or venous return.[7] Previous studies used the arterial waveform change of middle phalanx to estimate hemodynamic variables at the tilt table test.[8] However, some bias may arise when the device is applied on an elderly population with sclerotic arteries.[9] The new equipments that measure the bioreactance alternations of the thoracic wall are less influenced by the vascular properties and can better depict cardiovascular changes during the dynamic changes.[10] In the present study, we employed this non-invasive cardiac output system on MSA patients and healthy controls during the tilt table study, and attempted to explore the mechanism of OH and early subclinical signs of cardiovascular dysfunction in MSA patients.

## METHODS

We recruited 18 patients with possible MSA from the Neurology Outpatient Department of the National Taiwan University from September 2010 to March 2011. The diagnosis of MSA was based on the consensus conference in 2008.[11] All the patients had rapidly progressive Parkinsonism accompanied by poor responsiveness to levodopa and at least one symptom suggesting autonomic disturbance. Only males were included owing to the requirement of exposing anterior chest for hemodynamic measurement. Patients with pulmonary or cardiovascular diseases were excluded. All the patients were evaluated using the Unified Multiple System Atrophy Rating Scale (UMSARS)[12], which is a multidimensional, reliable and valid scale for semiquantitative clinical assessments of MSA patients. It comprises the following components: Part I, historical, 12 items; Part II, motor examination, 14 items; Part III, autonomic examination; and Part IV, global disability scale. Ten healthy adults without systemic diseases or medication affecting autonomic systems were chosen as controls. This study was approved by the Research Ethic Committee of the hospital and all subjects signed the informed consent form before participation.

### *Hemodynamic measurement*

Blood pressure was recorded by using a tonometric device (TANGO, SunTech Medical Instruments, Inc., North Carolina, USA) placed at the brachial artery distal to right elbow crease. The arm under test was placed parallel to the trunk at the same level of heart. Mean arterial pressure was defined as two third diastolic blood pressure plus one third systolic blood pressure. The NICOM (Non-invasive cardiac output measurement) system (Cheetah Reliant, Cheetah Medical, Inc., Oregon, USA) was used to measure hemodynamic alternations during the head-up tilt test. The skin of participants' front chest was wiped with alcohol and shaved if necessary. Four dual-electrode stickers were then attached to anterior apices and base of the thorax along bilateral mid-clavicular lines. Each dual-electrode is capable of transmitting and receiving electric current, whose changes vary proportionally to blood flow in the aorta. The NICOM system can estimate stroke volume by measuring the phase shifts and voltage difference between the applied and recorded current signals. The measurement correlates well with the values obtained by a Swan-Ganz catheter[10] and remains stable under dynamic conditions.[13] Cardiac output can be calculated through multiplying stroke volume by heart rate (HR), whereas total peripheral resistance is derived from mean arterial pressure divided by cardiac output. The hemodynamic variables were presented by their 30-second average.

### *Head-up tilt protocol*

The dopaminergic medication and therapy for OH were withheld 12 hours before the test. The studies were carried out in the morning at least 2 hours postprandially in temperature-controlled conditions (temperature 25-28°C). Five minutes supine rest was required prior to the initial 5 minutes of baseline measurement. Then the electrically-powered tilt table was tilted up to 60 degrees within 15 seconds for 10 minutes and returned to the horizontal plane with continuous observation for additional 5 minutes. If the participant complained of neurological or cardiovascular discomfort related to fall of blood pressure, he would be reclined to the supine position immediately.

### *Statistical analysis*

The hemodynamic variables and basic characteristics were analyzed by using nonparametric Kruskal-Wallis test (alpha=0.05) and post hoc Mann-Whitney U test with the Bonferroni correction. We compared the magnitude of hemodynamic changes between

the head-up tilt and tilt-reversal by employing repeated measures analysis of variance. All the analyses were performed using of SPSS software version 12 (SPSS, IBM Corporation, Somer, NY). Statistical significance was assumed when P values were less than 0.05.

## RESULTS

According to blood pressure recorded during the tilt table test, we divided the participants into three groups for analysis: controls and patients with- and without OH. OH referred to a drop in 20 mmHg of systolic blood pressure and a reduction in 10 mmHg of averaged diastolic blood pressure in comparison with baseline values.[13] The basic demographic data were listed in Table 1. The patients with OH were significantly older and had higher scores in UMSARS[14] part I than the other two groups. No significant difference existed regarding disease duration, Hoehn-Yahr stage, UMSARS part II and IV between patients with- and without OH.

At supine, blood pressure, HR, stroke volume, cardiac output and total peripheral resistance did not differ between groups. After head-up tilt, 5 patients fulfilled the criteria of OH, with a 23.7±4.8 mmHg drop in systolic blood pressure. One of the 5 patients complained of dizziness during postural challenge and was reclined to supine position at 6 minutes after tilting up. Systolic blood pressure reduced minimally in controls (1.4±5.8 mmHg); whereas it dropped more in patients without OH (5.7±8.8 mmHg). Stroke volume, cardiac output, total peripheral resistance and their changes from baseline remained similar among three groups (Table 2; Figure 1). HR elevated more significantly in controls than in patients with OH (6.5±2.5 vs -0.2±2.2 bpm; P=0.001) and without OH (6.5±2.5 vs 2.8±1.6; P=0.001). The patients without OH tended to raise HR more than those developing OH (2.8±1.6 vs -0.2±2.2 bpm; P=0.019) (Table 2).

After returning to supine position, patients with OH displayed a 18.2±10. 8 mmHg increase in systolic blood pressure compared with that during tilting up, whereas systolic blood pressure increased minimally in controls (2.6±6.1 mmHg) and patients without OH (0.7±9.1mmHg). Stroke volume, cardiac output, total peripheral resistance and the corresponding changes from head-up tilting showed no difference among three groups (Table 2; Fig 1). However, the HR decrease from the upright posture was significantly higher in controls than in patients without OH (8.0±2.9 vs 4.2±2.1 bpm; P=0.002) and with OH (8.0±2.9 vs 1.2±1.5 bpm; P=0.001) (Table 2). The patients with OH showed less HR decrease than patients without OH during tilt-reversal (1.2±1.5 vs 4.2±2.1 bpm, P=0.019).

Regarding the within group comparisons of hemodynamic changes, we found that the process of tilt-reversal elicited a significantly higher HR change than the head-up tilting in controls (8.0±2.9 vs 6.5±2.5 bpm; P=0.031). A similar tendency was observed in patients without OH (4.2±2.1 vs 2.8±1.6 bpm; P=0.032) but not in those with OH (1.2±1.5 vs -0.2±2.2 bpm; P=0.380) (Figure 2).

**Table 1 Basic characteristics in subjects with multiple system atrophy with or without postural hypotension and controls.**

| | Control n=10 | MSA (OH-) n=13 | MSA (OH+) n=5 | MSA (overall) n=18 |
|---|---|---|---|---|
| Age | 60.3±7.0* | 61.8±7.6† | 75.0±4.7†* | 65.5±6.8 |
| Body height(cm) | 166.1±7.2 | 167.4±6.5 | 162.3±4.6 | 166.0±6.0 |
| Body weight(kg) | 68.4±8.0 | 73.8±10.6 | 66.7±5.4 | 71.8±9.2 |
| Disease duration(year) | | 3.3±1.8 | 3.5±1.8 | 3.4±1.8 |
| Hoehn-Yahr stage | | 2.9±0.8 | 3.6±1.0 | 3.1±0.9 |
| UMSARS I | | 12.8±5.2† | 20.2±7.0† | 14.9±5.7 |
| UMSARS II | | 26.1±9.0 | 34.2±15.3 | 28.4±10.8 |
| UMSARS IV | | 0.9±1.0 | 2.0±1.3 | 1.2±1.1 |

Note: Values are mean ± S.D.; UMSARS: Unified Multiple System Atrophy Rating Scale; MSA (OH+): multiple system atrophy with postural hypotension; MSA (OH-): multiple system atrophy without postural hypotension; †or * indicated significant difference between MSA (OH+) and MSA (OH-) or between MSA (OH+) and control, respectively.

**Table 2 Values and changes in hemodynamic variables during the period of supine, head-up tilt and tilt-reversal in subjects with multiple system atrophy with or without postural hypotension and controls.**

| | Control n=10 | MSA (OH-) n=13 | MSA (OH+) n=5 | MSA (overall) n=18 |
|---|---|---|---|---|
| **Heart rate (HR)** | | | | |
| HR.Rest (bpm) | 66.7±7.6 | 75.4±9.9 | 73.8±13.1 | 75.0±10.8 |
| HR.Tilt (bpm) | 73.2±6.9 | 78.2±10.8 | 73.6±12.1 | 77.0±11.2 |
| HR.Reverse(bpm) | 65.2±6.6 | 74.0±11.0 | 72.4±12.5 | 73.6±11.4 |
| ∆ HR (bpm) (Tilt-Rest) | 6.49±2.47‡* | 2.75±1.61* | -0.18±2.15‡ | 1.94±1.76 |
| △ HR /HR rest (Tilt-Rest/Rest) | 10.0±4.4% ‡* | 3.5±1.9%* | 0.0±3.6%‡ | 2.5±2.4% |
| ∆ HR (bpm) (Tilt-Reverse) | 8.04±2.87‡* | 4.17±2.13* | 1.15±1.52‡ | 3.33±1.96 |
| △ HR/HR reverse (Tilt-Reverse/Reverse) | 12.5±4.8%‡* | 5.8±3.6%* | 1.6±2.3%‡ | 4.6±3.2% |
| ∆ HR (bpm) (Rest-Reverse) | 1.55±1.83 | 1.42±2.02 | 1.34±2.71 | 1.40±2.21 |
| ∆ HR (bpm) (Rest-Reverse/Rest) | 2.2±2.7% | 2.2±3.2% | 1.7±4.3% | 2.1±3.5% |
| **Cardiac Output (CO)** | | | | |
| CO.Rest (L/min) | 5.86±0.98 | 5.82±1.14 | 5.94±0.66 | 5.85±1.00 |
| CO.Tilt (L/min) | 5.71±0.81 | 5.16±1.21 | 5.10±0.89 | 5.14±1.12 |
| CO.Reverse (L/min) | 5.61±1.1 | 5.50±0.91 | 5.89±0.40 | 5.61±0.77 |
| ∆ CO (L/min) (Rest-Tilt) | 0.15±0.52 | 0.66±1.55 | 0.84±1.46 | 0.71±1.53 |
| △ CO/CO Rest (Rest-Tilt/ Rest) | 1.9±8.5% | 8.0±27.2% | 11.5±28.4% | 9.0±27.5% |
| ∆ CO (L/min) (Reverse-Tilt) | -0.10±0.71 | 0.34±1.32 | 0.78±1.09 | 0.46±1.26 |
| △ CO/CO Reverse (Reverse-Tilt/ Reverse) | 3.0±12.3% | 4.2±25.6% | 12.7±20.1% | 6.6±24.1% |
| ∆ CO (L/min) (Rest-Reverse) | 0.25±0.4 | 0.32±0.56 | 0.05±0.58 | 0.25±0.57 |
| ∆ CO/ CO Rest (Rest-Reverse/ Rest) | 4.3±6.7% | 4.4.±10.1% | -0.1±12.2% | 3.2±10.7% |
| **Stroke Volume (SV)** | | | | |
| SV.Rest (mL) | 85.1±16.8 | 78.1±12.8 | 83.6±20.4 | 79.6±14.9 |
| SV.Tilt (mL) | 77.1±12.5 | 69.4±17.7 | 70.3±12.7 | 69.7±16.3 |
| SV.Reverse (mL) | 82.5±16.1 | 75.6±9.6 | 83.3±12.7 | 77.7±10.5 |
| ∆ SV (mL) (Rest-Tilt) | 10.07±7.64 | 7.79±18.24 | 13.31±22.50 | 9.32±19.42 |
| △ SV/SV Rest (Rest-Tilt/ Rest) | 10.6±6.8% | 8.7±22.9% | 11.8±27.3% | 9.6±24.1% |
| ∆ SV (mL) (Reverse-Tilt) | 7.89±8.8 | 5.57±15.50 | 12.95±15.81 | 7.62±15.59 |
| △ SV/SV Reverse (Reverse-Tilt/ Reverse) | 8.4±8.4% | 7.2±20.3% | 14.3±19.7% | 9.2±20.1% |
| ∆ SV (mL) (Rest-Reverse) | 2.18±5.61 | 2.23±7.64 | 0.36±7.91 | 1.71±7.72 |
| ∆ SV/ SV Rest (Rest-Reverse/ Rest) | 2.1±6.5% | -1.8±10.5% | -1.6±10.3% | -1.7±10.4% |
| **Total Peripheral Resistance (TPR)** | | | | |
| TPR.Rest (mmHg.$L^{-1}$.$min^{-1}$) | 14.3±2.3 | 15.3±3.4 | 16.3±3.5 | 15.6±3.4 |
| TPR Tilt (mmHg.$L^{-1}$.$min^{-1}$) | 14.9±3.5 | 16.3±3.7 | 15.7±1.3 | 16.1±3.0 |
| TPR.Reverse (mmHg.$L^{-1}$.$min^{-1}$) | 15.1±2.6 | 15.9±2.9 | 15.5±2.2 | 15.8±2.7 |
| ∆ TPR (mmHg.$L^{-1}$.$min^{-1}$) (Rest-Tilt) | 0.58±1.86 | 1.03±5.07 | -0.58±3.87 | 0.58±4.74 |
| △ TPR/ TPR Rest (Rest-Tilt/ Rest) | 4.3±13.5% | 12.0±38.9% | 1.2±25.9% | 9.0±35.3% |
| ∆ TPR (mmHg.$L^{-1}$.$min^{-1}$) (Reverse-Tilt) | -0.20±2.17 | 0.46±4.52 | 0.22±2.06 | 0.39±3.84 |
| ∆ TPR /TVR Reverse (Reverse-Tilt/ Reverse) | 0.3±15.4% | 6.0±32.3% | 3.1±16.4% | 5.2±27.9% |
| ∆ TPR (mmHg.$L^{-1}$.$min^{-1}$) (Rest-Reverse) | -0.78±0.93 | -0.57±1.68 | 0.80±2.28 | -0.19±1.85 |
| ∆ TPR (TPR Rest) (Rest-Reverse/ Rest) | -5.3±7.0% | -5.0±10.9% | 2.8±12.4% | -2.8±11.3% |

Note: Values are mean ± S.D.; HR: heart rate; MSA (OH+): multiple system atrophy with postural hypotension; MSA (OH-): multiple system atrophy without postural hypotension; ∆: difference. ‡ or * indicated significant difference between MSA (OH+) and control or between MSA (OH-) and control, respectively. "Tilt-Rest/ Rest" indicates the difference of average values between the resting status and head-up tilt divided by the average values at the resting status. "Tilt-Reverse/Reverse" indicates the difference of average values between the status of head-up tilt and returning to supine divided by the average values at the posture after reclining to supine. "Rest-Reverse/Rest" indicates the difference of average values between the status of resting and returning to supine divided by the average values at the resting status.

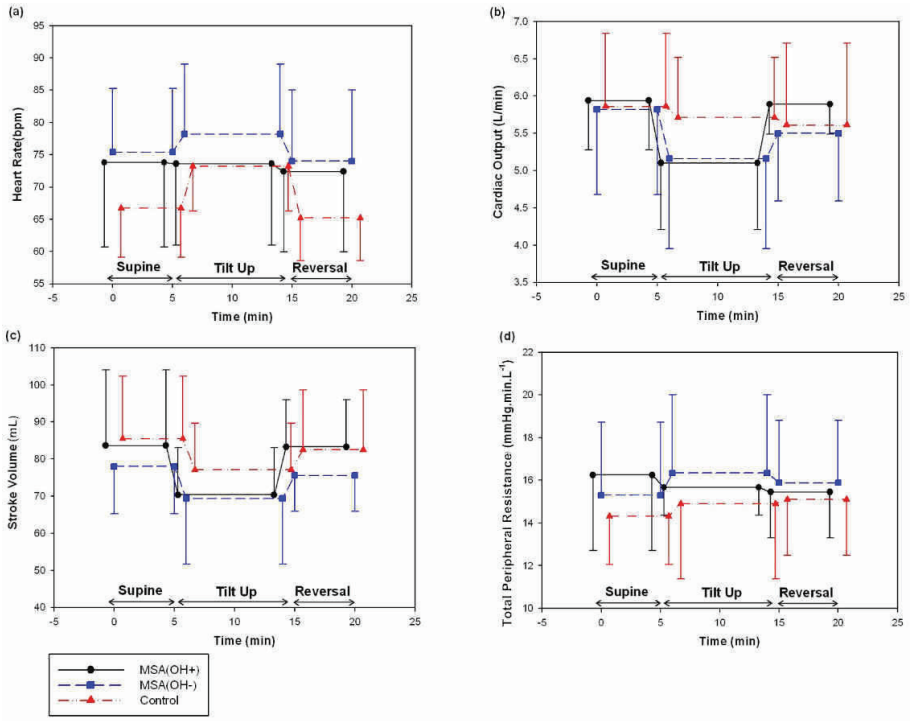


Figure 1. Changes of (a) heart rate, (b) cardiac output, (c) stroke volume, and (d) total peripheral resistance during the supine, tilt-up and tilt-reversal phase among three groups.

## DISCUSSION

The findings in this study showed blunted HR response to postural challenge in MSA patients. This impairment was more severe in patients with OH. The process of tilt-reversal resulted in higher HR change than that during head-up tilt, and the HR change was least in patients with OH. The patients with OH differed from those without OH by their older ages and higher scores in UMSARS part I.

HR increase upon tilting up is a normal response to compensate the reduction of stroke volume due to venous pooling. It is mediated through Baroreflex initially by eliminating parasympathetic outflow and followed by an increased release of norepinephrine from augmented sympathetic output. The reflex loop's integrity can be tested by the Valsalva maneuver, which causes temporary tachycardia by decreasing venous return when the participant forcefully exhales against a closed airway.[15] The correlation between RR intervals of heart beats and systolic blood pressure during certain phases of the Valsalva maneuver is used to represent Baroreflex sensitivity. Friedrich *et al* demonstrated blunted Baroreflex sensitivity in MSA patients[6], whereas Goldstein *et al* reported that only MSA patients with OH exhibited lower Baroreflex cardiovagal gain as compared to healthy controls.[16] Asahina *et al* demonstrated abnormal skin vasoconstrictive response in MSA patients and thus suggesting a disorders in the sympathetic neurohumoral systems.[17] In the present study, we would like to suggest that decreased HR response in MSA patients during postural challenge is strongly related to the impaired Baroreflex and subsequent sympathetic activation. In addition, head-up tilting reduces stoke volume more than the Valsalva maneuver. Therefore the difference of the reactive tachycardia can be magnified between MSA and controls regardless of OH. Because patients with early MSA may not develop symptomatic OH, the inadequate HR rise upon tilt testing can be a subclinical presentation of autonomic dysfunction in the cardiovascular system.

However, our finding is not consistent with Chandler's observation, which revealed no significant difference of HR elevation during postural challenge between MSA and healthy controls.[8] This may be explained by the different angles of table tilting during tests. Chandler *et al* used 45 degrees to ensure that the participants could tolerate the full course of head-up tilting.[8] However, 60 to 70 degrees of tilting angles are usually required for better sensitivity and

specificity to provoke OH.[18] Because exploring the mechanism of OH is the main purpose of this study, we set the tilting angle at 60 degrees and showed that the angle was adequate to discriminate varied HR response among controls and MSA patients.

Two major pathological mechanisms may result in OH, they are the failure of boosting vascular resistance and disproportionate reduction in cardiac output during postural challenge. Concerning the former mechanism, MSA patients have deficit in pre-ganglionic sympathetic neurotransmission[19], therefore have less peripheral vasoconstriction than patients with pure autonomic failure.[8] In this study, regulation of vascular impedance contributed modestly to OH in MSA patients owing to lack of difference in peripheral resistance and its associated changes (Table 2). For the second mechanism, it may derive from excessive stroke volume depletion or inadequate HR compensation. Although venous pooling plays a major role to diminish stroke volume, Lipp *et al* reported trivial influence from this factor because venous compliance was reduced in MSA patients.[20] Although the cardiac output was not significantly different among groups in the present study, we found that patients without OH were likely to elevate HR more than those with OH. Regarding the comparison with controls, we assumed that the HR responsiveness could determine whether OH happened or not.

Tilting back from the upright posture elicits replenishment of static blood into vascular beds of the upper body. Due to delayed dilatation of previous constrictive vessels, the blood pressure rebounds and reaches a higher level than baseline. This phenomenon lasts within 8 seconds after returning to supine in healthy adults[21] and may be prolonged with elevated values in patients with pure autonomic failure[22] or amyloidotic polyneuropathy.[23] In this study, we did not observe overshot blood pressure in MSA patients, probably because of relatively preserved sympathetic control at peripheral vasomotor systems.[22] However, our findings demonstrated that healthy controls exhibited a higher magnitude of HR changes in tilt reversal than in head-up tilt (Figure 2), which is consistent with the approximately 3 bpm in discrepancy according to Yograj *et al*'s observation.[24] The mechanism may arise from more intense blood pressure fluctuation against baroreceptors during tilt reversal. In our study, the average HR changes between patients with- and without OH seemed magnified upon recline. Thus the process of tilt reversal may be more useful than head-up tilt to detect the blunted HR response in MSA patients.

In the present study, there was no significant difference in basic characteristics except scores in UMSARS part I and age (Table 1). Scores in UMSARS Part I result from the performance

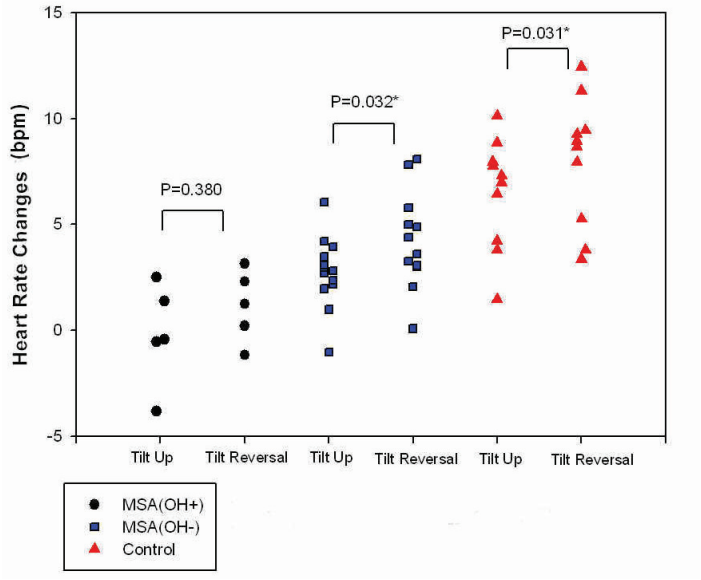


Figure 2. Comparison of heart rate changes between the process of tilt-up and tilt-reversal among three groups. The process of tilt-reversal elicited a significantly higher HR change than the head-up tilting in controls. A similar tendency was observed in patients without OH but not in those with OH. * indicated significant difference in heart rate changes between the process of tilt-up and tilt-reversal.

through historical review were based on patients and caregivers, and higher values in patients with OH implied more severe functional impairment due to disease progression. The average age of our patients without OH was 61.8 years, which was similar to the mean onset age of MSA according to Wullner *et al*'s report.[25] In contrast, those developing OH were approximately 13 years older. Ageing leads to an attenuated tilt increase in vascular resistance[26], with some studies supporting a deterioration of baroreflex function in the elderly.[27] Therefore, we propose that ageing worsens the abnormal baroreflex in MSA patients and also explains why postural hypotension tends to occur in older MSA participants.

Our results suggest that HRs are strongly related to blood pressure regulation during position changes in MSA patients. Nevertheless, current treatments against OH focus on augmenting peripheral vascular resistance or fluid retention.[7] Fludrocortisone, a synthetic agent with greater mineralocorticoid potency, is commonly used but may potentiate supine hypertension in MSA patients. We propose that future therapeutic strategies can consider pharmacology or exercise training directed at baroreflex function.[28]

The major limitation of our study was the inclusion criteria of the patients. Under the diagnosis of possible MSA, there were probability of including patients with other extrapyramidal syndromes. However, this design was necessary to detect early cardiovascular disturbance prior to the onset of OH. Thus follow-up of the clinical development was required in our patient group. Another concern was single gender in our study population. There was substantial evidence to show the differences in autonomic systems between sexes[29], which limited our results to apply only to male patients with MSA.

In conclusion, HR response during postural challenge varied between healthy adults and MSA patients. Impaired HR responsiveness contributes to OH and monitoring HR during the tilt table test may be a practical and useful method to detect early autonomic dysfunction in patients with MSA.

## DISCLOSURE

Conflict of interest: None

Source(s) of financial support: None

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