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Supine-to-standing transcranial Doppler test in patients with multiple system atrophy

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ABSTRACT

Background: Supine-to-standing test, a transcranial Doppler (TCD) based technique, has been recently developed to evaluate cardiovascular dysautonomia. We explored the value of supine-to-standing TCD test in predicting the course of multiple system atrophy (MSA) with orthostatic hypotension (OH).
Methods: By monitoring the signals of middle cerebral artery during supine-to-standing posture changes, the trend curves of cerebral blood flow velocities, pulsatility index and resistance index were obtained from 38 MSA patients with OH and 31 healthy subjects. The correlation between TCD findings and the clinical outcome of the patients, which was determined by follow-up structured phone interview, was analyzed. Adverse outcome was defined if a patient died, was in bed-ridden state or had recurrent syncope (>1 per month).
Results: Two characteristic TCD findings were revealed in the MSA patients but not in the controls, i.e. a blunted cerebral blood flow velocity rebound after standing and/or sustained higher pulsatility index upon standing than supine baseline. Structured phone interview was completed in 31 of the 38 patients (mean follow-up time, 20 ± 11 months). While no subject had recurrent syncope before enrollment, 12 patients developed an adverse outcome during follow-up. The coexistence of two characteristic TCD findings predicted adverse outcomes with positive predictive value 66.7% and negative predictive value 87.5%.
Conclusions: Supine-to-standing TCD test is valuable in predicting the course of MSA with OH at early stage. We hypothesize baroreflex failure effects and paradoxical cerebral vasoconstriction in response to OH may account for the TCD findings in MSA patients.

1. Introduction

Multiple system atrophy (MSA) is a rare neurodegenerative disease, characterized by autonomic dysfunction in combination with Parkinsonism, or cerebellar *ataxia* [1]. Early-onset orthostatic hypotension (OH) is frequently observed in MSA, occurring in 75%–81% of the patients [2,3]. It has been known that the OH in MSA is mainly caused by a degeneration of sympathetic neurons in central nervous system, including brain stem and intermediolateral cell column of spinal cord [4]. Comparatively, peripheral noradrenergic innervations are well preserved [5–7]. Therefore, MSA is a natural human model of central sympathetic failure. Clinically, OH has varied clinical presentations. It can substantially limit patients' quality of life and increase mortality, while it is asymptomatic or mildly symptomatic in some patients [8,9]. Until now, there has been no technique or biomarker which can reliably predict the course of OH in MSA patients after it is diagnosed.

Recently, a transcranial Doppler (TCD) based technique, i.e. supine-to-standing test, has been developed [10,11]. Cerebral blood flow change in response to orthostatic challenges can be evaluated in the initial (first 30 s) and early phases (1–2 min upright) after standing, which are mainly governed by the neural system [10,12]. This technique can be easily applied in daily out-clinics practice [10]. In the present pilot study, we sought to investigate the value of TCD in predicting the course of MSA with OH.

2. Methods

2.1. Study population

From July 2008 to September 2011, 38 patients with probable MSA and OH (30 male; mean age, 55 ± 7 years) and 31 healthy control subjects (21 male; mean age, 52 ± 10 years) were enrolled. The diagnosis of MSA was based on the established consensus criteria [1]. Magnetic resonance imaging of the brain and laboratory

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workup were performed in all patients to exclude other causes of Parkinsonism, ataxia and autonomic dysfunction. Patients were routinely classified as MSA-P if Parkinsonism was the main motor feature and as MSA-C if cerebellar features predominated [1]. OH is defined as a persistent fall in systolic blood pressure of at least 20 mm Hg or diastolic pressure of at least 10 mm Hg within 3 min in the standing-up position. Subjects with extracranial or intracranial artery stenosis, poor temporal window for TCD detection, and arrhythmia or pulmonary diseases displaying dyspnea were excluded [10]. Patients who were intolerant of postural change were also excluded. Administration of L-dopa and midodrine was permitted for symptoms relief. Written consensus was obtained from all the participants. The study was approved by the local ethics committee.

2.2. Supine-to-standing TCD test

Our TCD protocol was described elsewhere [10]. In brief, signals of middle cerebral artery (MCA) blood flow were recorded with 2 MHz probes through the detectable temporal window at a depth of 50–60 mm and maintained by a stable headset (Nicolet EME Pioneer 8080). First, subjects were maintained in a supine position for 2–3 min. Then, they were asked to stand up quickly within 8 s and kept in the upright position for 2–3 min. After that, the subjects returned to the supine position. The trend curves of systolic, diastolic and mean MCA blood flow velocity (mCBFV), pulsatility index (PI) and resistance index (RI) were obtained during the whole process. Blood pressures (BP) in supine and upright position (2 min after standing) were recorded.

2.3. TCD curves analysis

Generally, TCD curves (mCBFV, PI, and RI) in supine-to-standing test consist of two plateau curves representing supine position and an in-between plateau curve representing upright position (Figs. 1 and 2) [10]. For each subject, values of mCBFV and PI in supine and upright (1–2 min after standing) position were recorded.

In our previous study, it was observed that the mCBFV rapidly decreased when healthy subjects stood up, and then rebounded to the same level as the supine baseline or even higher within 30 s after standing (Fig. 1) [10]. In this study, we defined a "blunted CBFV rebound" if the rebound mCBFV did not reach the supine baseline level within 30 s after standing or even was absent (Fig. 2). The occurrence of blunted CBFV rebound was recorded in each group.

2.4. Follow-up and measurement of adverse outcomes associated with OH

Follow-up information, including the Self-report Orthostatic Grading Scale [13], frequency of syncope per month, bed-time per day, and death, was obtained by means of a structured phone interview with the patients or their caregivers. All interviews were performed by a neurologist (J. C) who was blinded to TCD results. The adverse outcome associated with OH was defined if the patients died, in bedridden state or had recurrent syncope (>1 per month). Symptomatic OH was diagnosed if the patients had Self-report Orthostatic Grading Scale >9 [13], and had no adverse outcome.

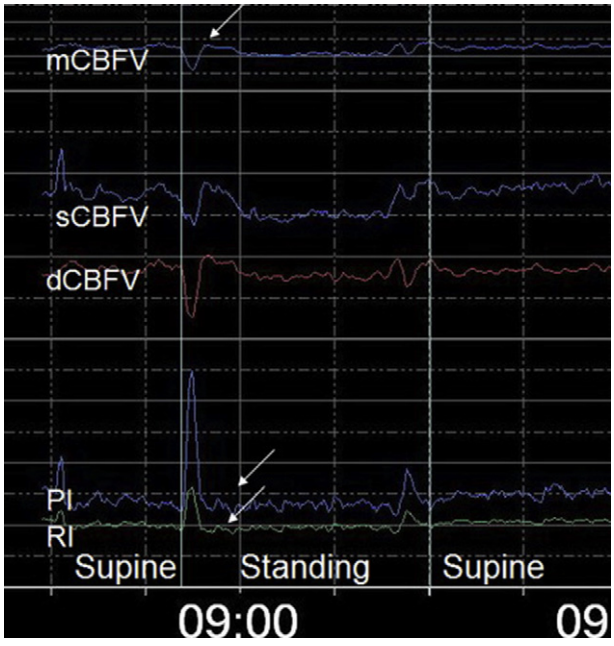

Fig. 1. Supine-to-standing transcranial Doppler test in a healthy control subject. In a healthy subject, a normal CBFV rebound (upper arrow) is present within 30 s after standing. During 1–2 min upon standing, PI and RI (lower arrows) recover to the supine baseline after a transient increase. Abbreviations: mCBFV = mean cerebral blood flow velocity; sCBFV = systolic cerebral blood flow velocity; dCBFV = diastolic cerebral blood flow velocity; PI = pulsatility index; RI = resistance index.

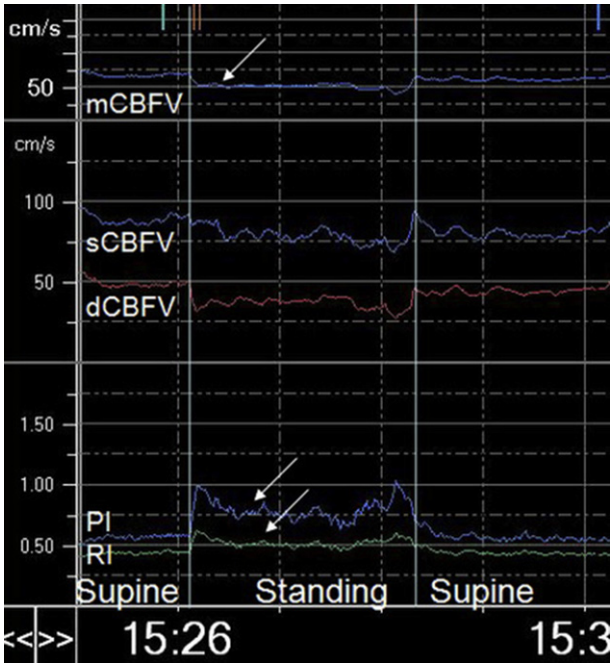

Fig. 2. Supine-to-standing transcranial Doppler test in a MSA patient. In a MSA patient with recurrent syncope, the CBFV rebound (upper arrow) is nearly absent. During 1–2 min upon standing, PI and RI (lower arrows) are at a sustained higher level than the supine baseline. Abbreviations: mCBFV = mean cerebral blood flow velocity; sCBFV = systolic cerebral blood flow velocity; dCBFV = diastolic cerebral blood flow velocity; PI = pulsatility index; RI = resistance index.

2.5. Statistical analysis

Data were analyzed using SPSS 12.0. X2 test and Fisher's exact test were applied to compare the between-group difference of count data. *T*-test and Wilcoxon test were used to compare the between-group difference of quantitative data. *P*-values < 0.05 were considered significant. Quantitative data were presented as mean $\pm$ S.D. and count data were presented with number (percentile).

3. Results

Thirty-one patients were classified as MSA-P, and 7 patients were classified as MSA-C. The average disease duration before TCD evaluation was 2.5 $\pm$ 1.6 years. None of the subjects had recurrent syncope before the enrollment.

3.1. TCD findings

Figs. 1 and 2 show the TCD curves of a healthy control and a MSA patient respectively. The baseline values of the monitored parameters and the changes during supine-to-standing TCD test are displayed in Table 1.

Overall, the curves of systolic, diastolic and mean CBFV displayed similar shapes in all subjects. A normal CBFV rebound was observed in all healthy controls, but only in 7/38 MSA patients ($P < 0.001$). Blunted CBFV rebound were seen in the remaining 31 patients. RI curve synchronized with PI curves in all subjects. In the initial stage (<30 s) after standing, PI curves were elevated steeply in both subject groups. In the early stage (first 1–2 min) upon being upright, PI recovered to baseline in all controls (Fig. 1), but