Cerebral autoregulation (CA) is defined as the ability of the brain to maintain cerebral blood flow (CBF) when cerebral perfusion pressure changes.\textsuperscript{1,2} Traditional approach to the evaluation of CA is to describe the relationship of arterial blood pressure (ABP) and CBF in a static fashion. Static CA capacity was first demonstrated by performing repeated static measurements of brain perfusion at different blood pressures to determine the blood pressure range in which CA is effective.\textsuperscript{3}

Xenon\textsuperscript{133} injection or inhalation methods for regional CBF measurement have often been used to study the status of cerebrovascular regulation.\textsuperscript{4,6} With the availability of transcranial Doppler ultrasonography (TCD), investigators are offered the opportunity to measure CA in a noninvasive and dynamic fashion because TCD-measured CBF velocity (CBFV) is a real-time parameter, which correlates well with CBF changes.\textsuperscript{7} Using TCD to measure variations of CBFV, previous researchers have been able to detect different hemodynamic changes in a dynamic fashion, including those resulting from chemically induced lactic acidosis.\textsuperscript{8-11} Orthostatic stress with head-up tilt (HUT) and induced hypotension with lower body negative pressure have often been used to provide perturbations to the autoregulatory response.\textsuperscript{11-14} Research in orthostatic changes of arterial blood pressure and CBFV are of particular interest in patients with orthostatic intolerance.

### Background

Regulation of cerebral blood flow during orthostatic stress has been a major research interest. The purpose of this study was to scan healthy volunteers and patients with orthostatic dizziness and autonomic dysfunction for differences in cerebral hemodynamic patterns during orthostasis.

### Methods

Thirteen patients with orthostatic dizziness and autonomic dysfunction and nine healthy volunteers were recruited for monitoring of variations in intracranial hemodynamics with transcranial Doppler ultrasound during a 30-minute head-up tilt. Heart rate and blood pressure were measured using surface electrocardiography and cuff sphygmomanometer, respectively. Cerebral blood flow velocity was continuously measured using transcranial Doppler ultrasonography.

### Results

The baseline mean cerebral blood flow velocity was significantly lower in the patient group ($p<0.05$). After tilting up, the extent of immediate decreases in systolic blood pressure and in the mean blood flow velocity was significantly more in the patients ($p<0.05$). However, the mean blood flow velocity remained significantly more retarded for up to 90 seconds after the initial drop in the patient group, while the blood pressure showed no significant difference between the patients and controls.

### Conclusions

Impaired dynamic cerebrovascular regulation can be documented as a delayed recovery of cerebral blood flow velocity upon orthostatic challenges, which may help verify the status of cerebrovascular regulation in patients with autonomic dysfunction.

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**Key Words**

orthostatic dizziness; autonomic dysfunction; transcranial Doppler ultrasound; cerebrovascular regulation; tilt table

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**Original Article**

**Dynamic Cerebrovascular Regulation in Patients with Autonomic Dysfunction: a Transcranial Doppler Study**

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**Conclusions.** Impaired dynamic cerebrovascular regulation can be documented as a delayed recovery of cerebral blood flow velocity upon orthostatic challenges, which may help verify the status of cerebrovascular regulation in patients with autonomic dysfunction.
ance, especially in those with autonomic dysfunction.\textsuperscript{13-16} Cerebrovascular regulation upon orthostatic challenges cannot be predicted in the supine position, nor can it be deduced from the orthostatic ABP changes alone.\textsuperscript{15} Therefore, orthostatic challenges such as HUT in conjunction with TCD and BP monitors are often used to evaluate the integrity of cerebrovascular regulation in patients with different etiologies of orthostatic intolerance.\textsuperscript{13-16} The pur pose of this study was to identify abnormal cerebral hemodynamic patterns during HUT in patients with autonomic dysfunction and orthostatic dizziness suggestive of impaired cerebrovascular regulation.

Orthostatic dizziness is defined as occurrence of dizziness in the upright posture, which is relieved by lying supine.\textsuperscript{17} Some clinical conditions associated with orthostatic dizziness other than autonomic dysfunction had been care fully excluded, which included but were not restricted to cardio genetic causes such as arrhythmia or congenital heart failure, Meniere’s disease or other autonomic dysfunction, postural tachycardia syndrome, pheochromocytoma, hypoglycemia, stroke, and use of medications or substances that might be associated with impaired balance.\textsuperscript{17,18} Based on this definition, patients with autonomic dysfunction and orthostatic dizziness were recruited if they had objective evidence of autonomic dysfunction and had experienced recurrent orthostatic dizziness in the preceding six months. In order to fully satisfy the inclusion and exclusion criteria, we thoroughly examined each patient’s history, gave a complete physical examination, performed 12-lead electrocardiogram, and conducted transthoracic echocardiography. We also performed a complete neurologic examination and an electroencephalogram, carotid and vertebral duplex examinations, transcranial Doppler examination, and computerized tomography of the brain, complete blood count, and serum chemistry tests. Abnormal autonomic skin responses and heart rate variability (R-R interval variation), according to the methods recommended by Shahani et al.,\textsuperscript{19,20} were used as the objective evidence of disordered autonomic function. These patients had also been evaluated by a cardiologist to exclude the possibility of dizziness from cardiovascular causes and by an otologist to exclude dizziness from the ear and vestibular system.

Head-up tilt test was performed on all patients and controls. All cardioactive medications were discontinued at least five half-lives before the study after consultation and approval by the rollators to exclude disturbances of the ear and vestibular system.

SUBJECTS AND METHODS

Thirteen patients with unexplained orthostatic dizziness and autonomic dysfunction were consecutively enrolled in this study. All had impaired heart rate variability and sympathetic skin response, and 4 of them had mild transient postural hypotension. Nine volunteers with or without orthostatic hypotension, might present with specific abnor malities in dynamic CBFV, which could be evaluated as delayed CBFV recovery after the HUT-induced initial decrease in CBFV. We hoped to verify if the usefulness of this approach, which might help resolve the diagnostic controversy regarding the integrity of CBFV in patients who have autonomic dysfunction with or without postural hypotension.
monitor. A cuff sphygmomanometer attached to the right upper limb was used for blood pressure measurement. Respiratory rate and depth were monitored every three minutes by direct observation. The right upper limb was placed on a side arm support such that ABP measurement was conducted uninterrupted at the heart level throughout supine rest and tilt. Blood pressure measurements were conducted every one minute during the supine rest and after the 6th minute of HUT and every 30 seconds during the first 5 minutes of HUT or if dizziness or syncope occurred.

The middle cerebral artery blood flow velocity (MCAFV) of left and right sides were recorded by a bilateral TCD monitor (Multi-Dop-X/TCD7, DWL, Sipplingen, Germany). The transducers were fixed in place, and MCAFV was continuously monitored at the depth of the best signal (44 to 55 mm). In patients with a poor temporal window on one side of the head, we chose the other side as representative. In those who had good bilateral win dows, data from both sides were adopted to avoid any selection bias. The MCAFV signals were acquired, displayed, and stored to floppy disk by Multi-Dop-X. Each participant stayed supine in the horizontal position for 5 minutes before the table was tilted head-up to 70 degrees. After an additional 30 minutes, the table was tilted back to a horizontal position, and 5 minutes later the investigation was finished. The table was rapidly lowered to the supine position if severe dizziness or syncope developed during the tilt test. The TCD data acquired during the basal supine rest position and during the 30 minutes of HUT were used for analysis.

Baseline systolic (SBP), diastolic (DBP) and mean BP (MBP) during supine rest were expressed as the averaged value during the 5 minutes of supine rest. Mean MCAFV during supine rest was similarly expressed. Lowest level of BP and mean MCAFV in the patients were 114.5 ± 17.9 mmHg, 67.1 ± 7.6 mmHg, and 85.2 ± 11.1 mmHg, respectively, in the supine position, and 101.3 ± 17 mmHg, 64.7 ± 8.8 mmHg, and 79.1 ± 12.4 mmHg, respectively, immediately after HUT. The mean MCAFV in the controls were 119.6 ± 8.9 mmHg, 72.5 ± 4.4 mmHg, and 90.6 ± 6.2 mmHg, respectively, in the supine position, and 118.6 ± 12.5 mmHg, 73.3 ± 5.5 mmHg, and 90.6 ± 7.3 mmHg, respectively, immediately in the HUT position. The mean and SD of the SBP, DBP and MBP in the patients were 114.5 ± 17.9 mmHg, 67.1 ± 7.6 mmHg, and 85.2 ± 11.1 mmHg, respectively, in the supine position, and 101.3 ± 17 mmHg, 64.7 ± 8.8 mmHg, and 79.1 ± 12.4 mmHg, respectively, immediately after HUT. The mean MCAFV in the patients were 114.5 ± 17.9 mmHg, 67.1 ± 7.6 mmHg, and 85.2 ± 11.1 mmHg, respectively, in the supine position, and 101.3 ± 17 mmHg, 64.7 ± 8.8 mmHg, and 79.1 ± 12.4 mmHg, respectively, immediately after HUT.

**RESULTS**

All the participants withstood the procedure well. The demographic data of these participants are listed in Table 1. The mean and SD of the SBP, DBP and MBP in the patients were 114.5 ± 17.9 mmHg, 67.1 ± 7.6 mmHg, and 85.2 ± 11.1 mmHg, respectively, in the supine position, and 101.3 ± 17 mmHg, 64.7 ± 8.8 mmHg, and 79.1 ± 12.4 mmHg, respectively, immediately after HUT. The mean MCAFV in the patients were 114.5 ± 17.9 mmHg, 67.1 ± 7.6 mmHg, and 85.2 ± 11.1 mmHg, respectively, in the supine position, and 101.3 ± 17 mmHg, 64.7 ± 8.8 mmHg, and 79.1 ± 12.4 mmHg, respectively, immediately after HUT.

<table>
<thead>
<tr>
<th>Table 1. Demographic data</th>
<th>Controls</th>
<th>Patients</th>
</tr>
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<tbody>
<tr>
<td>Mean age (years)</td>
<td>58.1 ± 12.6</td>
<td>71.3 ± 5.8</td>
</tr>
<tr>
<td>Sex Male</td>
<td>6</td>
<td>13</td>
</tr>
<tr>
<td>Female</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Hypertension</td>
<td>4</td>
<td>8</td>
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<tr>
<td>Diabetes mellitus</td>
<td>0</td>
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but such difference was not observed in DBP ($p = 0.15$) and MBP ($p = 0.55$). The mean and SD of the MCAFV (left and right) during supine rest were $46.9 \pm 14.2$ cm/sec in the patients and $70 \pm 16.2$ cm/sec in the controls, respectively, which was significantly lower in the patients ($p = 0.0067$). The immediate decrease in MCAFV was greater ($p = 0.025$) in the patients ($13.5 \pm 12.6\%$) than in the controls ($5 \pm 4.6\%$). After the immediate orthostatic decrease in BP, BP changes measured every 30 seconds during HUT were not different between patients and controls, including SBP, DBP, and MBP. The MCAFV averaged every 30 seconds after the initial drop remained retarded for up to 90 seconds in the patient group as compared with the controls (Fig. 1).

**DISCUSSION**

The main purpose of this study was achieved by recording and verifying the impaired dynamic cerebrovascular regulation during orthostasis in patients with orthostatic dizziness and autonomic dysfunction. Orthostatic dizziness is not uncommon in patients with autonomic dysfunction, especially in those with abnormal SSR. The orthostatic stimulus in duced by HUT was associated with more pronounced immediate decrease in systolic BP and MCAFV in the patients. This is compatible with the observations in patients with autonomic dysfunction from other investigators. However, the extent of ABP decrease was less in our patients because of less severe autonomic dysfunction. Despite the fact that the delayed differences in orthostatic ABP no longer existed between patients and controls, de crease in orthostatic MCAFV remained more pronounced in the patient group for up to 90 seconds. This discordant orthostatic ABP-MCAFV relationship would suggest an impairment in CA capacity in the patients, in which MCAFV was not adequately maintained.

Aaslid et al. first introduced the concept of dynamic CA by using TCD to monitor changes. Lagi et al. also used TCD to evaluate dynamic cerebrovascular regulation in 24 patients with severe postural hypotension in which induced hyperemia was used to provoke a significant decrease in ABP. This hyperemia stimulus produced comparable immediate decrease in ABP and CBFV in patients and controls. However, the recovery phase differed in which MCAFV rose significantly higher than ABP after 30 and 60 seconds in controls, but not in the patients. The authors suggested that the ability to maintain adequate CBF was not effective in these patients. Our study used a different stimulus (HUT) and produced differential hemodynamic impacts on our pa-
tients and controls. However, the results from Lagi et al.\textsuperscript{22} seem to support our findings, since de layed rise in CBFV relative to ABP was observed in our patients with autonomic dysfunction.

Daffertshofer and Hennerici\textsuperscript{13} concomitantly used TCD and HUT to monitor cerebral hemodynamics in a group of patients with cerebrovascular diseases. They found that some patients developed orthostatic hypotension (> 20% drop from the base line BP) with or without an excessive decrease in CBFV (> 20% de crease of the baseline CBFV) during HUT. They suggested that ex hausted local cerebrovascular reserve capacity existed in the former (excessive drop in ABP and CBFV) and intact reserve capacity in the latter patients (excessive drop in ABP only). In the ab sence of orthostatic hypotension, if CBFV fell excessively during HUT, excessive disturbance of cerebrovascular regulation was considered. How ever, it would be difficult to judge the status of CA in those patients who had less severe decreases in ABP and CBFV that did not reach the pathological level (> 20% decrease) as defined by the authors based on their criteria.

Novak et al.\textsuperscript{15} used a more sophisticated approach to evaluate CA in patients with orthostatic hypotension and normal controls. A flow-pressure regression curve was plotted for each participant with mean CBFV being the y axis and MBP the x axis, and 3 types of CA capacity were identified. All patients had excessive ABP drop during HUT. The controls and some patients showed normal CA in which CBFV was independent of ABP changes (absence of flow-pressure relationship). A linear flow-pressure relation ship could predict autoregulation in sufficiency. Patients with less orthostatic decrease in CBFV showed a pattern of expanded autoregulatory range, in which a flat slope of regression was identified. Those with excessive decrease in CBFV had a pattern of autoregulatory failure, in which a steep slope of regression was noted. This is a useful but complicated approach for evaluation of CA capacity in patients with orthostatic hypotension. However, there may be errors in judging CA status when there is greater fall of ABP in normal individuals or in milder forms of autonomic insufficiency when the extent of ABP fall is less than that of orthostatic hypotension such as our patients.

Bondar et al.\textsuperscript{22} used a different strategy to get the flow-pressure regression relationship in 11 patients with orthostatic hypotension and 8 healthy controls. Each participant received a graded-tilt protocol, with 5 minutes in each of the following positions - 10°, 10°, 30°, and 60° in addition to the supine position. Different extents of changes in ABP and flow velocity were recorded for each participant in each tilt position, which were used to plot a flow-pressure regression line. The slope of the patients’ regression line was more steep than that of the controls but not statistically significant. The authors concluded that the CA capacity in these patients was not abnormal. They concluded the patients’ orthostatic in tolerance to orthostatic ABP changes rather than impaired CA capacity. These findings are at odds with those of Novak et al.\textsuperscript{15} The small sample size of the study conducted by Bondar et al.\textsuperscript{22} could only partly account for the differences. Different study protocols and logic are the major causes of this disagreement. The protocol adopted by Novak et al.\textsuperscript{15} could induce a much larger decrease in ABP and CBFV in the patients. However, Bondar et al.\textsuperscript{22} tried to lessen the fluctuations in orthostatic BP during the graded tilts in the patients such that the recorded BP in the patients and in the controls could be compared in a similar autoregulatory range.

Tiecks et al.\textsuperscript{23} tried to evaluate CA capacity in a group of patients with unilateral or bilateral severe stenosis of the internal carotid artery. They continuously monitored ABP and CBFV changes, respectively with finger plethysmography and TCD, during Valsalva maneuver, which caused a decrease of ABP and CBFV in phase 2 (during forced bu ggle blowing) of the response. By late phase 2 and after a few seconds, CBFV rebound occurred earlier than that of ABP in normal cranial arterial territories, which was not observed on the stenotic side with impaired cerebrovascular regulation verified by CO\textsubscript{2} reactivity test. This study confirmed our supposition to our findings, since the normal CA capacity would allow the CBFV to return to base line earlier than ABP, when both CBFV and ABP were simultaneously decreased in a coronary artery. Failure of CBFV to return efficiently to base line would indicate an impaired CA capacity in CA.

Our study has the strength of simplicity and sensitivity to detect decreased CA capacity in patients with less...
severe autonomic involvement (without significant orthostatic hypotension). Never the less, errors may still occur in those with excessively and rapidly fluctuated ABP and/or CBFV during HUT. However, this is a very uncommon condition, and needs to be addressed by other approaches.

Our results support the following conclusions: (1) In patients with autonomic dysfunction and orthostatic dizziness suggesting impaired cerebrovascular regulation, cerebral hemodynamics showed a less efficient autoregulatory behavior, with the recovery of MCAFV lagging behind that of ABP during orthostasis; (2) HUT may provide a useful stimulus to induce perturbations of cerebrovascular regulation in patients with autonomic dysfunction, and the associated hemodynamic changes can be adequately and noninvasively evaluated in a dynamic fashion with TCD.

ACKNOWLEDGEMENT

This study was supported in part by the Yen-Tjing Ling Medical Foundation.

REFERENCES
