Cerebral autoregulation (CA) is defined as the ability of the brain to maintain cerebral blood flow (CBF) when cerebral perfusion pressure changes. 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. Using TCD to measure variations of CBFV, previous researchers have been able to detect different hemodynamic changes in a dynamic fashion, including chemical stimulation to test the vasomotor reserve (hypocapnea, hypercapnea or administration of acetazolamide) and induced percutaneous injections of ABP and/or CBFV to observe real-time changes in CBFV. To search on orthostatic changes of arterial blood pressure (ABP) and CBFV are of particular interest in patients with orthostatic intolerance, especially those with autonomic dysfunction.

Background. Regulation of cerebral blood flow during orthostatic stress has been a major research topic in patients with orthostatic intolerance such as autonomic dysfunction. Sponaneous fluctuations of middle cerebral artery blood flow velocity (MCAFV) recorded with transcranial Doppler (TCD) have been found to contain information related to cerebrovascular regulation, which can be deciphered with spectral analysis. The purpose of this study was to evaluate differences in cerebrovascular regulation between healthy volunteers and patients with autonomic dysfunction and orthostatic dizziness using spectral analysis of MCAFV in formation derived from TCD during supine rest and orthostasis.

Methods. Thirteen patients with autonomic dysfunction and orthostatic dizziness were found to have impaired cerebral autoregulation because of failure to maintain adequate cerebral blood flow velocity during a 30-minute head-up tilt study with concomitant TCD and cuff sphygmomanometer monitoring. The data of bilateral MCAFV were compared between these 13 patients and 9 healthy volunteers using spectral analysis.

Results. Spectral analysis of the MCAFV showed significantly decreased low frequency (LF) power in supine position in the patient group (p = 0.0002). In addition, the spectral power in the very low and low frequency (VLF & LF) ranges remained significantly lower in the patient group after tilting up (p < 0.05).

Conclusions. (1) Our study results further support the previous findings that the LF component of the spontaneous fluctuations of MCAFV is important for cerebrovascular regulation. (2) The decreased LF MCAFV power may be a useful indicator or marker of impaired cerebrovascular regulation in patients with autonomic dysfunction.

Key Words
autonomic dysfunction; cerebral vascular regulation; spectral analysis; tilt table; transcranial Doppler

Original Article
Spectral Analysis of Cerebrovascular Regulation in Patients with Autonomic Dysfunction

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Cerebral autoregulation (CA) is defined as the ability of the brain to maintain cerebral blood flow (CBF) when cerebral perfusion pressure changes. 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. Using TCD to measure spontaneous fluctuations of CBFV, previous researchers have been able to detect different hemodynamic changes in a dynamic fashion, including chemical stimulation to test the vasomotor reserve (hypocapnea, hypercapnea or administration of acetazolamide) and induced percutaneous injections of ABP and/or CBFV to observe real-time changes in CBFV. To search on orthostatic changes of arterial blood pressure (ABP) and CBFV are of particular interest in patients with orthostatic intolerance, especially those with autonomic dysfunction. How ever, cerebrovascular regulation upon orthostatic challenges can not be predicted in the supine position, nor can it be deduced from the orthostatic ABP changes alone. Therefore, orthostatic stress with head-up tilt (HUT) and induced hypotension with lower body negative pressure have been used to probe percutaneous injections.
METHODS

Thirteen patients with 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 volunteered with orthostatic dizziness and autonomic dysfunction were recruited from the neurologic out-patient department as controls. They included healthy individuals (5 persons) and those who were otherwise healthy except for mild sensorial hypertension (4 cases). None of the controls had clinical evidence of diabetes, peripheral neuropathy, abnormal sympathetic skin response or heart rate variability (R-R interval variation), according to the methods recommended by Shahani et al.,17,18 were used as the objective evidence of disordered autonomic function. These patients were also evaluated by a cardiologist to exclude the possibility of dizziness from cardio genetic causes and by an otolaryngologist to exclude disturbance of 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 with the responsible physicians for approval. Each participant

We further documented that the LF MCAFV component is strongly related to pressure-related mechanisms of cerebrovascular regulation in normal subjects.13 There fore, we used spectral analysis of MCAFV to evaluate a group of patients with autonomic dysfunction and healthy controls to address the two main purposes of this study: (1) description of the characteristics of spontaneous oscillations in MCAFV and (2) evaluation of the role of LF MCAFV spectral power as a marker of impaired cerebrovascular regulation in these patients.

Recent advances in frequency-domain analysis of the spontaneous fluctuations of CBFV have greatly expanded our insight into cerebrovascular regulation. In our previous study, we found that the fluctuations in MCAFV could be divided into three components at specific frequency ranges, designated as high-frequency (HF, 0.15 to 0.40 Hz), low-frequency (LF, 0.04 to 0.15 Hz), and very low-frequency (VLF, 0.016 to 0.04 Hz) components.13 We further documented that the LF MCAFV component is strongly related to pressure-related mechanisms of cerebrovascular regulation in normal subjects.13,14 Therefore, we used spectral analysis of MCAFV to evaluate a group of patients with autonomic dysfunction and healthy controls to address the two main purposes of this study: (1) description of the characteristics of spontaneous oscillations in MCAFV and (2) evaluation of the role of LF MCAFV spectral power as a marker of impaired cerebrovascular regulation in these patients.

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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 investigated each patient's history, gave a complete physical examination and 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 a lumbar puncture. Based on this definition, patients with autonomic dysfunction and orthostatic dizziness were recruited if they had objective evidence of disordered autonomic function. These patients were also evaluated by a cardiologist to exclude the possibility of dizziness from cardio genetic causes and by an otolaryngologist to exclude disturbance of the ear and vestibular system.

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stayed in a supine position on a motorized tilt table with foot board support. Heart rate and rhythm were cautiously evaluated using a standard electrocardiographic 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 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, Sippelingen, 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 windows, 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 horizontal 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 for 30 minutes during the supine rest position and during the 30-minute head-up tilt (divided into two 15-minute segments) for spectral analysis.

The analysis technique for MCAFV variability has been documented previously. The MCAFV signals were first normalized by mean MCAFV and were expressed by percentage variation from the mean MCAFV. This normalization procedure could exclude the recording bias in duced by the angle of the ultrasound transducer, and makes the consequent spectral and transfer function analysis independent of absolute value of mean MCAFV. Original and normalized MCAFV signals were subjected to off-line spectral analysis by the construction of average periodogram. For this purpose, a 288-second segment of stationary MCAFV signals was divided into eight sets of 64-second windows. Each set overlapped by 50%. Computer formation of the spectral component was performed using a fast Fourier transform. The MCAFV spectra obtained for the eight data sets were subsequently quantified. The computer program subsequently quantified each spectral component by the method of integration of power spectral density between two specified frequencies. We were particularly interested in the lower end of the frequency spectrum of MCAFV signals, such as very low-frequency (VLF, 0.016-0.04 Hz), low-frequency (LF, 0.04-0.15 Hz), and high-frequency (HF, 0.15-0.4 Hz). These frequency ranges were determined by heart rate variability as previously defined.

All the measurement values were expressed as mean ± SD. Wilcoxon 2-sample test was performed to test difference between cases and controls. The statistical significance was defined as p < 0.05.

RESULTS

All the participants withstood the procedure well although mild dizziness was complained by most patients during HUT. The study included 13 patients with autonomic dysfunction (mean age of 71.3 ± 5.8 years, all males) and 9 health controls (mean age 58.1 ± 12.6 years, 6 males). Eight patients and 4 control patients had hypertension, defined as SBP and DBP greater or equal to 140 and 80 mmHg, respectively, measured twice at least 4 hours apart. Diabetes mellitus was present in two patients, but none in controls.

Some of the study results have been accepted for publication in a separate paper, including the ABP and MCAFV in the supine and tilt-up positions, showing the excessive orthostatic decrease in CBFV, but not in ABP in these patients as compared with the controls. The mean and SD of the VLF, LF and HF power of MCAFV during supine rest were 2.83 ± 2.73 mm Hg², 0.225 ±
0.13 unit$^2$, $0.896 \pm 0.69$ unit$^2$ respectively in the patients and $4.34 \pm 1.69$ unit$^2$, $1.24 \pm 0.97$ unit$^2$, $0.69 \pm 0.36$ unit$^2$ respectively in the controls. The LF power was significantly lower in the patient group ($P = 0.002$), but the VLF power was not significantly lower in them ($p = 0.0995$). The MCAFV spectral powers in the three frequency ranges were measured in the first and second 15 minutes during the 30-minute HUT. The baseline power as well as the spectral power of two periods during HUT in the VLF, LF, and HF ranges are respectively depicted in Figs. 1 to 3. It is evident that the VLF and LF MCAFV powers during orthostasis were significantly lower in the

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**Fig. 1.** Time course of spectral power changes of MCAFV in the VLF range.

**Fig. 2.** Time course of spectral power changes of MCAFV in the LF range.
patients than in the controls (Fig. 1 and 2). There was no difference in the HF MCAFV power between these 2 groups, either before or during HUT (Fig. 3).

**DISCUSSION**

There are two main findings in this study: (1) The characteristics of spontaneous oscillations in MCAFV in the supine position and during orthostasis were described in the frequency domain in patients with autonomic dysfunction; (2) LF MCAFV spectral power was significantly decreased in patients with autonomic dysfunction and impaired cerebrovascular regulation in the supine position and during orthostasis.

The physiological significance of the spontaneous fluctuation of CBFV in the VLF, LF and HF ranges is only incompletely understood. Our previous study revealed that the LF component seems to play a major role in pressure-modulation, serving to modulate the ABP variations. The VLF component is considered independent of pressure-modulation mechanisms of cerebrovascular regulation, although its role in other mechanisms is highly suspected. The role of HF component in pressure-modulation may be minimal since it seems to passively reflect the ABP variations; however, its role in other mechanisms of cerebrovascular regulation awaits further evaluation.

The importance of these slow CBFV oscillations in cerebrovascular regulation was further supported by another study using transfer function analysis of ABP and CBFV in patients with carotid stenosis. Decreased VLF, LF and HF magnitude and decreased LF transfer phase angle were associated with impaired CO$_2$ reactivity in patients with carotid stenosis of greater than 50%. The transfer magnitude in each frequency range is approximately the square root of the ratio of MCAFV power to the ABP power in each frequency range given good coherence. Therefore, a decreased LF magnitude might result from a decreased LF MCAFV power and/or increased LF ABP power. Since hypertension, which is associated with increased LF ABP power, was common in patients with carotid stenosis, this study was not able to discriminate which of the two factors, decreased LF MCAFV power or increased LF ABP power, was responsible for the observed association of decreased LF magnitude and decreased CO$_2$ reactivity. Our study seemed to address this issue, although spectral analysis of ABP was not conducted because of...
lack of continuous beat-to-beat ABP monitoring. Since the patients in our study had autonomic dysfunction and relatively lower ABP, we would expect the LF ABP power in the patients to be less than that in the controls. The association of decreased LF MCAFV power and impaired cerebrovascular regulation is thus supported in our study. The role of VLF component is much less understood. The decreased VLF MCAFV power found in our patients, nonsignificantly in the supine position and significantly during orthostasis, would also suggest it as an important marker of disordered cerebrovascular regulation in patients with autonomic dysfunction. The decreased HF magi tude in patients with severe carotid stenosis and impaired cerebrovascular reserve. How ever, the coherence between ABP and MCAFV in the VLF range is usually less than satisfactory. Therefore, the correlation of decreased VLF magnitude and decreased VLF MCAFV power might not be as robust as that in the LF and HF ranges. Nevertheless, the decreased VLF MCAFV power found in our patients, nonsignificantly in the supine position and significantly during orthostasis, would also suggest it as an important marker of disordered cerebrovascular regulation in patients with autonomic dysfunction. The decreased HF magnitude in patients with severe carotid stenosis would also suggest decreased HF MCAFV power or in increased HF ABP power. Blaber et al. observed an increase in HF ABP power during HUT in patients with autonomic failure, but the HF MCAFV power or HF gain in the supine position during HUT was not mentioned. Therefore, it would be difficult to judge the role of HF MCAFV power and cerebrovascular regulation in their study. Nevertheless, our study results would suggest that HF MCAFV power might not be a sensitive marker of impaired cerebrovascular regulation in patients with autonomic dysfunction.

Blaber et al. observed a higher supine LF magnitude in 8 patients with autonomic failure than that of controls. The LF magnitude decreased significantly in both groups during head-up tilt. The higher LF magnitude in these patients could be attributed to either an increase in LF MCAFV power or a decrease in LF ABP power. A decrease in supine ABP power in patients with autonomic failure was reported by these authors in a separate publication. The LF MCAFV power in these patients was not discussed, however. Therefore, the study results of these researches did not contradict ours.

However, some as assessments must be made in order for this study to evaluate cerebrovascular regulation with TCD. The validity of using TCD to estimate MCA flow has been previously studied, and a good correlation between MCAFV and MCA flow was reported. In addition, it has been verified that there was little or no change of MCA stem diameter (the insonated segment in transcranial Doppler sonography) during different autoregulatory tests such that MCAFV changes can be related to CBF changes. Therefore, relative changes in MCAFV should represent change in CBF during rest and autoregulation tests. In this study, we managed the MCAFV data as a percentage variation from the mean to represent relative change in CBF.

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