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Effects of Different Classes of Antihypertensive Drugs on Cerebral Hemodynamics in Elderly Hypertensive Patients

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Abstract

Background

This study was designed to estimate the effect of different classes of antihypertensive drugs on cerebral hemodynamics in elderly stroke-free, non-diabetic hypertensive patients by applying frequency-domain techniques.

Methods

A total of 60 hypertensive patients divided into 15 unmedicated (HT), 15 nifedepine sustained release form (CCB), 15 atenolol (BB), and 15 valsartan (AIIA) treatment groups and 15 age-matched healthy volunteers (CON) were studied prospectively. Variability of arterial blood pressure (ABP) and middle cerebral artery flow velocity (MCAFV) detected by transcranial Doppler sonography were diffracted into 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). Cerebral hemodynamics was quantified by ABP-MCAFV transfer function.

Results

ABP and MCAFV were statistically different between CON and HT groups, but not significantly different among CON, CCB, BB, and AIIA groups. The LF phase and HF magnitude in the HT, CCB and BB groups were significantly attenuated than those of the CON group, but not statistically different between the AIIA and CON groups. There were no statistically differences in VLF and LF transfer magnitude among the five groups.
Conclusions

Though cerebral vasomotor reserve and cerebral blood flow are impaired in unmedicated hypertensive patients, the cerebral autoregulatory response was preserved both in controlled and uncontrolled hypertension. The nifedipine, atenolol, and valsartan are all effective as monotherapy for controlling ABP and restoring cerebral blood flow. The valsartan has the effect to normalize the changes in cerebral vasomotor reserve to a level similar as age-matched healthy subjects.

Keywords: Hypertension; transcranial Doppler; cerebral vasomotor reserve; cerebral autoregulation; frequency-domain analysis
Hypertension is a major risk factor for stroke and ischemic heart disease.\textsuperscript{1} Most burden of stroke is attributable to non-optimal blood pressure. In cerebral hemodynamics, reductions in cerebral blood flow (CBF) and increases in cerebrovascular resistance have been observed by $^{133}$Xe-CT or PET study in hypertensive patients.\textsuperscript{2,3} The benefits of reducing blood pressure on the risks of major cardiovascular or cerebrovascular diseases are well established,\textsuperscript{3,4} but uncertainty remains about the comparative effects of different classes of antihypertensive drugs on cerebral hemodynamics.

More recently, using the frequency-domain techniques to assess the relationship between middle cerebral blood flow velocity (MCAFV) detected by transcranial Doppler (TCD) sonography and systemic arterial blood pressure (ABP) has been determined to be a safe and convenient method for evaluating cerebral hemodynamics.\textsuperscript{5,6} Previous research has suggested that low-frequency (LF, 0.04 ~ 0.15 Hz) fluctuations of MCAFV represent cerebral autoregulatory processes.\textsuperscript{5-7} It has also been demonstrated that LF phase and high-frequency (HF, 0.15 ~ 0.4 Hz) magnitude of ABP-MCAFV transfer function may provide valid evaluation of carotid artery stenosis\textsuperscript{8,9} and cerebral vasomotor activity or vasomotor reserve in humans.\textsuperscript{8,10}

Thus, this study was designed to estimate the effect of different classes of antihypertensive drugs, including calcium channel blockers, beta-blockers, and angiotensin II receptor antagonists on cerebral hemodynamics in elderly stroke-free, non diabetic
hypertensive patients by using frequency-domain techniques. We expected this study would suggest some consideration for clinical physicians in managing these patients.

**Methods**

**Study sample and experimental setup**

This was a prospective comparison of effects of different antihypertensive drugs on cerebral hemodynamics. A total of 60 subjects from the out-patient department of Hualien Tzu Chi General Hospital participated in this study. They were all newly diagnosed as essential hypertension by cardiologists. These subjects were divided into unmedicated (HT, n = 15), calcium channel blocker (CCB, n = 15, Nifedipine sustained release form 20 ~ 40 mg twice per day), beta-blocker (BB, n = 15, Atenolol 50 ~ 100 mg once daily), and angiotensin II receptor antagonist (AIIA, n = 15, Valsartan 80~160 mg once daily) groups. The control group comprised 15 age-matched healthy volunteers (CON). The HT group didn’t receive a placebo or any other cardiovascular medications. The dosage of antihypertensive drugs was adjusted every week to reach the goal of ABP < 140/90 mmHg. All subjects were screened with a complete medical history, physical examinations, ECG, and blood tests to exclude diabetes mellitus, malignancy, and acute cerebrovascular or cardiovascular diseases. Furthermore, no subjects were receiving the second antihypertensive medication or using drugs reported to influence cardiovascular functions, such as hypnotics or autonomic blockers. After a 4-week treatment, these subjects underwent the recording of ABP and MCA芙V. The procedures used in this study
were approved by the Human Research Committee of Tzu Chi University and Hospital, and all subjects gave informed consent.

**Recording of ABP, MCAVF**

Instantaneous ABP and MCAVF recordings were taken in a sitting position for 5 min. The ABP was recorded non-invasively using continuous blood pressure monitor (CBM-700, COLIN, Japan). The MCAVF was recorded using a TCD monitor (DEL EZ-DOP, DWL, Germany) at the depth of the best signal (44-55 mm). The ABP and MCAVF signals were recorded using a 12-bit analog-to-digital converter (PCL-818, Advantech, Taiwan) with a sampling rate of 1024 Hz. All these biological signals were acquired, displayed, and stored on a personal computer (IBM-PC compatible).

**Auto-spectral Analysis of ABP and MCAVF**

The analysis technique for ABP and MCAVF variations was previously documented.5,8 The MCAVF signals were first normalized by mean MCAVF and were expressed by percentage variation from the mean MCAVF. This normalization procedure could exclude the recording bias induced by the angle of the ultrasound transducer, and makes the consequent spectral and transfer function analysis independent of the absolute value of the mean MCAVF. The original ABP and normalized MCAVF signals were subject to off-line spectral analysis by the construction of average periodogram. For this purpose, a 288-s segment of stable ABP
and MCAFV signals was divided into eight sets of 64-s windows. Each set overlapped the next set by 50%. Computation of the spectrum was performed using fast Fourier transform (FFT). The ABP and MCAFV spectra obtained for the eight data sets were subsequently averaged to minimize contributions from variable noise and to sharpen reproducible spectral components. The computer program subsequently quantified each spectral component by the method of integration. We focused on the lower end of the frequency, including very-low-frequency (VLF, 0.016 ~ 0.04 Hz), LF (0.04 ~ 0.15 Hz) and HF (0.15 ~ 0.4 Hz).

**Cross-spectral Analysis of ABP and MCAFV**

Cross-spectral analysis was generated from the same eight data sets of ABP and MCAFV signals used in the average periodogram analysis.\(^{11}\) We used a magnitude-squared coherence function: 
\[ k^2(f) = \frac{|S_{VB}(f)|^2}{S_{BB}(f) \times S_{VV}(f)}, \]
where \(S_{BB}(f)\) and \(S_{VV}(f)\) are the respective power spectrum of the ABP and MCAFV signals, and \(S_{VB}(f)\) is their cross-spectrum. The value of the coherence function ranges from 0 to 1 and provides an assessment of the linear relation at each frequency and of the statistical reliability of the transfer function. For this purpose, a coherence \(\geq 0.5\) was considered to be statistically significant.\(^{5,12}\) The transfer function, \(H(f) = S_{VB}/S_{BB}(f)\) with a magnitude defined as \([H_R(f)]^2 + [H_I(f)]^2\)^{1/2} where \(H_R(f)\) and \(H_I(f)\) include the real and imaginary parts of the complex transfer function, is expressed as unit/mm Hg. The phase of transfer function is defined as \(\Phi(f) = \tan^{-1} [H_I(f)/ H_R(f)]\) with the unit of degree.

The coherence, transfer phase and magnitude were quantified in individual VLF, LF and HF
Statistical Methods

All measured values are expressed as means ± SE. Natural logarithm transformation was applied to the spectral power of ABP and MCAFV to adjust for the skewness of the distribution. Data were analyzed using non parametric analysis of variance (ANOVA), followed by the Dunn’s test, and statistical significance was set at the $P < 0.05$ level.

Results

Demographic and baseline data for each group are given in Table 1. Age and body mass index were not statistically different among these groups. Mean ABP was significant higher and MCAFV was significant lower in the HT group compared with the CON, CCB, BB and AIIA groups ($P < 0.05$). But there were no significantly different among the CON, CCB, BB and AIIA groups in ABP and MCAFV. The heart rate was significantly increased in the CCB group than the CON group ($P < 0.01$).

Fluctuation quantification and the transfer function analysis of each component for the ABP and MCAFV spectrum are statistically described in Fig. 1. In hypertensive patients both with and without medical treatment, the LF spectral power of ABP was all significantly lower than that of the CON group ($P < 0.01$). The LF transfer phase and HF transfer magnitude in the HT, CCB and BB groups were significant attenuated than those of the CON group ($P < 0.05$). Instead, the AIIA group had significantly higher LF phase and HF magnitude than those
of the HT group ($P < 0.01$), but no significant differences compared with the CON group. There were no statistically differences in VLF and LF transfer magnitude among the five groups.

**Discussion**

Using transfer function analysis between ABP and MCAFV, we found that cerebral vasomotor reserve and CBF are impaired in unmedicated elderly hypertensive patients, but the cerebral autoregulatory response was preserved both in controlled and uncontrolled hypertension. Despite the similar effects on ABP and MCAFV, the valsartan had a more significant improvement in cerebral vasomotor reserve than the other classes of antihypertensive drugs.

It is widely recognized that CBF is usually decreased in chronic hypertensive patients.\(^2,3\) This CBF reduction might partially reflect hypertension-related reversible vascular alternations that are responsible for cerebral ischemia. It had been reported that hypertensive subjects with blood pressure lowering regiments didn’t compromise CBF.\(^{14,15}\) Furthermore, aggressive antihypertensive therapy, no matter what classes of antihypertensive drugs had appeared to restore MCAFV in our study. These findings are quite compatible with the previous study\(^{16}\) that well controlling blood pressure in hypertensive patients could restore the CBF and then reduce the risks for stroke and cognitive declines.

Spontaneous fluctuations of ABP can be classified into various frequency components
with different underlying mechanisms. The HF component originates in cardiac output variations induced by respiratory movement.\textsuperscript{17,18} The LF component originates from fluctuations in sympathetic vasomotor control by the central nervous system.\textsuperscript{19} In this study, the LF power of ABP was significantly lower in both controlled and uncontrolled hypertensive patients compared with age-matched healthy subjects. This implies that sympathetic vasomotor control of vessels in chronic essential hypertension is decreased; this renders these patients unable to maintain a steady blood pressure in the face of various dynamic physiological changes.\textsuperscript{20} It may be one of the possible causes that made these hypertensive patients experienced with orthostatic hypotension or syncope.

Assessment of cerebral vasomotor reserve from spontaneous fluctuations of ABP and MCAFV is attractive because it does not require any external blood pressure manipulation or CO\textsubscript{2} inhalation that can produce unexpected complications. The transfer phase between ABP and MCAFV may originate from the resistance reaction latency of cerebral vessels in response to ABP variations.\textsuperscript{21,22} The transfer magnitudes may reflect that changes in vessel diameter of cerebral arterioles attempt to minimize the effect of blood pressure changes during cerebral autoregulation. In previous studies, a strongly positive correlation existed between the LF phase as well as the HF magnitude of ABP-MCAFV transfer function and CO\textsubscript{2} vasomotor reactivity in humans.\textsuperscript{8} So these indicate that the LF transfer phase and HF transfer magnitude may serve as guides for evaluating cerebral vasomotor reactivity or
In this study, we found both the LF phase and HF magnitude of ABP-MCAFV transfer function in the AIIA group was significantly higher than those in the HT group. This may suggest that cerebral vasomotor reserve declines in elderly unmedicated hypertensive patients, and an AIIA may normalize the changes to a level similar to those in age-matched healthy subjects. The increased LF phase and HF magnitude resulting from an AIIA administration in hypertensive patients may be related to a decrease in the medial thickness of the cerebral arteries, inhibition of injury-related proliferation of smooth muscle, acceleration in vascular variability and an increase in the capacity of cerebral vessels to vasodilate in the face of cerebral hemodynamic changes.

Our previous study had found that the LF fluctuations of MCAFV response to that of ABP was not passive, and it played a major role in pressure-modulation, serving to modulate the ABP variability. The LF magnitude of MCAFV-ABP transfer function viewed as changes in amplitude in MCAFV corresponding to changes in ABP at LF range is now widely accepted as index of cerebral autoregulatory processes. In this study, we found LF power of ABP variability in controlled and uncontrolled hypertensive patients significantly reduced than normotensive subjects. The LF power of MCAFV variability was also slightly attenuated in hypertensive patients. That made the transfer of blood pressure to flow velocity, that is LF magnitude of MCAFV-ABP transfer function have no significant differences between hypertensive and normotensive subjects. These findings suggested that dynamic cerebral
autoregulatory response remains intact in controlled and even uncontrolled hypertension. It was quite compatible with other previous research.\textsuperscript{26,27}

The reliability of cerebral blood flow velocity measured by TCD as a surrogate of cerebral blood flow in healthy individuals has been discussed before,\textsuperscript{28} and the good correlation of MCAFV with cerebral blood flow has been proved under experimental conditions. But the limitation of this study is the problem of cardiac arrhythmia that may make frequency-domain analysis of cardiovascular parameters hard to be interpreted.

In conclusion, this study defines transfer function analysis of spontaneous fluctuations between ABP and MCAFV offering a simple and convenient method for evaluating cerebral hemodynamics. Though cerebral vasomotor reserve and CBF are impaired in unmedicated elderly hypertensive patients, the cerebral autoregulatory response was preserved both in controlled and uncontrolled hypertension. Nifedipine sustained release form, atenolol and valsartan were all effective as monotherapy for controlling blood pressure and restoring CBF. Furthermore, valsartan has the effect to normalize the changes in cerebral vasomotor reserve in these elderly stroke-free, non-diabetic hypertensive patients to a level similar as aged-matched healthy subjects.

**Acknowledgment:**

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References


Table 1. Demographic information and baseline characteristics of each group

<table>
<thead>
<tr>
<th></th>
<th>CON</th>
<th>HT</th>
<th>CCB</th>
<th>BB</th>
<th>AIIA</th>
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<tr>
<td>n (M:F)</td>
<td>15 (8:7)</td>
<td>15 (8:7)</td>
<td>15 (7:8)</td>
<td>15 (7:8)</td>
<td>15 (8:7)</td>
</tr>
<tr>
<td>Medications</td>
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<td>nil</td>
<td>Nifedipine</td>
<td>Atenolol</td>
<td>Valsartan</td>
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<tr>
<td>Age, years</td>
<td>59.5 ± 2.2</td>
<td>62.8 ± 3.5</td>
<td>58.4 ± 5.4</td>
<td>60.4 ± 4.9</td>
<td>64.1 ± 3.3</td>
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<tr>
<td>BMI, kg/m²</td>
<td>23.3 ± 0.6</td>
<td>23.6 ± 1.0</td>
<td>22.6 ± 0.7</td>
<td>24.0 ± 1.1</td>
<td>23.2 ± 0.9</td>
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<tr>
<td>MBP, mmHg</td>
<td>88.5 ± 2.3</td>
<td>110.1 ± 3.5*</td>
<td>96.8 ± 5.6†</td>
<td>96.6 ± 3.6†</td>
<td>98.7 ± 3.3†</td>
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<tr>
<td>MCAFV, cm/s</td>
<td>57.8 ± 1.7</td>
<td>47.4 ± 1.6*</td>
<td>55.2 ± 2.8†</td>
<td>58.9 ± 4.9†</td>
<td>56.5 ± 2.3†</td>
</tr>
<tr>
<td>HR, bpm</td>
<td>62.4 ± 3.3</td>
<td>68.3 ± 2.7</td>
<td>76.1 ± 4.4*</td>
<td>60.2 ± 3.1</td>
<td>69.1 ± 2.5</td>
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</tbody>
</table>

Values are presented as means ± SE; n, no. of subjects/group; M, male; F, female; CON, age-matched healthy subjects; HT, hypertensive patients without medical treatment; CCB, hypertensive patients with a calcium channel blocker; BB, hypertensive patients with a beta blocker; AIIA, hypertensive patients with an angiotensin II receptor antagonist; BMI, body mass index; MBP, mean blood pressure; MCAFV, middle cerebral artery flow velocity; HR, heart rate. *P < 0.05 vs CON; †P < 0.05 vs HT by Dunn’s test.
FIG. 1. Variability in very-low-frequency (VLF), low-frequency (LF) and high-frequency (HF) of arterial blood pressure (ABP) and middle cerebral artery flow velocity (MCAFV); as well as the transfer phase and transfer magnitude between ABP and MCAFV in age-matched healthy subjects (CON, n = 15), hypertensive patients without medical treatment (HT, n = 15), hypertensive patients with a calcium channel blocker (CCB, n = 15), a beta blocker (BB, n = 15) and an angiotensin II receptor antagonist (AIIA, n = 15). Ln: natural logarithm. Values are presented as means ± SE. *P < 0.05 vs CON; †P < 0.05 vs HT by Dunn’s test.