Yonsei Medical Journal
Vol. 39, No. 4, pp. 322~327, 1998

Cerebral Hemodynamic Changes Induced by Sympathetic Stimulation Tests

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Sympathetic neuronal activity is primarily responsible for the neurogenic control of cerebral autoregulation. The stimulation of sympathetic nerves causes both large arterial constriction and small vessel dilation in experimental animals. However, the role of the sympathetic nervous system in the control of cerebral hemodynamics has yet to be clarified in humans. In order to assess the effect of sympathetic activation on human cerebral hemodynamics, we performed a simultaneous transcranial Doppler (TCD) monitoring of bilateral middle cerebral arterial flow velocity in 16 healthy male volunteers (mean age 26) during well-known sympathetic activation measures such as isometric hand-grip exercise (IHE) and cold pressor test (CPT). Blood pressure was checked manually before and at each minute during tests. The mean arterial pressure (MAP) was calculated as (systolic pressure + 2 X diastolic pressure)/3. There was a significant increase in MCA flow velocities during both sympathetic activation tests. The percent increase of diastolic velocity (36% with IHE and 24% with CPT) was significantly higher than systolic velocity (21% with IHE and 9% with CPT). The pulsatility index was significantly decreased during the tests (from 0.75 to 0.58 with IHE and from 0.81 to 0.63 with CPT). These results suggest that sympathetic activation increases MCA flow velocities, related with a reduction in small vessel resistance and/or a constriction of large arteries.

Key Words: Sympathetic nervous system, cerebrovascular circulation, cerebral arteries, transcranial Doppler ultrasonography, vascular resistance, heart function tests

The autonomic regulation of cerebral blood flow (CBF) in humans has long been a subject of considerable interest in studying the mechanisms of various neurovascular disorders such as hypertensive encephalopathy, migraine and various types of syncope. In experimental animals, an electrical stimulation of the sympathetic nerves induced a constriction of the large cerebral arteries (Harper *et al.* 1972; Kuschinsky and Wahl, 1975; Wei *et al.* 1975; Baumbach and Heistad, 1983), which resulted in a moderate reduction in CBF (Lacombe *et al.* 1977; Edvinsson, 1982; Busija, 1986; Morita-Tsuzuki *et al.* 1993). During increased arterial pressure, these sympathetically-mediated vascular changes extend the upper limit of autoregulation and have an important role in protecting the brain from hypertensive damage (Bill and Linder, 1976; Busija *et al.* 1980; Beausang-Linder and Bill, 1981; Tamaki and Heistad, 1986). Since the capacity of cerebral vessels to respond to autonomic stimulation is variable among different species (Heistad *et al.* 1978; Busija *et al.* 1980), it seems inappropriate to apply the results of animal experiments to human cerebrovascular physiology.

The introduction of transcranial Doppler ultrasonography (TCD) by Aaslid *et al.* (1982) offers a new non-invasive tool for monitoring cerebral hemo-

Received April 21, 1998
Accepted July 4, 1998
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dynamic changes during various autonomic manipulations. However, previous studies investigating the effect of sympathetic stimulation on CBF velocity using TCD have failed to show consistent results (Wahlgren *et al.* 1992; Micieli *et al.* 1994; Thompsen *et al.* 1995). In order to investigate the functional role of sympathetic nerves in regulating human cerebral hemodynamics, therefore, we performed TCD with a specially designed head-piece suitable for monitoring flow velocity of the middle cerebral artery (MCA) at the same insonation angle, in healthy volunteers, during non-invasive cardiovascular autonomic tests.

MATERIALS AND METHODS

The subjects were 16 healthy male volunteers (age, 23~36 years; mean, 26 years old). They were selected from medical students or doctors who consented to participate in this study after a full explanation of its purposes, risks and potential benefits. None of them had a previous history suggesting cerebral or cardiovascular illnesses, or were taking drugs that were supposed to influence autonomic functions.

All subjects rested in a sitting position at least for 20 minutes before the autonomic function tests, including isometric hand-grip exercise (IHE) and cold pressor tests (CPT). Prior to these tests, the baseline blood pressure and the baseline TCD measurements were checked. IHE was performed for 5 minutes with sustained isometric right hand-gripping at 30% maximum effort. CPT was performed for 1 minute by placing the subject's right hand in ice-water. During these tests, flow velocities of bilateral MCA were continuously and simultaneously monitored by TCD and blood pressure was manually measured at each minute. The mean arterial pressure was calculated as (systolic pressure + 2 x diastolic pressure) / 3.

TCD examinations were performed using a TCD monitoring instrument (Pioneer, EME, berlingen, Germany) and according to examination techniques similar to those previously described (Fujioka and Douville, 1992). Doppler signals from the main stem of bilateral MCA were obtained continuously and simultaneously with two 2 MHz probes attached to a headpiece, through a trans-temporal window at a depth between 56~60 mm. The headpiece was specially designed to prevent the probes from changing insonation angle during monitoring. For each artery, the mean (Vm), systolic (Vs) and diastolic velocities (Vd) were measured, and the Gosling pulsatility index (PI) was calculated automatically.

Data were expressed as means±standard deviations. Statistical analyses were performed using paired and unpaired t-test as well as simple and stepwise regression analysis. P values of less than 0.05 were regarded as significant.

RESULTS

Both IHE and CPT were successfully performed in all subjects, and Doppler signals were successfully obtained from 27 MCAs. Before IHE, the baseline MAP was 91±12 mmHg and MCA velocities were 58±11 (Vm), 88±19 (Vs) and 44±8 cm/sec (Vd). During IHE, the MAP increased significantly to 106±8 (at 1 minute), 112±10 (at 2 minute), 118±13 (at 3 minute), 122±10 (at 4 minute) and 124±11 (at 5 minute). MCA velocities were also increased to 64±14, 92±19, 50±12 (at 1 minute), 67±18, 92±21, 51±14 (at 2 minute), 70±21, 94±27, 55±13 (at 3 minute), 74±15, 98±27, 58±14 (at 4 minute) and 78±14, 104±19, 59±11 (at 5 minute). During CPT, the baseline MAP, 95±8, was also increased to 114±6 mmHg, and baseline MCA velocities, 59±14 (Vm), 87±19 (Vs), 42±11 (Vd), were also increased to 70±21, 95±23, 53±17 cm/sec. Gosling pulsatility index was significantly decreased from 0.75±0.11 to 0.67±0.12 (at 1 minute), 0.64±0.11 (at 2 minute), 0.59±0.11 (at 3 minute), 0.59±0.12 (at 4 minute) and 0.58±0.09 (at 5 minute) during IHE, and from 0.82±0.13 to 0.63±0.12 during CPT. The MAP and all TCD measurements except Vs were significantly changed after one minute of IHE (Table 1). The changes in Vs were still not significant at 3 minutes of IHE. Although all TCD measurements were significantly changed after CPT, the significance of Vs change (P=0.02) was lower than that of Vm and

Table 1. Transcranial Doppler measurements during autonomic tests

Autonomic tests	MAP	MCA measurements			
		Vm	Vs	Vd	PI
IHE					
Baseline	91±12	58±11	88±19	44±9	0.75±0.16
1 minute	106±8^{C}	64±14^{C}	92±19	50±12^{B}	0.67±0.12^{C}
2 minute	112±10^{C}	67±18^{C}	92±21^{A}	51±14^{B}	0.64±0.11^{C}
3 minute	118±13^{C}	70±21^{C}	94±27	55±13^{C}	0.59±0.11^{C}
4 minute	122±10^{C}	74±15^{C}	98±27^{A}	58±14^{C}	0.59±0.12^{C}
5 minute	124±11^{C}	78±14^{C}	104±19^{C}	59±11^{C}	0.58±0.09^{C}
CPT					
Baseline	95±8	59±14	87±19	42±11	0.82±0.13
1 minute	114±6^{C}	70±21^{C}	95±23^{A}	53±17^{C}	0.63±0.12^{C}

Data are means±standard deviations. A; $p<0.05$, B; $p<0.005$, C; $p<0.0005$, compared with baseline values, analyzed by paired t-test. Vm; mean velocity, Vs; systolic velocity, Vd; diastolic velocity, PI; Gosling pulsatility index

Table 2. Velocity and pulsatility measurements of left and right MCA during autonomic tests

Autonomic tests	Vm		PI	
	Right	Left	Right	Left
IHE				
Baseline	59±11	57±11	0.77±0.14	0.73±0.17
1 minute	64±13	65±16	0.67±0.09	0.67±0.14
2 minute	67±14	67±21	0.64±0.10	0.64±0.13
3 minute	74±17	66±25	0.60±0.10	0.58±0.13
4 minute	74±14	74±17	0.58±0.11	0.59±0.14
5 minute	79±14	77±14	0.58±0.08	0.58±0.11
CPT				
Baseline	61±15	56±12	0.82±0.13	0.81±0.15
1 minute	73±22	68±20	0.63±0.11	0.63±0.12

Data are means±standard deviations. None of the above comparisons is significant, analyzed by paired t-test. Vm; mean velocity, PI; Gosling pulsatility index.

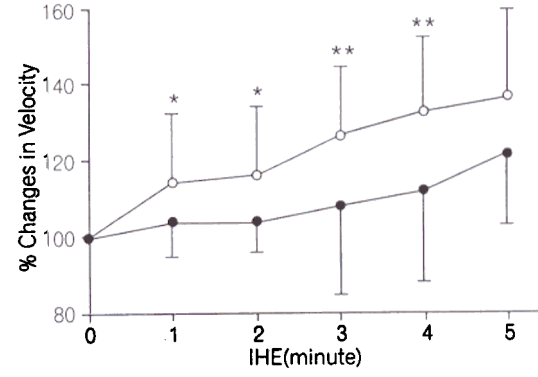

*Fig. 1. The percent changes in systolic and diastolic velocity of MCA during isometric hand-grip exercise (IHE). ○; systolic velocity, ●; diastolic velocity. *; $p<0.01$, **; $p<0.001$, analyzed by paired t-test.*

Vd ($P<0.0005$) (Table 1). The velocity and pulsatility measurements during both IHE and CPT were comparable between right and left MCA (Table 2).

During IHE, the percent changes of MAP were 117±15, 123±15, 131±20, 135±17 and 136±11% at every minute, and those of MCA velocities were; Vm, 111±12, 114±12, 120±26, 127±14, 136±19%; Vs, 104±9, 104±8, 108±23, 112±24, 121±18%; Vd, 114±18, 116±18, 126±18, 132±20, 136±23%, at every minute. After CPT, the percent change of MAP was 120±9%, and that of MCA velocities was 120±21% (Vm), 109±18% (Vs), 127±24% (Vd). The percent changes of Vd were significantly higher than those of Vs during both IHE and CPT (Fig. 1).

DISCUSSION

The present results clearly showed a significant increase in MCA flow velocity during both sympathetic activation measures employed in this study.

Thompsen *et al.* also demonstrated significantly -increased MCA flow velocity during CPT in migraine patients, which was consistent with our results (Thompsen *et al.* 1995). However, Micieli *et al.* presented quite opposite findings shown a significant reduction in MCA velocity during 5 minutes of CPT (Micieli *et al.* 1994). According to Jorgensen *et al.* static exercise of one leg for three minutes did not increase the MCA velocity (Jorgensen *et al.* 1992). The reason why these similarly-designed studies showed inconsistent results is unclear. Since subtle changes in insonation angle may cause significant changes in velocity measurements in TCD, it seems inappropriate to monitor MCA velocity continuously for several minutes by the hand-held probe used in those studies. Instead, we used a specially designed headpiece which enabled us to fix the probe at the same angle for a long time. Thus our study could convincingly provide more reliable data than previous studies.

A dynamic exercise of limbs has shown to result in a significant increase in contralateral hemispheric CBF (Olesen, 1971; Thomas *et al.* 1989). In contrast, a static exercise is not associated with an increase in global hemispheric CBF (Rogers *et al.* 1990; Friedman *et al.* 1991), although some increase (about 10%) in premotor and motor sensory regional CBF has been observed (Friedman *et al.* 1991). In this study, the velocity increase in MCA contralateral to the gripping hand was not higher than the other side. Although a regional CBF increase related with static exercises may occur bilaterally (Friedman *et al.* 1991), our results clearly showed that CPT, in addition to IHE, also induced a significant increase of MCA velocity. Thus, the increase in MCA velocity during static hand-gripping appears to result from the sympathetic activation rather than the exercise-related cerebral activation.

Sympathetic stimulation, besides its effect on cerebral vessels, also increases cardiac output. In this study, the blood pressure was also significantly increased along with MCA velocity changes, which suggested the sympathetic activation of cardiac function. However, the changes in cardiac output are known to have little effect on CBF if the autoregulation is intact (Bouma and Muizelaar, 1990). Schregel *et al.* demonstrated only a modest increase (15%) of the MCA velocity in patients with heart disease during exercise, while cardiac index was remarkably increased by up to more than 300% (Schregel *et al.* 1989). In addition to the changes in cardiac output, blood pressure elevation itself increases the cerebral perfusion pressure that can affect the MCA flow velocity. In healthy people with intact cerebral autoregulatory mechanisms, however, the change in CBF as well as MCA flow velocity induced by blood pressure change usually lasts for only a few seconds (Aaslid *et al.* 1989; Newell *et al.* 1994). Thus the persistent increase of the MCA velocity during sympathetic stimulation tests observed in this study does not appear to be directly related to the blood pressure elevation. In this study, moreover, the increase of diastolic velocity significantly exceeded that of systolic velocity. Since diastolic velocity is mainly influenced by vascular resistances, the MCA velocity increase observed in this study reflects cerebrovascular circulatory changes rather than cardiac activation.

Increased MCA velocity may result either from the MCA constriction or from dilation of distal vessels, or both. PCO_2 elevation also causes a significant dilation in small arteries and arterioles, which results in the MCA velocity elevation. However, previous reports have repeatedly demonstrated no significant changes in PCO_2 during both IHE and CPT (Rogers *et al.* 1990; Friedman *et al.* 1991; Jorgensen *et al.* 1992; Micieli *et al.* 1994; Thompsen *et al.* 1995). Thus the effect of PCO_2 changes on the present results could be minimal, although we did not monitor PCO_2 in each subject.

Harper *et al.* suggested that sympathetic stimulation constricted large cerebral arteries, but dilated small vessels (Harper *et al.* 1972). Direct observation of pial arteries demonstrated that sympathetic stimulation constricted large arteries, but had little or no effect on smaller pial vessels (Kuschinsky and Wahl, 1975; Wei *et al.* 1975). Baumbach and Heistad also demonstrated that the electrical stimulation of a sympathetic trunk in experimental animals significantly increased large artery resistances and reduced the pial artery pressure, while CBF and total cerebrovascular resistance did not change significantly (Baumbach and Heistad, 1983). In addition, norepinephrine administration increases ten-

sion of basilar arteries, but decreases tension of pial arteries (Harder *et al.* 1981). Thus, these studies suggest that either electrical or chemical stimulation of the sympathetic nervous system not only increases the resistance of large cerebral arteries, but also decreases small vessel resistances which prevents a reduction of CBF. In addition to these animal studies, the constriction of large cerebral arteries induced by sympathetic stimulation was also demonstrated in humans. Wahlgren et al. showed a marked and rapid increase in MCA velocity after the electrical stimulation of thoracic sympathetic trunk in three patients who received surgery for palmar hyperhidrosis (Wahlgren *et al.* 1992). When the stimulation was discontinued, MCA velocity returned more slowly to baseline values than blood pressure and heart rate. Since the duration of the MCA velocity increase was longer than expected autoregulatory responses, they suggested that the MCA velocity increase was partly caused by the MCA constriction.

Considering the results of those previous studies in humans as well as experimental animals, the MCA velocity increase with reduced pulsatility observed in this study resulted partly from constriction of MCA and/or dilation of small cerebral vessels. The density of adrenergic fibers are most abundant in large cerebral arteries at the base of the brain and over its surface, while smaller arteries or arterioles have much less adrenergic innervations (Nielson and Owman, 1967; Purdy and Bevan, 1977). Instead, small cerebral vessels are innervated mainly by secondary systems arising from the locus ceruleus (Itakura *et al.* 1977; Kobayashi *et al.* 1985), while adrenergic fibers innervating large arteries originate from ipsilateral superior cervical ganglion (Nielson and Owman, 1967). Various types of adrenergic receptors are found in the cortical microvessels (Harik *et al.* 1981; Edvinsson, 1982; O'Neill *et al.* 1988). Among them, the α_1-adrenergic receptors mediate vasoconstirction, while β-adrenergic receptors mediate vasodilation (Edvinsson, 1982; Winquist *et al.* 1982; Wroblewska *et al.* 1984). Since β_2 receptors are much more numerous than α receptors, β receptor-mediated vasodilation occurs mainly in small cerebral vessels, while α receptor -mediated vasoconstriction preferentially affects large cerebral arteries (Fitch *et al.* 1975). Thus the stimulation of sympathetic system increases resistance selectively in large vessels, but within the autoregulatory range there is little change in CBF because there is also a fall in the pial vessel resistance (Baumbach and Heistad, 1983), which is caused by either autoregulatory or β-adrenergic receptor-mediated responses. Aaslid *et al.* documented that the cross-sectional area of MCA does not change during stepwise reductions of arterial blood pressure (Aaslid *et al.* 1989), but Kontos using the published data of Aaslid *et al.* came to the conclusion that significant change in the arterial diameter does occur (Kontos, 1989). In conclusion, although the MCA velocity increase during autonomic tests of sympathetic stimulation appears to be related with a complex rather than a single mechanism, our results suggest that cerebrovascular changes, either large artery constriction or small vessel dilation or both, have at least a partial but significant role. The combination of cardiovascular autonomic tests, such as IHE and CPT, with TCD appears to be an easier and useful tool for investigating the functional activation of a sympathetic system to brain vessels in various functional disorders of cerebral circulation caused by different neurological pathologies.

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