Research Article

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Autoregulatory cerebral vasodilation occurs during orthostatic hypotension in patients with primary autonomic failure

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It is unclear whether patients with autonomic failure autoregulate cerebral blood flow during hypotension. The objective in this study was to examine cerebral autoregulatory capacity in patients with autonomic failure by studying changes in middle cerebral artery blood flow velocity using transcranial Doppler ultrasonography before, during, and after tilt-induced hypotension. Nine patients with primary autonomic failure were evaluated. Mean arterial pressure and middle cerebral artery blood flow velocity were simultaneously recorded while the patients were in the supine position, during 60° head-up tilt, and after they were returned to the horizontal position. The results were as follows: during tilt-induced hypotension, mean arterial pressure decreased significantly more than middle cerebral artery mean blood flow velocity (58% versus 36%, $p < 0.0002$). After return to the horizontal position, mean arterial pressure returned to baseline, and middle cerebral artery blood flow velocity transiently increased above pretilt value ($p < 0.02$). It is concluded that cerebral autoregulatory vasodilation occurs in patients with autonomic failure. This was demonstrated by a more pronounced decline in mean arterial pressure than in middle cerebral artery blood flow velocity during hypotension and by a transient increase in middle cerebral artery blood flow velocity (ie, hyperemic response) after blood pressure was restored.

Key words: autoregulation, autonomic failure, transcranial Doppler.

The role of the autonomic nervous system in cerebral autoregulation is unknown [1–4]. Because patients with autonomic failure are unable to adequately regulate their systemic blood pressure, it has been suggested that their ability to autoregulate cerebral circulation may also be compromised [5,6]. Others have suggested that autoregulation may actually be enhanced in patients with autonomic failure, with the lower limit of autoregulation occurring at lower than expected arterial pressures, thus enabling these patients to tolerate lower blood pressures than a normal population [7]. Although several blood flow and transcranial Doppler studies during hypotension in patients with autonomic failure have demonstrated preservation of cerebral autoregulation [3,7–12], some studies have suggested defective autoregulation in these patients [5,6,13], in addition to one study that showed both defective and preserved autoregulation [14].

The autoregulatory process for maintenance of cerebral blood flow during hypotension is cerebral vasodilation, which can be measured with transcranial Doppler ultrasonography (TCD). We examined a group of patients with autonomic failure and used TCD to assess changes in cerebral blood flow velocity during hypotension induced by head-up tilt. Specifically, we sought to determine whether cerebral vasodilation occurs in response to hypotension in patients with primary autonomic failure.

Patients and methods

Nine patients with orthostatic hypotension caused by primary autonomic failure were evaluated. There were eight men and one woman (median age 72 y, range 40–82 y). Three patients had pure autonomic failure, and six had multiple system atrophy by previously defined diagnostic criteria [15]. Electrocardiograms were recorded from precordial leads. Mean arterial blood pressure (MAP) was continuously monitored with a photoplethysmography device (Finapres; Ohmeda, Engelwood, CO, USA) attached to the second finger of the left hand. The left arm was extended and held level to the heart to ensure that recorded MAPs were at heart level. With the patient in the upright position, MAP at brain level was calculated by subtracting 20 mm Hg from MAP at heart level. This was done because the vertical distance between the heart and the brain results in a reduction in hydrostatic pressure at brain level of approximately 20 mm Hg when the head is above the level of the heart [16]. All subsequent mention of MAP refers to MAP at brain level.

Mean blood flow velocity (MBFV) was measured in the left middle cerebral artery by use of a 2.0-MHz, range-gated, pulsed transcranial Doppler ultrasound system (CDS/Medasonics, Fremont, CA). The transducer was strapped to the patient's head with a Velcro band to obtain continuous readings in the middle cerebral artery through the temporal ultrasonic window. The highest MBFV recorded between the depths of 50 and 60 mm was used [17].

The MAP and MBFV were recorded simultaneously for 5 minutes with patients in the baseline supine position, during 60° passive head-up tilt, and after they were returned to the horizontal position.

The MAP and MBFV were plotted against time for each patient. The MAP (determined by visual inspection) at

Table 1. Patient data

Patient	Age	Sex	Diagnosis	MAP (mm Hg)			MBFV (m/sec)		
				Baseline	Tilt	Post tilt	Baseline	Tilt	Post tilt
1	79	M	PAF	117	68	115	42	31	45
2	61	M	PAF	121	31	115	74	34	91
3	82	M	PAF	100	33	105	27	15	32
4	72	M	MSA	84	38	88	42	33	45
5	69	M	MSA	130	33	101	36	18	47
6	38	M	MSA	111	25	70	53	26	76
7	72	M	MSA	110	70	100	42	33	42
8	79	F	MSA	89	40	99	41	36	48
9	57	M	MSA	130	77	131	38	25	42

PAF = pure autonomic failure; MSA = multiple system atrophy; MAP = mean arterial blood pressure; MBFV = mean blood flow velocity.

which MBFV began to fall was identified as the lower limit of autoregulation. The difference in percent change between MAP and MBFV during and after tilt was calculated. If the percent decrease during hypotension was less for MBFV than for MAP, we assumed that autoregulatory cerebral vasodilation had occurred. If the percent decrease for MBFV was the same as the percent decrease for MAP, autoregulation was assumed to be defective (ie, flow was pressure dependent). Changes in MAP and MBFV were evaluated by one-way repeated measures analysis of variance, followed by multiple mean comparison tests. Linear regression analysis was used to determine the effect of supine MAP on the lower limit of autoregulation.

Two assumptions were made for this study. One was that the diameter of the middle cerebral artery trunk at the insonation point remained constant during orthostasis with autoregulatory changes taking place primarily at the level of the distal arterioles [18–20]. This assumption was made because blood flow through a vessel is equal to blood flow velocity times the cross-sectional area of the vessel, and changes in velocity correlate with flow only if the diameter of the middle cerebral artery at the point of insonation does not change. The second assumption was that intracranial pressure remained constant during testing. Because cerebral perfusion pressure is the MAP at brain level minus intracranial pressure, changes in cerebral perfusion pressure are directly reflected by changes in MAP at brain level only if intracranial pressure remains constant [1].

Results

Patient data are shown in Table 1. With patients in the supine position, MAP was 110 ± 16 mm Hg (mean ± SD, range 84–130 mm Hg), and MBFV was 44 ± 12 cm/sec (range 27–74 cm/sec). During tilt, MAP fell to 46 ± 19 mm Hg (range 25–77 mm Hg, $p < 0.001$), and MBFV dropped to 28 ± 7 cm/sec (range 15–34 cm/sec, $p < 0.001$). The MAP decreased significantly more than MBFV (58% versus 36%, $p < 0.0002$).

When patients were returned to the supine position after tilt, MAP rose to 103 ± 16 mm Hg during the first minute, a value slightly lower but not significantly different from the pretilt mean of 110 mm Hg. By contrast, MBFV increased to 52 ± 18 cm/sec, a significant increase above pretilt level of 44 cm/sec ($p < 0.02$). This increase in MBFV was transient, with a subsequent decline to baseline values. The lower limit of autoregulation ranged from 40 to 110 mm Hg, with an average of 70 ± 21 mm Hg. There was a significant correlation between the lower limit of autoregulation and baseline MAPs with the lower limit of autoregulation occurring at higher MAPs in those with higher baseline blood pressures ($r = 0.7$, $p < 0.04$) (Fig. 1).

Cases and examples

Case 1. Figure 2 shows the results of testing on a 69-year-old man with multiple system atrophy. The MAP is shown in the upper tracing and MBFV in the lower tracing. Baseline supine MAP is approximately 130 mm Hg. After tilt, MAP falls rapidly to 60 mm Hg. There is minimal change in middle cerebral artery MBFV, which remains at approximately 36 cm/sec despite the fall in MAP; thus, cerebral vasodilation has occurred, and autoregulation has been effective. When MAP falls below 60 mm Hg, MBFV begins to fall (first arrow); hence, 60 mm Hg is this patient's lower limit of autoregulation. As MAP falls to a low of 33 mm Hg,

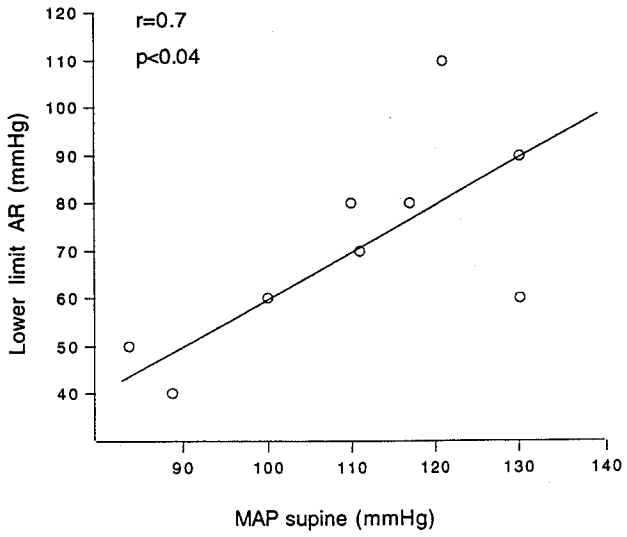

Figure 1. Relationship between lower limit of autoregulation and supine mean arterial pressure.

regulation was shown to be higher in those with hypertension than in normotensive control subjects [28,29]. The lower limit of autoregulation may be similarly elevated in patients with autonomic failure who have supine hypertension, resulting in pressure-dependent flow velocities at blood pressures higher than expected. This may account for the interpretation of abnormal autoregulation in other studies [5].

A limitation of our study is the lack of P_{CO_2} measurements. No change was measured in P_{CO_2} levels during similar tilt-table testing in another study [7]. A slight fall in P_{CO_2} secondary to hyperventilation occurred in patients during tilt-table testing in other reports [5,14]. This fall in P_{CO_2} resulted in a drop in MBFV of 14% to 16% in some patients, unassociated with a fall in MAP [14,30]. Even if some degree of MBFV decline in our patients had been secondary to hypocapnia, our results would not have been affected because MBFV still decreased significantly less than MAP, and the major fall in MBFV clearly occurred in association with a decreasing MAP. Indeed, if some of the decline in MBVF had been caused by hypocapnia, the percentage decrease in MBVF associated with a declining MAP would have been even less than we reported, strengthening the finding of intact autoregulation.

Another possible limitation of this study was the assumption of constant intracranial pressure. If intracranial pressure decreased significantly during head-up tilt, cerebral perfusion pressure would be higher for a given MAP regardless of autoregulatory capability. In a study by Rosner and Coley [16], head elevation was shown to result in small decreases in intracranial pressure in some patients, but there was no associated change in cerebral perfusion pressure. We therefore believe it unlikely that the minimal intracranial pressure changes that may occur with head elevation would have significantly changed our findings.

We conclude that in patients with primary autonomic failure, orthostatic hypotension induces autoregulatory cerebral vasodilation. This was demonstrated by the occurrence of a significantly greater decrease in MAP than MBFV during tilt-induced hypotension and by the maintenance of MBFV until MAP fell below the lower limit of autoregulation, which was found to be similar to that in a normal population. In addition, we have shown that a transient hyperemic response occurs after tilt-induced hypotension, which also indicates an active autoregulatory response.

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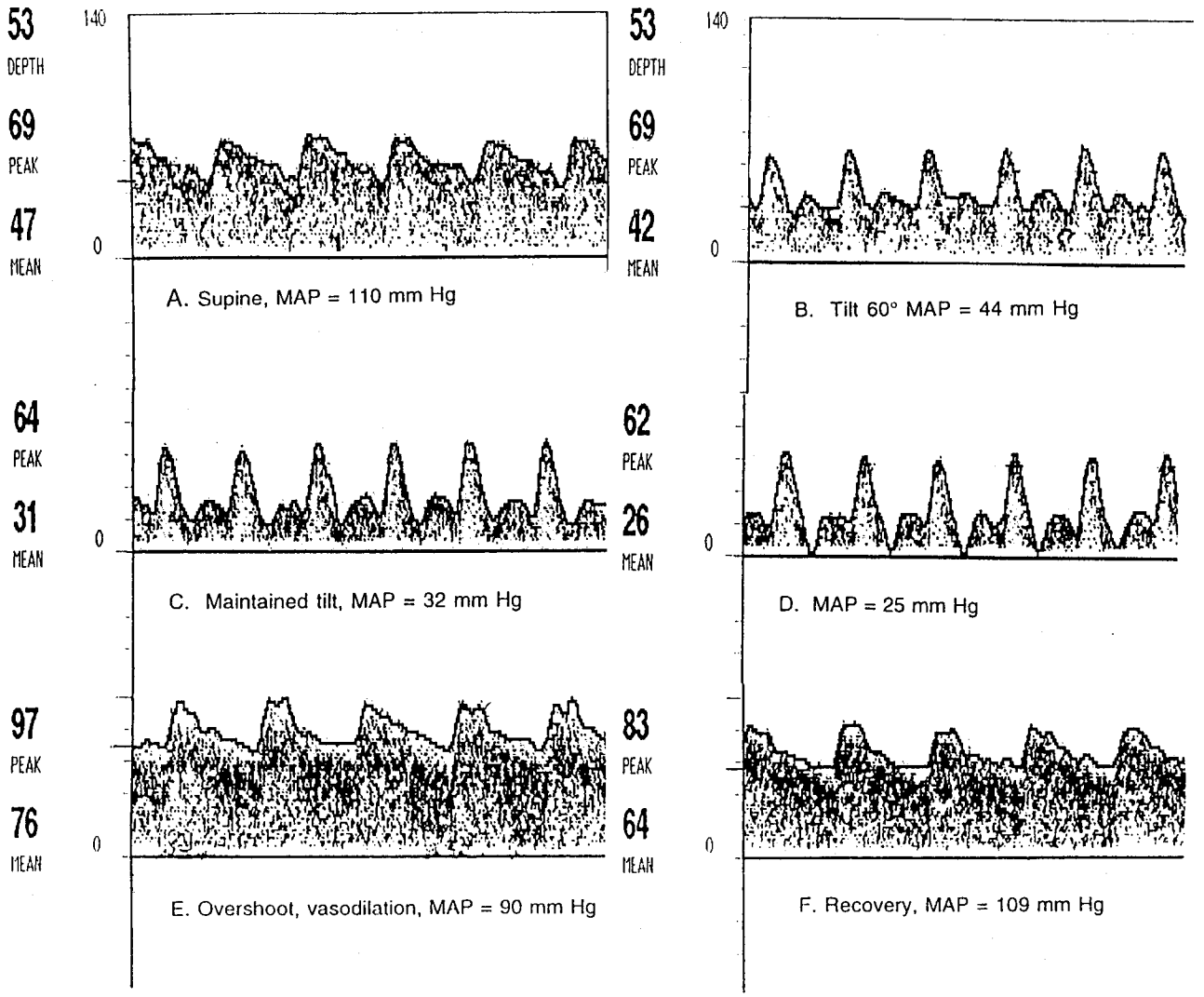

Figure 3. (**A**) Before tilt, baseline mean arterial pressure (MAP) is 110 mm Hg, and baseline middle cerebral artery mean blood flow velocity (MBFV) is 47 cm/sec. (**B**) After tilt, MAP falls to 44 mm Hg, and MBFV decreases to 42 cm/sec. (**C**) MAP falls further to 32 mm Hg, and MBFV falls to 31 cm/sec as tilt continues. (**D**) MAP decreases to a low of 25 mm Hg, and MBFV decreases to 26 cm/sec. (**E**) After the patient is placed back into the horizontal position, MAP increases to 90 mm Hg, and MBFV increases to 76 cm/sec, which is an overshoot of the pretilt level of 47 cm/sec. (**F**) As the patient remains in the horizontal position, MBFV decreases to 64 cm/sec as MAP increases to the baseline value.

and is considered to be a marker of cerebral autoregulation [21,22]. To our knowledge, a transient hyperemic response after hypotension in patients with primary autonomic failure has not been previously demonstrated.

Several blood flow studies using the xenon washout technique have also demonstrated preservation of the autoregulatory response in autonomic failure patients by showing no change in cerebral blood flow during tilt-induced hypotension [7,3,11,12]. Other studies, however, have reported that cerebral autoregulation may be impaired in patients with autonomic failure. These studies used different techniques to measure blood flow in addition to pharmacologic manipulations during testing that could have affected blood flow and contributed to the variation in results [5,13]. It is also not clear from these reports whether cerebral blood flow fell during hypotension because the lower limit of autoregulation had been reached [5,6,14].

Transcranial Doppler ultrasonography is a noninvasive method that can be used to monitor cerebral hemodynamics and autoregulatory capacity by measuring changes in cerebral blood flow velocity and vascular resistance that occur in response to changes in arterial blood pressure [18,19]. Although this technique does not measure blood flow volume, changes in blood flow velocities measured by TCD have been shown to parallel changes in cerebral blood flow volume [19,23–25]. The lower limit of autoregulation derived from TCD measurements was shown to be similar to values calculated from cerebral blood flow measurements in previous studies [25,26]. In our patients, the average lower limit of autoregulation was 70 mm Hg. This is within the 60 to 80 mm Hg range of the lower limit of autoregulation in a normal population [7,27,28]. There were differences in the lower limit of autoregulation between patients, ranging from 40 to 110 mm Hg. The lower limit of autoregulation occurred at higher pressures in patients with higher supine blood pressure, consistent with a shift to the right of the autoregulatory curve [1,27]. In a study of cerebral autoregulation in hypertensive individuals, the lower limit of auto-

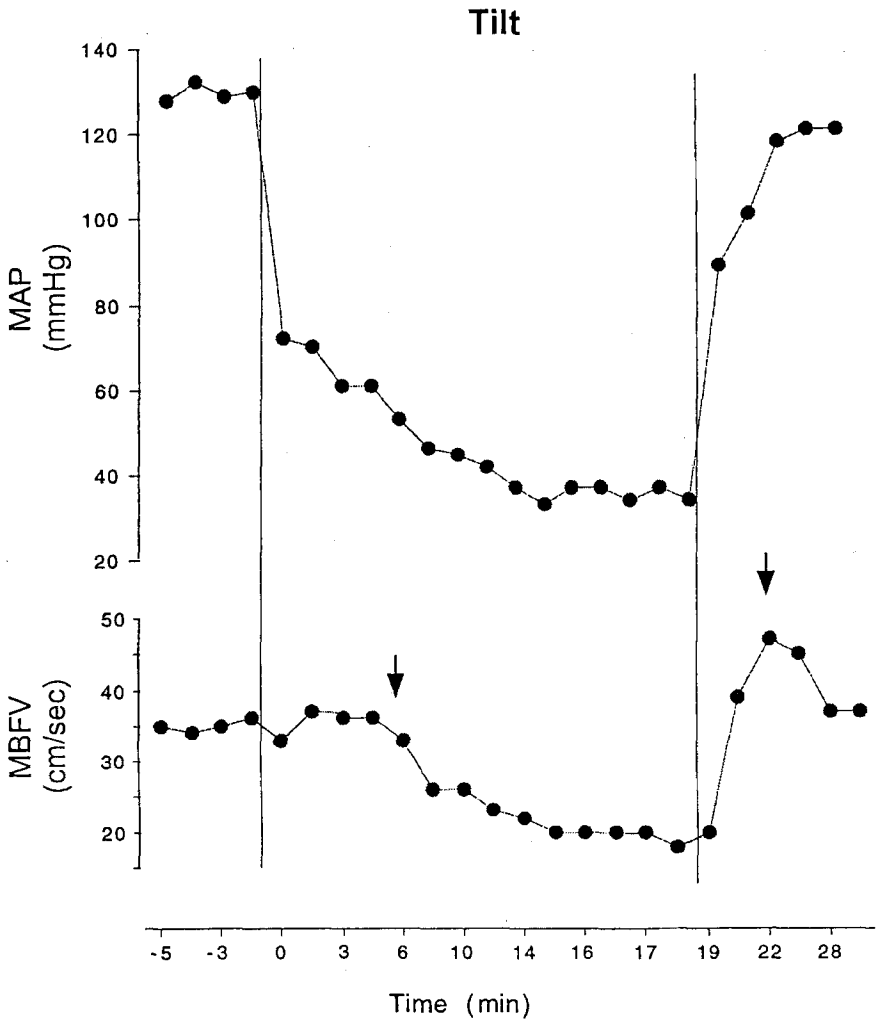

Figure 2. Mean arterial pressure (MAP) before tilt is 130 mm Hg. After start of tilt (first vertical line), MAP falls to 60 mm Hg with minimal change in middle cerebral artery mean blood flow velocity (MBFV), which remains at 36 cm/sec despite the fall in MAP. When MAP falls below 60 mm Hg, MBFV begins to fall (first arrow), indicating that the lower limit of autoregulation has been reached. MAP continues to fall to a low of 33 mm Hg, and the MBVF decreases to 18 cm/sec. After the patient is placed back into the horizontal position (second vertical line), MAP increases close to pretilt levels, while the MBFV increases to a level above its pretilt value (second arrow) and then declines to baseline.

MBFV decreases to 18 cm/sec. When the patient was returned to the horizontal position (second vertical line), MAP increases close to the pretilt level while MBFV increases to a level above its pretilt value (second arrow). MBFV then returns to baseline while MAP remains unchanged. This transient overshoot in MBFV is consistent with autoregulatory vasodilation in response to severe hypotension.

Case 2. Figure 3 shows changes in TCD waveforms during hypotension in a 38-year-old man with multiple system atrophy. The baseline MAP is 110 mm Hg, and the baseline middle cerebral artery MBFV is 47 cm/sec. After tilt, MAP falls to 25 mm Hg and MBFV decreases to 26 cm/sec. This 77% decrease in MAP is associated with a decrease of only 47% in MBFV, indicating an autoregulatory response. When the patient is placed into the supine position, MAP increases to 90 mm Hg, which is below the baseline pressure, while MBFV increases to 76 cm/sec, which is above the pretilt level. Subsequently, MBFV begins to decrease as the MAP returns to baseline. The transient overshoot of MBFV indicates a vasodilatory response of the distal cerebral vasculature.

Discussion

This study shows that autoregulation of the cerebral circulation occurs in response to a fall in arterial pressure in patients with primary autonomic failure. After head-up tilt, middle cerebral artery MBFV decreased significantly less than MAP ($p < 0.0002$), indicating that cerebrovascular resistance decreased to compensate for the fall in blood pressure consistent with an autoregulatory vasodilatory response. Moreover, when patients were returned to the horizontal position after tilt-induced hypotension, MAP returned to baseline while MBFV first increased above the pretilt value and then declined to baseline. This transient overshoot of MBFV unassociated with a similar rise in MAP is consistent with a transient hyperemic response resulting from compensatory vasodilation and indicates active autoregulation [21,22]. A similar transient hyperemic response was shown to occur in the middle cerebral artery after the release of temporary carotid artery compression in the neck of healthy volunteers, but was not present in neurosurgical patients with subarachnoid hemorrhage or arteriovenous malformations where impaired autoregulation commonly occurs [22]. The transient hyperemic response is caused by compensatory vasodilation of the small distal cerebral vessels