Cerebrovascular Regulation in Preganglionic and Postganglionic Autonomic Insufficiency

BY JOHN J. CARONNA, M.D., AND FRED PLUM, M.D.

Abstract: Cerebral blood flow was measured in four subjects with chronic idiopathic autonomic insufficiency using $^{85}$Kr inhalation, cerebral A-V samples for scintillation counting, and $O_2$ content determination. Blood pressure was varied by up or down tilting and L-norepinephrine infusion. In three patients with typical Shy-Drager syndrome and preganglionic denervation, CBF regulation to pressure and $P_{aCO_2}$ change was intact. In a fourth patient with postganglionic denervation, CBF autoregulation was absent to changes in blood pressure but was preserved normally to increases or decreases in $P_{aCO_2}$. CBF and $CMRO_2$ at rest were normal (52.6 cc and 3.1 cc). Hyperventilation to $P_{aCO_2}$ 34.3 mm failed to restore autoregulation to increased blood pressure. The results imply a functional role for postganglionic autonomic fibers in CBF autoregulation.

Additional Key Words
CBF autoregulation  Shy-Drager syndrome  orthostatic hypertension

We have measured CBF in four patients with IAI and severe orthostatic hypotension. Differences between their responses provided inferences about the relative influence of preganglionic and postganglionic innervation on the cerebral vascular bed.

Methods
Cerebral blood flow was measured by the inert gas technique. A jugular bulb and femoral or brachial artery were cannulated for sampling and continuous monitoring of the arterial blood pressure. Three subjects (Patients #1, 3, and 4) breathed $^{85}$Kr 70 $\mu$Ci/liter from a 300-liter reservoir containing either room air or 5% CO$_2$ in air. Nose clips and a mouthpiece with a one-way valve were employed. Exhaled air was collected in Douglas bags and emptied under a hood. Calculations of CBF were based on ten paired arterial and cerebral venous samples drawn at intervals over 16 minutes during desaturation. After 20 to 30 minutes of inhalation of $^{85}$Kr, samples were obtained and prepared for liquid scintillation counting by the method of Smith and associates.

In one subject (Patient #2), CBF changes were estimated from cerebral A-V differences for oxygen in samples obtained during cardiac catheterization studies. In each experiment, cerebral metabolism was assumed to remain constant, and serial acute changes in CBF were estimated from repeated Van Slyke manometric measurements of cerebral arteriovenous oxygen content differences. In one case (Patient #3) oxygen contents were determined by a total $O_2$ content analyzer (Lexington Instrument Corp., Waltham, Massachusetts). These values were checked against the oxygen content calculated from the blood hemoglobin, percent saturation and $P_{Hb}$. Simultaneous arterial-jugular venous samples were taken repeatedly for blood gas determinations. The pH of the blood was measured on a
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Radiometer PM 27 pH meter. The partial pressure of carbon dioxide in the blood as well as the actual bicarbonate concentrations were determined by Astrup’s method using the Radiometer AME-1 Blood Gas Analyzer and the Siggaard-Andersen nomogram. The oxygen tension of the blood (PO2) was measured with a Clark electrode in the Radiometer AME-1 analyzer. Blood oxygen saturation and hemoglobin were determined spectrophotometrically with an Instrumentation Laboratory Model 182 oximeter. All acid base values were corrected for blood-oxygen desaturation.

Procedures

Four subjects with IAI volunteered to undergo testing after full explanation of the procedures involved. The alert, unmedicated subjects reclined on a hospital bed for measurements of CBF and CMRO2 at rest and during inhalation of 5% CO2. After control values had been obtained, hypertension was induced in every case with intravenous L-norepinephrine (Levophed) at a rate of 1 to 2 μg/min in patients #2, 3 and 4, or at 9 μg/min in patient #1. When mean blood pressure (BP) had returned to normal, the subjects were transferred to a tilt table. Hypertension was produced in patient #1 by head-down tilting to 15°. In all subjects hypotension was induced by 20° to 30° of head-up tilting. Simultaneous arterial and jugular venous samples for oxygen content and blood gas measurement were drawn only after at least two minutes of hypertension or hypotension had occurred in order to permit adequate time for any CBF autoregulatory responses to take place.

Clinical Material and the Nature of the Autonomic Defects

CASE 1

A 41-year-old man had tremor and clumsiness of the right hand for six months. In 1965, he had difficulty in maintaining an erection and had occasional lightheadedness when standing. By 1967, he noticed difficulty with handwriting, and he began to fall when skiing. In 1969, he developed rigidity of his extremities and lightheadedness upon standing. His medical history and family history were noncontributory.

Blood pressure (BP) and pulse were 120/80 and 80 recumbent, and 75/50 and 88 standing. There was a fixed split of the second heart sound; general examination was otherwise normal. Gait was lurching and unsteady, especially on turning. The right arm was held in a flexed position. There was cog wheel rigidity and tremor of the right hand and foot. The facies were masked and anisocoria with a Horner’s syndrome alternating from side to side was present. The ciliospinal reflex was present bilaterally. Fasciculations were present in the right deltoid muscle and the intrinsic muscles of the right hand. Sensation was normal. Deep tendon reflexes were 2+ and symmetrical. Plantar response was flexor. There was a positive glabellar reflex.

Normal laboratory tests included CBC, electrolytes, BUN, creatinine, glucose tolerance test, tests of thyroid and adrenal function, serology and EEG. EKG showed a right bundle branch block. Twenty-four-hour urine for vanilmandelic acid (VMA) was 16.5 μg (normal 11 to 25) and for catecholamines was 98 μg (normal 8 to 160). EMG revealed fibrillation potentials in both tibialis anterior muscles and abnormally low conduction velocities for both common peroneal and tibial nerves. Ventilatory CO2 response was 1.6 L/mm Hg ΔPaco2 (normal).

Autonomic tests revealed no elevation of the BP with cold pressor, no BP “overshoot” after Valsalva maneuver, and a 20/12 mm Hg fall in BP with 0.4 mg of nitroglycerine sublingually. In a 54.5°C hot room, the patient maintained his body temperature and sweated over his face, neck and axillae. Finger and toe temperature measurements suggested normal vasodilation. In a 27°C cold room, he maintained body temperature and shivered, and finger and toe temperature measurements suggested normal vasoconstriction. Pilo-erection occurred over the chest, arms and legs. A blood pressure rise of 25/15 mm Hg occurred with L-norepinephrine infusion at 8.0 μg/min. This is a normal response.

The patient was begun on levodopa for his extrapyramidal symptoms, and tranylcypromine (Parnate) and high-tyramine-content cheddar cheese for his orthostatic hypotension. Transient improvement in both spheres occurred, but he worsened in 1972 with urinary frequency and chronic constipation. Repeat autonomic testing was unchanged. Pupillary responses to 4% cocaine and 2.5% methacholine were normal. A cystogram revealed bladder atony with a large residual. An esophagram revealed decreased peristalsis and dilatation; however, the remainder of the G.I. series and a barium enema were normal. All medications were withdrawn and cerebral blood flow measurement carried out.

The patient underwent suprapubic cystostomy and is being maintained on levodopa, trihexyphenidyl HCl, tranylcypromine, fludrocortisone acetate, and elastic stockings with only partial relief of symptoms.

CASE 2

A 69-year-old man complained of “dizzy spells” on standing. On many occasions while upright he would begin to run and shout insulting remarks to those around him after which he would lose consciousness and fall. Fifteen years before he had noted impotence and occasional syncope while riding up in elevators. Treatment with mineralocorticoids and elastic stockings had provided only temporary improvement. Recently he had noted a lack of sweating, urinary frequency as well as chronic weakness, and “faint feelings” when arising in the morning. The family history was noncontributory.

Blood pressure and pulse were as follows: supine: 150/90 and 86; standing for 90 seconds: BP unobtainable, pulse 88. Clinical examination, cardiac catheterization and cineangiograms demonstrated the hemodynamic and angiographical abnormalities of hypertrophic obliterative disease of the left ventricle. General examination was otherwise unremarkable.

The patient was alert and oriented, but inappropriately jocular. There was no evidence of dementia on formal testing. The right pupil was 3.5 mm and the left
3.0 mm. Motor strength was normal bilaterally, but tonus was increased in the right upper extremity and associated movements when walking were decreased bilaterally. The stretch reflexes were brisk, plantar responses were flexor. Suck, snout, and glabellar reflexes were present. Sensation and coordination were intact. The following laboratory studies were normal: glucose tolerance tests, serology, EEG, A.M. and P.M. cortisols, thyroid scan, radioactive iodine uptake, plasma volume (52 cc/kg), blood volume (76 cc/kg), and 24-hour urine catecholamine excretion (11 µg/ml).

Autonomic testing was abnormal. Carotid sinus massage and IV atropine produced no change in heart rate. Blood pressure and pulse were unaltered during immersion of the right hand in ice water for five minutes. There was no “overshoot” of BP following the Valsalva maneuver. Moderate denervation hypersensitivity to catecholamines was present: an infusion of L-norepinephrine 1.5 to 2 µg/min intravenously produced a rise in BP from 130/64 to 180/65 and an increase in heart rate of seven beats per minute. Thermal sweating was absent over the trunk and extremities but present on the forehead. Intraconjunctival instillation of 2.5% methacholine produced no change in pupillary diameter. Four percent cocaine drops produced mydriasis bilaterally.

Cerebral blood flow measurements at rest and during alterations of BP were carried out at the time of cardiac catheterization.

Tranylcyromine, 20 mg daily, produced a marked and persistent elevation in supine and standing BP, and the patient was discharged without other medications.

**CASE 3**

A 69-year-old man had frequent attacks of orthostatic syncope for eight years. In 1964, he first noted lightheadedness when arising from a chair and occasional syncope after standing for long periods. In 1967, he developed xerostomia, anhidrosis, and impotence. Orthostatic hypotension and urinary incontinence were documented in 1969 by his physician. In the 12 months preceding admission, symptoms progressed so that he could not stand upright for more than a few minutes without experiencing lightheadedness, blurring of vision, and eventual loss of consciousness. He had a peptic ulcer requiring subtotal gastrectomy in 1955. Family history was noncontributory.

Recumbent blood pressure was labile ranging from 170/100 mm Hg to 100/60 mm Hg, but fell rapidly to 70/50 mm Hg on standing. Pulse was regular and constant at 60. General examination was unremarkable. On neurological examination, there was anisocoria, the left pupil being 4 mm, the right 2 mm; both reacted to light and accommodation. Motor strength and coordination were intact. Perception to all sensory modalities was moderately diminished in the distal lower extremities. Ankle jerks were absent. Plantar responses were flexor. Laboratory studies including CBC, ESR, electrolytes, BUN, glucose tolerance test, serum B12 level, A.M. and P.M. cortisols, 24-hour urine hydroxyketosteroids and ketosteroids, VMA (2.9 µg/24 hour), catecholamines (40 µg/24 hour), blood and plasma volume, EKG, EEG, LP, skull and chest x-rays were normal.

Serologic tests of blood and CSF were nonreactive. There were no fibrillations or fasciculations on the EMG, but there was a slight decrease in voluntary motor unit potentials. Motor conduction velocity was slowed in the upper and lower extremities; sensory latency was prolonged in both ulnar nerves. Gastrocnemius biopsy was indicative of chronic denervation atrophy of muscle fibers. Blood vessels were normal, and metachromatic stains for amyloid were negative.

Autonomic tests were abnormal. There was no BP “overshoot” after the Valsalva maneuver. Moderate denervation hypersensitivity was present: 1.5 to 2.0 µg/min of L-norepinephrine given intravenously produced a BP rise of 46/26 mm Hg and a decline in heart rate of four beats per minute. Thermal sweating was present in patches over the trunk and extremities, but the injection of 10 mg of betahaneol produced generalized sweating and increased salivation, lacrimation, and hypotension. Intraconjunctival instillation of methacholine produced no change in pupillary size; cocaine drops produced mydriasis on the left but not on the right. The ciliospinal reflex was present only on the left.

CBF measurements were carried out prior to starting treatment (table 1).

The patient is currently under treatment with elastic leotards, high NaCl diet, fludrocortisone, tranylcypromine and hydroxyamphetamine hydrobromide.

TABLE 1

<table>
<thead>
<tr>
<th>Patient #1</th>
<th>CBF</th>
<th>BP</th>
<th>Paco2</th>
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<tr>
<td>Control</td>
<td>49.8</td>
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<td>32.0</td>
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<tr>
<td>Hypocapnia</td>
<td>45.8</td>
<td>95</td>
<td>25</td>
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<td>5% CO2 inhaled</td>
<td>64.9</td>
<td>99</td>
<td>37.5</td>
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<td>L-norepinephrine</td>
<td>49.3</td>
<td>123</td>
<td>28.5</td>
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<td>20° head-up tilt</td>
<td>37.9</td>
<td>76</td>
<td>30.8</td>
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<th>A-V O2</th>
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<td>77</td>
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<td>25° head-up tilt</td>
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<td>56</td>
<td>30.6</td>
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<td>4 min</td>
<td>6.15</td>
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<td>31.6</td>
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<tr>
<td>L-norepinephrine</td>
<td>5.4</td>
<td>103</td>
<td>32.0</td>
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<table>
<thead>
<tr>
<th>Patient #3</th>
<th>CBF</th>
<th>BP</th>
<th>Paco2</th>
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</thead>
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<tr>
<td>Control</td>
<td>58.8</td>
<td>117</td>
<td>41.3</td>
</tr>
<tr>
<td>Hypocapnia</td>
<td>50.9</td>
<td>94</td>
<td>27.0</td>
</tr>
<tr>
<td>5% CO2 inhaled</td>
<td>80.0</td>
<td>131</td>
<td>46.4</td>
</tr>
<tr>
<td>L-norepinephrine</td>
<td>58.8</td>
<td>137</td>
<td>42.0</td>
</tr>
<tr>
<td>Head-up tilt</td>
<td>56.0</td>
<td>96</td>
<td>41.0</td>
</tr>
</tbody>
</table>
(Paredrine), with some improvement of his orthostatic hypotension.

**CASE 4**

A 59-year-old man was unable to work as a barber because of orthostatic hypotension. Since 1960, he had noted progressive fatigue, anhidrosis with heat intolerance, xerostomia and impotence. In 1962, he had fainted while waiting in a theater line. Subsequently, episodes of syncope became more frequent, and he had taken methylphenidate hydrochloride (Ritalin) for "low blood pressure" without improvement.

Blood pressure was 110/70 mm Hg supine, but fell to 60/40 mm Hg after the patient stood for five minutes. The pulse was regular at 76/min and did not increase as BP declined. Respirations were regular at 18/min and rectal temperature was 37°C. Except for moderate obesity, the general examination was unremarkable. He was alert, oriented, and able to give an accurate history. The pupils were miotic—right 2 mm, and left 2.5 mm. The remainder of the nonautonomic neurological examination was normal. The following laboratory studies were normal: CSF examination, two-hour postprandial glucose, serologic tests for syphilis in blood and spinal fluid, PBI, thyroid scan, A.M. and P.M. cortisols, blood and plasma volume, 24-hour urine catecholamine excretion (20 μg/ml), EKG and EEG.

Autonomic testing revealed extensive postganglionic sympathetic and parasympathetic denervation. There was no "overshoot" of blood pressure during Valsalva maneuver, no hypertension during mental arithmetic or immersion of a hand in ice water, and no change in heart rate during carotid sinus massage or following 1 mg atropine IV. Thermal sweating was absent over the entire body, and no sweating occurred after the subcutaneous injection of 10 mg of pilocarpine. L-norepinephrine infusion at 0.5 μg/min produced a rise in supine BP from 100/70 to 200/100 mm Hg without a change in heart rate.

Oral administration of the MAO inhibitor, tranylcyromine (Parnate), 20 mg/day, failed to alter blood pressure significantly. Pupillary testing revealed no response to locally instilled 2.5% methacholine, which is a normal response. No ciliospinal response was present on either side, and local instillation of 4% cocaine drops produced no mydriasis over a several-hour period. Respiratory response to 5% CO₂ inhalation was 1.4 L/mm Hg ΔPₐCO₂ which is a normal response.

Treatment with MAO inhibitors, amphetamines, and mineralocorticoids only partially improved the orthostatic hypotension, and an inflatable antigravity suit is presently required to maintain his BP in the upright posture.

Cerebral blood flow measurements were made off all medications on three separate occasions over a seven-month period.

**Results**

**CLINICAL AUTONOMIC TESTING**

Any attempt to define the site of a lesion in the autonomic nervous system antemortem is hampered by the lack of histological material, for with clinical and pharmacological responses alone, it is often difficult to pinpoint whether disordered function represents central or peripheral denervation. This is especially true in IAI, which is not a single nosological entity, but a manifestation of several distinct disease processes which produce autonomic defects of varying patterns and severity. Within these limitations, nevertheless, we were able to discern a significant relationship between the type of autonomic denervation and the responsiveness of the cerebrovascular bed to changes in systemic pressure.

In patients #1, 2, and 3, who had the classical Shy-Drager syndrome, clinical and pharmacological tests indicated the presence of a predominantly central or preganglionic autonomic lesion. Previous studies have indicated that this syndrome is the result of a central lesion involving the brainstem and intermediolateral cell column of the spinal cord. Patient #4 had the most severe orthostatic hypotension, but clinically was not typical of the Shy-Drager syndrome because he had no evidence of a degenerative disease of the central nervous system. The results of autonomic testing led us to conclude that he had peripheral or postganglionic autonomic insufficiency (table 2).

(1) Testing of sweating revealed patchy anhidrosis in patients #1, 2, and 3 with preganglionic lesions, while only patient #4 showed absent sweating both to heat and to 10 mg of pilocarpine.

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Responses to Autonomic Testing in the Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient</td>
<td>#1</td>
</tr>
<tr>
<td>(1) Sweating</td>
<td>Patchy</td>
</tr>
<tr>
<td>(A) Thermal</td>
<td>Present*</td>
</tr>
<tr>
<td>(B) Drug</td>
<td>Present</td>
</tr>
<tr>
<td>(2) Hypertension to L-norepinephrine</td>
<td>Present</td>
</tr>
<tr>
<td>(3) Pupil dilation to 4% cocaine</td>
<td>Present</td>
</tr>
</tbody>
</table>

*Bethanochol (Urecholine) 10 to 20 mg S.Q.
†Pilocarpine 10 mg IM.
‡Present OS, absent OD.
intramuscularly. Anhidrosis unresponsive to cholinergic agents is consistent with a third-order sympathetic neuron lesion, in which atrophy of sweat glands would be expected.10,21

(2) Patient #4 showed the most marked denervation hypersensitivity as manifested by excessive hypertension to norepinephrine infusion.22

(3) Only patient #4 had an absent ciliospinal response bilaterally. This reflex requires the integrity of the postganglionic sympathetic fibers.28 Instillation of a 4% solution of cocaine produces pupillary dilatation in the normal subject and in the presence of a lesion of the first sympathetic neuron but not when the second-order or third-order neuron is involved.24,25 Only patient #4 had no mydriasis to 4% cocaine drops in either eye.

**REGULATION OF CBF TO CHANGES IN BLOOD PRESSURE AND CO2**

In patients #1, 2, and 3, CBF regulation to changes in blood pressure and arterial P4CO2 (PaCO2) was intact. In figure 1, changes in CBF expressed as percent change from control are plotted against changes in BP (diastolic plus one-third pulse pressure) induced by tilting or pressor agents. The values for CBF in these patients fall on or near the theoretical line of autoregulation.20

The actual blood flow results in patients #1, 2, and 3 are presented in table 1. In patient #2, cerebral A-V oxygen content differences were not significantly different at rest and during L-norepinephrine infusion, implying that CBF remained constant during hypertension. During head-up tilting, CBF, as estimated from the widened cerebral A-V oxygen difference, declined.

In patients #1 and #3, CBF at rest was normal, and CMRO2 was 3.45 and 2.84 cc/100 gm/min, respectively. In each case, CBF declined during voluntary hyperventilation and increased to a normal degree during 5% CO2 inhalation (Patient #1: 1.6 ± 0.5 cc; Patient #3: 4 cc/mm Hg ΔPacO2). During L-norepinephrine-induced hypertension in either case, CBF did not increase over control values. In patient #1, during head-up tilting CBF declined to 37.9 cc, although BP was still 76 mm Hg. For reasons discussed subsequently, we suspect that this did not by itself indicate a loss of cerebral autoregulation.

In patient #4 repeated CBF measurements over a period of several months demonstrated that his cerebral vessels had lost their capacity to constrict or dilate in response to an altered blood pressure yet retained their normal responsiveness to CO2 (fig. 2 and table 3). Mean resting CBF and CMRO2 were normal. Mean rate of change of CBF was 2.31 ± 0.45 cc/mm Hg ΔPacO2 (normal). Hypertension, whether induced by tilting or L-norepinephrine, caused proportional increases in CBF regardless of the PacO2. Hyperventilation sufficient to lower PacO2 to 34.3 mm Hg failed to restore autoregulation to increased blood pressure (fig. 2).

**Discussion of CBF Results**

During head-up tilting in patients #1 and #4, the cerebral A-V oxygen difference widened and CBF declined, although the BP was still greater than 70 mm Hg, the theoretical "floor" of autoregulation. Nevertheless, this does not conclusively indicate that
autoregulation was lost for several reasons. Arterial pressure at the cerebral midparietal level during head-up tilting is several mm Hg lower than BP measured at the heart level. If BP were corrected for this difference, mean systemic pressure would approach the lower limit of BP (50 to 60 mm Hg) at which cerebrovascular autoregulation occurs. We did not correct the BP to estimated pressure at the cerebral midparietal level since the value obtained is not useful unless jugular venous pressure is known. Cerebral perfusion pressure (arterial pressure minus jugular venous pressure) was probably below the autoregulatory "floor," but was not measured. Therefore, we have based our conclusions concerning CBF regulation in all four patients on changes in CBF during both supine hypertension induced by L-norepinephrine, which does not normally increase CBF or alter CMRO₂,²⁷ and on changes induced by hypercarbia or hypocarbia.

Also, at low systemic blood pressures during head-up tilting three of our patients (Patients #1, 2, and 4) became restless and tended to hyperventilate. We may assume that errors in CBF estimation were introduced due to changes in Pa CO₂ and possibly changes in CMRO₂.

The effect of idiopathic autonomic insufficiency on CBF autoregulation is unclear from published reports. Skinhoj and associates²⁸ studied one case and found a normal autoregulation. Gotoh and associates²⁹ and Meyer and co-workers³⁰ reported several patients with autonomic insufficiency in whom autoregulation to pressure was lost during head-up and head-down tilt. None of the above reports detailed whether the major autonomic defects were preganglionic or postganglionic in origin.

Our results in four patients suggest that the presence or absence of autoregulation of the cerebral vessels to blood pressure changes depends on

**TABLE 3**

Changes in CBF in Response to Changes in Arterial CO₂ Tension and Blood Pressure in Patient #4

<table>
<thead>
<tr>
<th></th>
<th>CBF cc/100 gm/min</th>
<th>BP mm Hg</th>
<th>Pa CO₂ mm Hg</th>
</tr>
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<tbody>
<tr>
<td>Control</td>
<td>52.6 ± 1.7</td>
<td>87.5 ± 0.6</td>
<td>37.7 ± 0.7</td>
</tr>
<tr>
<td>5% CO₂ inhaled</td>
<td>66.2 ± 2.8</td>
<td>91.5 ± 0.6</td>
<td>44.5 ± 1.5</td>
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<tr>
<td>L-norepinephrine</td>
<td>76.4 ± 4.6</td>
<td>117.7 ± 8.1</td>
<td>41.3 ± 1.8</td>
</tr>
<tr>
<td>Head-up tilt</td>
<td>34.0 ± 3.1</td>
<td>71.8 ± 3.2</td>
<td>40.7 ± 3.0</td>
</tr>
<tr>
<td>Head-down tilt</td>
<td>69.0</td>
<td>90</td>
<td>43</td>
</tr>
<tr>
<td>Hypocapnia</td>
<td>43.0</td>
<td>127</td>
<td>34.3</td>
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whether the site of the autonomic dysfunction is central (preganglionic) or peripheral (postganglionic). The intact autoregulation of CBF, which we observed in our patients #1, 2, and 3 with preganglionic lesions, confirms the results of Reivich (reported by Schwarz31) and of Skinhoj et al., who found intact CBF autoregulation in the Shy-Drager syndrome.

In patient #4, who had both more severe orthostatic hypotension and postganglionic autonomic denervation, cerebral vascular regulation to blood pressure changes was chronically absent and could not be restored by hypocapnia. Everything points to the autonomic denervation per se being at fault here. It is unlikely that one can attribute the defective autoregulation to a hypothetical metabolic abnormality causing tissue acidosis,32 since the defect was observed repeatedly over a several-month-long period, during which the patient was otherwise in good neurological health. Furthermore, the degree of experimentally induced hypocapnia during voluntary hyperventilation was entirely adequate to raise the tissue pH as Paulson et al.8 did in patients with the “dissociated vasoparalysis” of acute brain damage, yet autoregulation failed to return.

These results imply a functional role for the autonomic nerves in CBF autoregulation. Exactly how these nerves mediate the vascular responses to pressure changes remains unknown, but whatever the mechanism, it appears to differ from the metabolic factors that regulate changes in CBF to changes in CO2 and oxygen.

Acknowledgments

We thank Drs. Susan Kline and Thomas Tuttle for assistance in studying patient #2.

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Stroke. 1973;4:12-19
doi: 10.1161/01.STR.4.1.12

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