Cerebral Autoregulation in Man

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Abstract: Autoregulation was tested by regional blood flow (rCBF) and cardiohemodynamic measurements before and after induced systemic arterial hypertension in 16 patients with varying neurological disorders. Hypertension was induced by increasing the arterial blood pressure by an intravenous infusion of Aramine. Seven (Group 1) of the patients had a mean increase in mean arterial pressure (MAP) of 32 mm Hg and had preserved autoregulation while nine (Group 2) with a 56 mm Hg increase in MAP showed complete or mixed loss of autoregulation. Group 1 had a higher baseline mean CBF than did the group with loss of autoregulation. The group with loss of autoregulation also generally had more severe involvement on the cerebral angiogram than did the other. Baseline cardiac index and cardiac work were lower in the group with loss of autoregulation. During Aramine infusion the MAP was increased by 38% in Group 1 and 59% in Group 2. The mean CBF was essentially unchanged in Group 1 but increased 24% in Group 2. When autoregulation is lost, rCBF may increase homogeneously or heterogeneously with some areas increasing while others remained unchanged or even decreased. In four instances there was an intracerebral steal during induced hypertension with a fall in rCBF. Whether or not autoregulation is preserved could be related to: (1) the greater induced increase in MAP in Group 2 than Group 1, (2) greater angiographical involvement with a lower baseline in CBF in Group 2 than in Group 1 or (3) a direct or indirect influence of various cardiovascular factors.

Introduction

Cerebral autoregulation is one of the main factors controlling cerebral circulation. The classical studies on pial arteries of Forbes¹ and Fog² first showed that intrinsic regulation permits a fluctuation in blood pressure over a wide range without changes in blood flow. Several studies in animals and, more recently, in man have shown that under certain circumstances cerebral autoregulation may be impaired or lost, and that cerebral blood flow will become passively dependent on changes in arterial blood pressure. Harper,³ Waltz,⁴ and recently Symon et al.⁵ have demonstrated this in animals while others⁶-¹² have shown in man that there may be regional or total loss of autoregulation to induced hypertension. The purpose of this study was to determine the circumstances of the loss or presence of cerebral autoregulation to induced hypertension in patients with various neurological diseases. Shanbrom and Levy¹⁴ and Wise et al.¹⁵-¹⁶ have shown that in some patients clinical symptoms may occur when blood pressure is decreased and may be reversed with an elevation of blood pressure. This implies that cerebral circulation in some patients could be sustained by therapeutically controlling the blood pressure to maintain optimum cerebral perfusion pressure and cerebral blood flow. The implications of induced hypertension as a form of treatment in stroke or other neurological disorders or its contraindications need to be established.

Methods

Sixteen patients with various neurological disorders on the neurological and medical services of the Philadelphia General Hospital were studied. All patients had diagnostic cerebral angiography. On the basis of clinical examination and angiographical findings the patients were separated into the following diagnostic categories: Nine patients had cerebrovascular disease, four had a seizure disorder, one had presenile dementia, one had a skull fracture with cerebral contusion, and one had chronic alcoholism with peripheral neuropathy. All patients with cerebrovascular disease, four had a seizure disorder, one had presenile dementia, one had a skull fracture with cerebral contusion, and one had chronic alcoholism with peripheral neuropathy. All patients with cerebrovascular disease had symptoms at least two weeks prior to these studies. The clinical history, diagnosis, and angiographical findings are given below. Informed consent was obtained from each patient to carry out the cerebral blood flow (CBF) and cardiohemodynamic measures with CO₂ inhalation and induced hypertension.
TABLE 1

Effects of CO₂ Inhalation and of Induced Hypertension on Cerebral Blood Flow and Cardiac Function. Group 1 – Autoregulation Preserved

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<th>CO₂</th>
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Regional cerebral blood flow (rCBF) measurements were performed by the Xenon injection method of Lassen and Ingvar that has been adapted for use in our laboratory. The regional cerebral blood flow study was carried out after cerebral angiography. Approximately 2 mc of 133Xenon in saline was injected into a catheter in the internal carotid artery. The clearance of Xenon was monitored by up to eight scintillation detectors contained in a collimator block. Each detector saw an area of brain approximately 1½ inches in diameter. The clearance curve from each probe was analyzed by the Sveinsdottir computer program. In each study cerebral blood flow was determined as regional CBF calculated as the uncorrected (for Pco₂) stochastic ten-minute rCBF value and as mean CBF or an average of all rCBF values. Cerebral vascular resistance (CVR) was also calculated.

Cardiohemodynamic studies were carried out via right-sided cardiac catheterization via the antecubital vein. Cardiac output was determined from the dye dilution curve obtained by continuous recording of dye concentration with a Gilford densitometer curve using a Gilford computer. Mean arterial blood pressure (MAP) was continuously monitored by a Statham strain gauge connected to the catheter in the internal carotid artery. In each study central venous, right atrial, right ventricular, pulmonary artery, and pulmonary wedge pressures were obtained. EKG was monitored through conventional limb leads. Cardiac work (CW) was calculated for mean arterial blood pressure and cardiac output. The total systemic resistance (TSVR) was calculated according to Poiseuille's law. Arterial carbon dioxide tension was determined by the Radiometer method.

Regional cerebral blood flow and cardiac hemodynamic...
measurements were performed in this group to patients as follows: The first baseline or control measurement was performed in the resting condition. Second, 15 minutes later, 5% carbon dioxide in air was administered via a face mask. Five minutes after carbon dioxide inhalation, the second rCBF and cardiohemodynamic measurements were performed. Thirty minutes after the CO2 studies, a second control rCBF and cardiohemodynamic measurements were obtained. Fifteen minutes after the conclusion of the second control study the patient was given an intravenous infusion of Aramine, 15 mg in 250 ml of saline (over a 30-minute period). Arterial Pco2, samples were determined in the middle of each rCBF study at the same time the cardiohemodynamic studies were performed.

As described previously, 21 significant changes in the hemispheric mean CBF and rCBF were based on data obtained from measurements in normal patients and serial measurements in the same patient. A significant change in rCBF is considered to have occurred when the rCBF value changes by ± 7% from the control study. For the purposes of this study, however, a change in mean CBF of 15% was considered more appropriately to be significant.

**Results**

The 16 patients were separated into two groups on the basis of the percentage change in the mean CBF following induced hypertension by Aramine infusion. Seven patients, Group 2, with loss of autoregulation had a 15% increase (except for 12.5% in Patient No. 10) in mean CBF during Aramine infusion. The separation into two groups was made on no other basis than the change in mean CBF during induced hypertension.

The individual rCBF and mean CBF during the first control, CO2 study, second control and Aramine

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<th>A</th>
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<0.05 NS <0.01 NS

![FIGURE 1](http://stroke.ahajournals.org/)

**FIGURE 1**

The results of rCBF measurement in nine patients (Group 2) with loss of autoregulation. The results during CO2 inhalation are in the left column and for induced hypertension with Aramine are in the right column of each patient. The mean CBF for each study is at the bottom of each column and the Pco2 and MAP are at the top of each column. CO2 studies were not carried out in Patients 15 and 16.
study are given in figures 1 and 2 along with Pco2 and MAP values. The mean CBF for each case along with the MAP, CVR, Pco2, CI, CW, and TSVR for each patient are given in figures 3 and 4 and in tables 1 and 2 that include the paired t-test results between the control and experimental measurement. The history, clinical diagnosis, cerebral angiographical finding, and cerebral blood flow for each patient are cited below.

Cardiohemodynamic results will be described by West et al.22

GROUP 1—AUTOREGULATION PRESERVED

1. History: A 53-year-old man, a known chronic alcoholic, was admitted to the hospital for progressive confusion...
and weight loss of several weeks' duration. Examination: Hepatomegaly, generalized muscle atrophy, faint tremor of the outstretched hands. There was loss of sensation to pain and touch of lower extremities with diminished deep tendon reflexes. Mild dementia on mental status examination.

Clinical Diagnosis: Chronic alcoholism; peripheral neuropathy.

Cerebral Angiogram: Right carotid angiogram was normal.

Cerebral Blood Flow Studies: Baseline mean CBF was minimally decreased to 40 ml/100 gm per minute. During CO₂ inhalation (with an 11 mm Hg Pco₂ and 5 mm Hg MAP increase), there was a 15% heterogeneous increase in rCBF to a mean CBF of 46 ml/100 gm per minute. Two probes over separate regions (the mid-

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The mean values are in the black bars, the CO₂ study in the white and the autoregulation test in the cross-hatched bar. Mean values for each parameter and the percent change are shown.
parietal and anterior temporal regions, respectively) failed to respond to hypercapnia. Hence, there was a loss of capacity for cerebral vasodilatation in these regions. During Aramine infusion with a 60 mm Hg increase in MAP, the CBF essentially was unchanged, being 40 before and 39 ml/100 gm per minute after Aramine, which indicated the presence of cerebral autoregulation.

2. History: A 37-year-old man was admitted to the hospital having been found unconscious on the highway by the police. When he did not regain consciousness in jail, he was admitted to the hospital. Examination: Patient was unresponsive; eyes moved equally to both sides; there was greater muscle tone on the right than on the left. There was clonus on the right side. Right Babinski sign. Skull x-rays showed multiple fractures. Craniotomy revealed cerebral contusion with no subdural hematoma.

Clinical Diagnosis: Skull fracture with cerebral contusion.

Cerebral Angiogram: Left carotid angiogram showed a deep posterior temporal space-occupying lesion which was considered to be a post-traumatic intracerebral hematoma.

Cerebral Blood Flow Studies: Baseline mean CBF was markedly decreased to 24 ml/100 gm per minute. During CO₂ inhalation (with a 9 mm Hg Pco₂ and 8 mm Hg MAP increase), there was a 50% homogeneous increase in mean CBF to 36 ml/100 gm per minute. One region showed a marked response with an increase in rCBF to 58 ml/100 gm per minute. During Aramine infusion with a 25 mm Hg increase in MAP, there was essentially no change in the mean CBF with a value of 24 before and 26 ml/100 gm per minute afterward. The minimal increase in mean CBF was not significant and indicates the presence of autoregulation. The CBF study was performed two weeks following head trauma.

3. History: A 51-year-old man was admitted to the hospital because of sudden weakness of his right arm and leg. He had had hypertension and congestive heart failure for several years and had a right hemiparesis which improved in November, 1969. Neurological examination: Patient was alert and cooperative but had difficulty speaking and understanding. There was a right lower facial weakness and a right hemiparesis, arm greater than leg. Deep tendon reflexes were increased on the right. Right Babinski sign.

Clinical Diagnosis: Cerebral infarction in the distribution of the left middle cerebral artery.

Cerebral Angiogram: Left carotid angiogram showed small vessel disease of moderate severity involving the lenticulostriate arteries. The remainder of the cerebral angiogram was normal.

Cerebral Blood Flow Studies: Baseline mean CBF was in the lower limits of normal — 44 ml/100 gm per minute. During CO₂ inhalation (with a 4 mm Hg Pco₂ and 18 mm Hg MAP increase), there was 27% heterogeneous increase in rCBF to mean CBF to 56 ml/100 gm per minute. Two probes over the anterior and posterior temporal regions did not respond to CO₂. During Aramine infusion with an increase in MAP of 39 mm Hg, there was essentially no change in mean CBF. The increase of mean CBF of 2 ml/100 gm per minute was not significant and indicates that autoregulation was intact.

4. History: A 63-year-old man was admitted to the hospital because of seizures. History of hypertension. Examination: The patient was confused and disoriented to time and place. Neurological examination: A mild right hemiparesis was present which cleared during the first ten days of hospitalization. The blood pressure ranged between 210/110 and 150/80.

Clinical Diagnosis: Seizure disorder; hypertension.

Cerebral Angiogram: Left carotid angiogram was normal except for some atherosclerotic changes in the peripheral branches of the middle cerebral artery.

Cerebral Blood Flow Studies: Baseline mean cerebral blood flow was in the lower limits of normal — 42 ml/100 gm per minute. During CO₂ inhalation (with an 8 mm Hg MAP increase), there was a 55% homogeneous increase in mean CBF to 65 ml/100 gm per minute. During Aramine infusion with a 10 mm Hg increase in MAP there was no change in rCBF except for one area over the posterior temporal region which showed a regional loss of autoregulation with increase in rCBF from 40 to 51 ml/100 gm per minute. The increase in mean CBF of 2 ml/100 gm per minute was not significant and indicates that autoregulation was intact.

5. History: A 40-year-old woman was admitted to the hospital because of focal left-sided seizures. The patient had been disabled since childhood because of a severe childhood illness (? encephalitis). She had been under custodial care and she was unable to care for herself. Neurological examination: She was alert but disoriented to time and place. She obeyed simple commands but had a short attention span. Severe bilateral nystagmus was present. Left spastic hemiparesis with increased deep tendon reflexes.

Clinical Diagnosis: Jacksonian epilepsy, secondary to childhood illness.

Cerebral Angiogram: Shift of the intracranial structures to the right indicating decrease in size of the right cerebral hemisphere. No evidence of a mass lesion on the left. Normal intracranial vasculature.

Cerebral Blood Flow Studies: Baseline mean CBF was normal — 56 ml/100 gm per minute. During CO₂ inhalation (with a 13 mm Hg Pco₂ and 19 mm Hg MAP increase) there was a 138% increase in mean CBF to 133 ml/100 gm per minute. During Aramine infusion with a 37 mm Hg increase in MAP, the CBF remained essentially unchanged, 73 and 75 ml/100 gm per minute, respectively, indicating intact autoregulation.

6. History: A 63-year-old man with hypertension for several years was admitted to the hospital because of generalized headaches. Three days before admission he had weakness of his right arm and leg with difficulty speaking. Examination: Blood pressure 190/90; cardiac enlargement. Neurological examination: The patient was alert with mild aphasia and right hemiparesis with increased deep tendon reflexes.

Clinical Diagnosis: Cerebral infarction in the distribution of the left middle cerebral artery.

Cerebral Angiogram: Left carotid angiogram showed mild atherosclerosis of the proximal middle cerebral; severe small vessel disease involving the lenticulostriate vessels.

Cerebral Blood Flow Studies: Baseline mean CBF was decreased to 31 ml/100 gm per minute. During CO₂
CEREBRAL AUTOREGULATION IN MAN

inhalation (with a 6 mm Hg Pco, and 5 mm Hg MAP increase), there was a heterogeneous rCBF response with a 10% increase in mean CBF of 34 ml/100 gm per minute. Probe 3, in the midtemporal region, showed an intracerebral steal during hypercapnia with a 17% decrease in rCBF from 29 to 24 ml/100 gm per minute. During Aramine infusion with an increase in MAP of 30 mm Hg there was an insignificant increase in mean CBF except for the region seen by probe 3. Again, there was an 11% decrease in rCBF from 37 to 33 ml/100 gm per minute, indicating a possible intracerebral steal during Aramine infusion. Autoregulation was otherwise intact.

7. History: A 61-year-old man was admitted to the hospital because of weakness of his right arm and leg which occurred early in the morning of the day of admission. No history of hypertension and diabetes. Neurological examination: He was alert and oriented. His eyes were deviated to the right. There was a left lower facial weakness and a left hemiplegia with increased deep tendon reflexes.

Clinical Diagnosis: Cerebral infarction in the distribution of the right middle cerebral artery.

Cerebral Angiogram: Normal right carotid angiogram except for severe small vessel disease involving the lenticulostriate arteries.

Cerebral Blood Flow Studies: Baseline mean CBF was normal — 50 ml/100 gm per minute. During CO₂ inhalation (with a 4 mm Hg Pco, and 5 mm Hg MAP increase), there was a 30% heterogeneous rCBF response with an increase in mean CBF to 65 ml/100 gm per minute. Probe 5 in the anterior midparietal region showed a focal loss of vasomotor response to hypercapnia. During Aramine infusion with a 26 mm Hg increase in MAP there again was a heterogeneous rCBF response. The mean CBF decreased significantly from 51 to 49 ml/100 gm per minute, indicating a loss of autoregulation in all regions.

8. History: A 63-year-old man was admitted to the hospital because of inability to move left arm and leg and inability to speak of one day’s duration. He had had hypertension and a “left-sided” stroke in November, 1968, with reasonable recovery. Examination: Blood pressure 140/100. Neurological examination: Patient was unable to speak but was alert. There was a right lower facial weakness. He moved his right leg to painful stimuli but was unable to move his right arm. Right Babinski sign.

Clinical Diagnosis: Cerebral infarction in the distribution of the left common carotid artery; hypertension; hypertensive heart disease.

Cerebral Angiogram: Left carotid angiogram showed anterior cerebral artery occlusion below the genu with nonfilling of its branches and avascularity of the frontal area; basilar artery occlusion in the midbasilar portion.

Cerebral Blood Flow Studies: Baseline mean CBF was decreased to 35 ml/100 gm per minute. During CO₂ inhalation (with 10 mm Hg Pco, and 7 mm Hg MAP increase), the rCBF increased homogeneously with the mean CBF increasing 66% to 59 ml/100 gm per minute. Probes Nos. 4 and 8 were over the anterior cerebral artery territory. The rCBF value for Probe 4 was increased over the mean CBF to 44 ml/100 gm per minute, while Probe 8 was decreased below the mean to 28 ml/100 gm per minute. Although the mean CBF value for the second control study was the same — 35 ml/100 gm per minute — both Probes 4 and 8 were decreased to 28 and 26 ml/100 gm per minute, respectively. During infusion of Aramine with a 95 mm Hg increase in MAP, all rCBF values increased 29% in a homogeneous fashion from a mean CBF of 45 ml/100 gm per minute, indicating loss of autoregulation in all regions.

9. History: A 66-year-old man had dizziness and double vision with weakness of his left leg and falling to the ground four days prior to admission. His face was noted to be twisted to the right and he had difficulty speaking. In the past he had had hypertension and episodes of dizziness and numbness of his left arm. He had hypertension for three years. Examination: Blood pressure 125/76. Neurological examination: He had left facial weakness and left hemiparesis. Patient was alert, oriented, and cooperative.

Clinical Diagnosis: Cerebral infarction in the distribution of the right middle cerebral artery; hypertension; hypertensive cardiovascular disease.

Cerebral Angiogram: Right carotid angiogram showed diffuse arteriosclerotic disease involving both intracranial and extracranial vessels.

Cerebral Blood Flow Studies: Baseline mean CBF was decreased to 34 ml/100 gm per minute. During CO₂ inhalation (with a 6 mm Hg Pco, and 48 mm Hg MAP increase), there was a 71% homogeneous increase in mean CBF to 58 ml/100 gm per minute. During Aramine infusion with a 67 mm Hg increase in MAP, the mean CBF increased homogeneously, 47% from 34 to 50 ml/100 gm per minute, indicating a loss of autoregulation in all regions.

10. History: A 61-year-old man was admitted to the hospital because of episodes of syncope the day of admission. He had had three heart attacks in ten years and diabetes for seven years. He had hypertension for 15 to 20 years and had congestive heart failure. Examination: Blood pressure 200/100. Apical systolic murmur. Neurological examination: He was alert, oriented, and dysarthric. He had left lower facial weakness, and weakness and sensory loss of the left arm and leg. Left Babinski sign.

Clinical Diagnosis: Cerebral infarction in the distribution of the right common carotid artery; hypertension, diabetes; hypertensive heart disease.

Cerebral Angiogram: Bilateral carotid arteriogram showed right common carotid artery occlusion with a normal left carotid arteriogram.

Cerebral Blood Flow Studies: Baseline mean CBF was decreased to 35 ml/100 gm per minute. During CO₂ inhalation (with a 9 mm Hg Pco, and 37 mm Hg MAP increase), the mean CBF increased 26% to 44 ml/100 gm per minute. All rCBF values increased in a...
homogeneous fashion. The baseline CBF prior to Aramine infusion was the same as the first control value. Following Aramine infusion with a 103 mm Hg increase in MAP, the mean CBF increased homogeneously 29% from 35 to 45 ml/100 gm per minute, indicating a loss of autoregulation in all regions.

11. History: A 51-year-old man was admitted to the hospital because of disorientation and frosthite of his hands and toes. Following partial amputation of his right toes in February, he was transferred to the Neurosurgical Service in May for evaluation for dementia.

Clinical Diagnosis: Peripheral vascular disease; presenile dementia.

Cerebral Angiogram: Left carotid angiogram showed internal carotid artery stenosis in the cavernous sinus region. Filling of the superior cerebellar artery via carotid artery injection indicated basilar artery stenosis or occlusion. Anterior and middle cerebral arteries appeared normal in caliber and course.

Cerebral Blood Flow Studies: Baseline mean CBF was in the lower limits of normal, 45 ml/100 gm per minute. During CO₂ inhalation (with a 19 mm Hg MAP increase), the mean CBF increased heterogeneously only 4% to 47 ml/100 gm per minute. Probe 6 over the superior posterior frontal region showed an intracerebral steal with a 36% fall in the rCBF from 42 to 27 ml/100 gm per minute. During Aramine infusion, the MAP increased 47 mm Hg and all rCBF values increased 29% in a homogeneous fashion from 38 to 49 ml/100 gm per minute, indicating a loss of autoregulation in all regions. The control rCBF value prior to the Aramine infusion for Probe 6 remained low, 23 ml/100 gm per minute. Probe 6, however, as did all other regions, showed loss of autoregulation with increase in rCBF.

12. History: A 59-year-old man, a known alcoholic with epilepsy, was admitted to the hospital after having been found unconscious in the street. The patient had had two previous operations for a subdural hematoma and was being treated for post-traumatic epilepsy. Examination: Blood pressure 140/60. Neurological examination: He remained stuporous for 16 days when he was described to be alert and responsive, but moderately demented. There were no focal neurological signs.

Clinical Diagnosis: Chronic alcoholism; post-traumatic epilepsy.

Cerebral Angiogram: Left carotid angiogram showed a subdural hematoma with shift of the anterior cerebral artery to the right and compression of the right cerebral hemisphere.

Cerebral Blood Flow Studies: Baseline mean CBF was decreased to 31 ml/100 gm per minute. During CO₂ inhalation (with a 6 mm Hg Pco₂ and 5 mm Hg MAP increase), there was a homogeneously 23% increase in mean CBF to 38 ml/100 gm per minute except over Probe 5 in the inferior anterior parietal region, where there was an intracerebral steal with a 68% decrease in flow from 28 to 9 ml/100 gm per minute. During Aramine infusion with a 25 mm Hg increase in the MAP, there was a 21% heterogeneous increase in the mean CBF from 34 to 41 ml/100 gm per minute. Three regions had a greater increase in rCBF than did the other four, indicating a mixed loss of autoregulation.

Probe 5 showed essentially no change in rCBF during the Aramine study (fig. 5).

13. History: A 62-year-old woman was admitted to the hospital because of inability to walk of one week’s duration. She had had hypertension for ten years. Five days prior to admission she developed weakness of her right arm and her leg weakness became worse. Examination: Blood pressure 220/110. Systolic murmur and cardiomegaly. Neurological examination: She was oriented to person but not to time or place. Mild facial weakness with moderate weakness of her right arm and greater weakness of her right leg. There was generalized hyperreflexia, more so on the right. Right Babinski sign.

Clinical Diagnosis: Cerebral infarction in the distribution of the left middle cerebral artery; hypertension.

Cerebral Angiogram: Left carotid angiogram showed severe diffuse arteriosclerotic vascular disease with multiple focal stenotic lesions intracranially.

Cerebral Blood Flow Studies: Baseline mean CBF was decreased to 31 ml/100 gm per minute. During CO₂ inhalation (with a 12 mm Hg Pco₂ and 44 mm Hg MAP increase), there was a 65% heterogeneous increase to 51 ml/100 gm per minute. Probe 4 in the anterior parietal region showed a marked rCBF increase, namely, from 34 to 104 ml/100 gm per minute. During Aramine infusion with an increase in the MAP of 65 mm Hg, there was a 19% heterogeneous increase in mean CBF from 26 to 31 ml/100 gm per minute. Probe 4, however, showed a change in rCBF of only 32 to 34 ml/100 gm per minute, indicating a mixed loss of autoregulation.

14. History: A 54-year-old woman with hypertension and diabetes of several years’ duration had mental changes and seizures five days prior to admission to the hospital. She was unconscious for a period of five minutes during which her head and eyes were deviated to the right. She remained confused on regaining consciousness. Examination: Blood pressure 210/110. Neurological examination: She was alert and oriented with loss of recent memory. There was no weakness of her arms or legs. Sensation and cranial nerve examination were normal. Deep tendon reflexes were equal and symmetrical.

Clinical Diagnosis: Seizure disorder with dementia; hypertension; diabetes mellitus.

Cerebral Angiogram: Right carotid angiogram showed no focal flow abnormalities and no evidence of intracranial vascular disease or mass lesion.

Cerebral Blood Flow Studies: Baseline mean CBF was in the lower limits of normal — 43 ml/100 gm per minute. During CO₂ inhalation (with a 5 mm Hg Pco₂ and 16 mm Hg MAP increase), there was a 19% heterogeneous increase in all but two regions with a mean CBF increase to 51 ml/100 gm per minute. Probe 2 showed an intracerebral steal with a fall in rCBF from 80 to 60 ml/100 gm per minute. Probe 1, in the midparietal region, showed an 11% fall in rCBF from 36 to 32 ml/100 gm per minute. During Aramine infusion with an increase in MAP of 22 mm Hg and with the mean CBF increasing 16% from 43 to 51 ml/100 gm per minute, there was a heterogeneous rCBF response with a mixed loss of...
autoregulation. Two probes showed a marked increase in rCBF while three others showed only moderate increase in rCBF. Probe 1 again showed an 11% decrease in flow from 63 to 56 ml/100 gm per minute. The increase in rCBF value in Probe 1 from the CO₂ to the second control study can possibly be related to a focal loss of autoregulation between the two studies.

15. History: A 45-year-old woman with hypertension and diabetes of five years' duration was admitted to the hospital because of right-sided focal seizures intermittently for one week prior to admission. Seizures had increased in severity the day of admission. One year ago the patient had an episode of loss of consciousness with residual right-sided weakness. Examination: The patient was having focal tonic seizures of the right side of her face and her arm. Blood pressure 190/80. Following seizures patient had flaccid paralysis of the right arm with increased deep tendon reflexes.

Clinical Diagnosis: Cerebral infarction in the distribution of the left middle cerebral artery.

Cerebral Angiogram: Right carotid angiogram showed occlusion of the middle cerebral artery at its origin and stenosis of the anterior cerebral artery. There was collateral circulation into the middle cerebral artery territory from anastomotic channels from the anterior cerebral artery.

Cerebral Blood Flow Studies: Baseline mean CBF was decreased to 23 ml/100 gm per minute. During Aramine infusion with an increase in MAP of 47 mm Hg, rCBF increased heterogeneously 30% to a mean CBF to 30 ml/100 gm per minute. There was a loss of autoregulation in two regions, but autoregulation remained preserved in two other regions, indicating a mixed loss of autoregulation.

16. History: A 67-year-old man had a sudden onset of hemiparesis five weeks prior to hospital admission. Since that time, he had been unable to walk and was incontinent. History of hypertension. Neurological examination: The patient was alert but disoriented. There was some dysarthria. The patient stated he was left-handed. There was a right homonymous hemianopia, a right central facial weakness and severe right hemiparesis with increased deep tendon reflexes. Right Babinski sign.

Clinical Diagnosis: Cerebral infarction in the distribution of the left middle cerebral artery.

Cerebral Angiogram: Left carotid angiogram showed occlusion of the posterior parietal temporal branches of the middle cerebral artery.

Cerebral Blood Flow Studies: Baseline mean CBF was decreased markedly to 24 ml/100 gm per minute. During Aramine infusion with a 33 mm Hg increase in MAP, the mean CBF increased 12.5% to 27 ml/100 gm.
per minute. There was a heterogeneous rCBF response with three probes showing an increase in rCBF with a focal loss of autoregulation. Two other probes showed no change in rCBF during Aramine infusion, indicating a mixed loss of autoregulation.

The control mean CBF for Group 1 with preserved autoregulation was greater (41 versus 36 ml/100 gm per minute) than in Group 2 with loss of autoregulation. Baseline MAP, however, was greater (101 versus 92 mm Hg) in the group with loss of autoregulation than in the other. The baseline CVR was approximately the same in the two groups, namely, 2.4 and 2.8 mm Hg per milliliter per 100 gm per minute. In the group with preserved autoregulation, the cardiac index was greater (2.84 versus 1.91 l/m²/minute) than in the group with loss of autoregulation. Similarly, cardiac output was greater (7.4 versus 4.7 kg/m/minute) in Group 1 as compared to Group 2.

During CO₂ inhalation, the mean CBF increased to 51% from 41 to 62 ml/100 gm per minute in Group 1. In Group 2 the mean CBF increased only 39% from 36 to 50 ml/100 gm per minute during CO₂ inhalation. The regional blood flow responses in the two groups were approximately the same, namely, some patients showed a homogeneous rCBF response while others showed mixed or heterogeneous rCBF responses to CO₂ inhalation. In four instances (Patients Nos. 6, 11, 12, and 14) there was a mixed loss of autoregulation. The cardiohemodynamic parameters showed a greater increase in cardiac index (26% versus 52%) and in cardiac work (4% versus 31%) in Group 1 as compared to Group 2. TSVR decreased approximately the same in both groups in CO₂ inhalation.

During Aramine infusion the MAP increased from 38% (from 88 to 121 mm Hg) in Group 1 and 59% (95 to 151 mm Hg) in Group 2. The mean CBF was essentially unchanged in Group 1 with preserved autoregulation but increased 24% (from 31 to 41 ml/100 gm per minute) in Group 2 with loss of autoregulation. The cardiohemodynamic parameters (CI and CW) changed 13% (4% and 56%, respectively) in Group 1 than in the group with loss of autoregulation where the CI and CW were increased 31% and 126%, respectively. TSVR increased only 9% in Group 1 whereas in Group 2 it increased 20%. As shown in figures 1 and 2, when autoregulation is lost the rCBF may increase homogeneously or heterogeneously with some areas increasing while others remain unchanged or even decreased. In three instances (Patients Nos. 6, 7, and 14) there was an intracerebral steal with a fall in rCBF during Aramine infusion.

Discussion

In his classical review to show normal autoregulation in man, Lassen summarized 376 CBF measurements from 11 groups of subjects during drug-induced hypotension and hypertension, hypertensive toxemia of pregnancy and essential hypertension. Lassen demonstrated that the CBF remained in essentially normal range at blood pressures varying from an MAP of 170 to 50 mm Hg where there was an abrupt loss of autoregulation with a drop in CBF from approximately 55 to 30 ml/100 gm per minute. This summary of clinical studies in man supported the hypothesis of Forbes and Fog that there is an active regulation of cerebrovascular tone in the face of variations in blood pressure. Autoregulation was considered to be due to a direct effect of smooth muscles of change in pressure, that is, the Bayliss effect, where increases in intravascular pressure cause vasoconstriction and decreases the contrary vasodilatation. This work has subsequently been confirmed by many investigators, particularly Harper and recently in man by Olesen.

The first rCBF study in man of the loss of autoregulation was by Høedt-Rasmussen et al. from Lassen's laboratory. Six cases of acute apoplexy were examined by Xenon injection rCBF method. Five cases were studied before and after the intramuscular injection of 5 mg of Aramine. In patients with hyperemic rCBF foci, there was regional loss of autoregulation, that is, with induced MAP change the focal rCBF change exceeded that of the surrounding regions.

Agnoli et al. performed a study of autoregulation similar to this one by the intravenous infusion of angiotensin to increase the blood pressure 30 to 40 mm Hg. All patients were normotensive and rCBF was measured by the isotope clearance method. Fifteen control subjects with various neurological disorders or psychoneurosis had preserved autoregulation. A mean increase in blood pressure of 34.7 mm Hg caused only a mean increase of blood flow of 0.26 ml/100 gm per minute. In this study those in Group 1 with preserved autoregulation had a mean increase of 8 ml/100 gm per minute in Group 2 compared to Group 1. In general, these results were confirmed in man by Olesen.
CEREBRAL AUTOREGULATION IN MAN

Fieschi et al. who examined 21 patients from the same day to four days after their stroke. Nine of these patients with stroke under two days were studied during the intravenous infusion of angiotensin which increased the mean blood pressure from 22 to 57 mm Hg. Of these nine patients tested three showed autoregulation, while in the remaining six autoregulation was lost in two or three regions of the hemisphere examined. These authors concluded that treatment with a hypertensive agent should be appropriate in cases of loss of autoregulation with a very low flow. Fieschi et al. discussed the discrepancies between autoregulation and CO2 reactivity of cerebral blood vessels. They found that in acute focal brain lesions the vasomotor responses are regionally altered and often so in a discrepant manner. That is, about 50% of the regions had impaired autoregulation with preserved response to CO2 or vice versa. Lassen and Paulson also have discussed such discrepancies and dissociations, and these are described in the results of the present report.

The other study of cerebral autoregulation was in the series by Paulson who tested autoregulation by the intravenous infusion of Aramine or angiotensin. Five of ten patients with middle cerebral artery occlusion showed loss of autoregulation while five did not. Focal regions in five instances showed a 14% to 74% increase in rCBF. In another study of 31 patients with “apoplexy without arterial occlusion” Paulson tested autoregulation by raising the blood pressure with Aramine or angiotensin or lowering it with Ansolysen. Twenty-two tests of autoregulation were made and in three patients there was global loss of autoregulation “as flow in the nonfocal areas increased almost in proportion to the pressure increase.” In these three instances, however, there was a paradoxical decrease in flow in the focal regions. This paradoxical response during induced hypertension is similar to the steal syndrome observed during induced hypercapnia. This steal syndrome was observed in three instances (Patients Nos. 6, 7 and 14) in the present study. In the report of Skinhøj et al. of autoregulation in patients with transient ischemic attacks they found only one instance of loss of autoregulation out of 12 patients studied. This patient had focal rCBF abnormalities as well.

A quantitative evaluation of autoregulation was proposed by Olesen, previous studies having regard to autoregulation as an all-or-none phenomenon. By dividing the percent change in rCBF by the percent change in MAP, Olesen calculated the “vasoreactivity impairment index” (VI). He studied 15 patients with “minor diseases or chronic states . . . without signs of acute brain disease” by changing the MAP 30%. Blood pressure was elevated by angiotensin or levarterenol or lowered with trimethylphap. The latter does not change CBF after intracarotid infusion. Previously Olesen had found that intracarotid epinephrine, norepinephrine, or angiotensin did not change CBF; hence these drugs acted to change only MAP. In his study of 15 patients, the mean VI was −1.0 ± 7.2 with MAP elevation and −1.6 ± 4.8 on lowering MAP with mean CBF values by 63 and 62, and 45.6 and 44.6 ml/100 gm per minute, respectively; hence autoregulation remained intact in this group. This is similar to the findings in Group 1 of the present report. Loss of autoregulation with regional changes in rCBF and VI was described in six additional patients. Normally the VI is zero but with increasing impairment of autoregulation it increases. Quantitative evaluation of autoregulation impairment was also determined by Meyer et al., who calculated the “autoregulation index” (AI) by dividing the change in CBF by the change in cerebral perfusion pressure (CPP).

The upper and lower limits of autoregulation were defined by Strandgaard. This was done by the arteriovenous method and by raising and lowering the blood pressure in hypertensive and normal man. All patients had intact autoregulation, but in untreated hypertensive patients the lower blood pressure limit of autoregulation was shifted upward. In some normotensive patients under antihypertensive therapy, an almost normal lower limit of autoregulation was found. Strandgaard suggested that the shift upward of the autoregulation curve in hypertensive patients was caused by arteriolar hypertrophy and that this was probably important in understanding the pathogenesis of hypertensive encephalopathy.

Examination of metabolic parameters of autoregulation by Hoyer et al. led them to conclude that blood flow is kept constant at wide pressure ranges because at lower CPP there is lactacidosis and the liberation of CO2 out of bicarbonate reserves. Contrary findings were reported in a study of six anesthetized patients with loss of autoregulation by Paulson, Olesen, and Christensen, who found that autoregulation could be restored by hypocapnia or lowering of the CO2. Only one of four patients examined had CSF lactacidosis. They felt that dissociated vasoparalysis due to slight tissue acidosis had not been clarified.

Conclusions

In these two groups of patients, with a variety of neurological diseases, the loss or presence of autoregulation could be related (1) to a lower baseline CBF in the group with loss of autoregulation, (2) to a greater induced rise in mean arterial blood pressure in Group 2 than in Group 1, (3) to a direct or indirect influence of local metabolic or neurogenic reflexes or (4) to the influence of cardiovascular reflexes in relation to the neurogenic control of cerebral circulation.

Finally, the results of this study might imply that cerebral circulation in some patients could be sustained therapeutically by controlling the blood
pressure to maintain an optimal cerebral perfusion pressure and, hence, CBF and cerebral perfusion. This was implied in the papers by Shanbrom and Levy and Wise. To further evaluate this, however, one would have to test each patient to establish the loss or presence of autoregulation. The clinical usefulness or implications of induced hypertension as a form of treatment in stroke has not been proved by this or other studies, but it should continue to be evaluated in light of these findings and those noted by others.

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