CEREBRAL HEMODYNAMICS DURING CEREBRAL ISCHEMIA
INDUCED BY ACUTE HYPOTENSION

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The extreme dependence of the brain upon its
circulation is well recognized. A cessation of the cerebral circulation for only a
few minutes, as occurs in cardiac arrest, results in irreversible brain damage. The brain, for the most
part, is an aerobic organ and its large oxygen demands probably account for its unusual suscepti-
bility to circulatory disturbances.

The oxygen consumed by the normal adult brain
(3.5 cc. per 100 Gm. per min.) is extracted from approximately 800 cc. of blood passing through it
each minute. The minimum blood flow require-
ments of the brain, i.e., the rate at which signs of
cerebral ischemia become manifest, have not been accurately determined. Previous efforts to esti-
mate the critical rate have been made both in ani-
mals (1) and in man (2) but the procedures utilized for the determination of cerebral blood flow were not sufficiently quantitative to warrant defi-
nite conclusions.

In order to study this problem, cerebral hemody-
amic and metabolic changes were determined before and during acute reductions in arterial pres-
sure induced by drug administration and/or postural adjustments.

MATERIALS AND METHOD

Forty-four patients were studied. The subjects in
whom hypotension was drug-induced were separated into the following four groups so that the influence of age and hypertension on the susceptibility of the brain to
cerebral ischemia could be determined: Group 1, seven normotensive subjects under 50 years of age; Group 2, ten normotensive subjects over 60 years of age; Group 3, eight patients with essential hypertension; and Group 4, seven patients with malignant hypertension. In seven subjects, the mean arterial pressure was reduced signifi-
cantly below normal but not to the extent of inducing signs of cerebral ischemia. Five patients with spontaneous postural hypotension were also studied.

Control studies were obtained after the subject had been tilted (head up) 30 to 40 degrees for a period of at least 30 minutes. The subjects in the drug-induced hypotension group were then given a 1 per cent solution of hexamethonium 1 intravenously at a rate of 1 mg. of the ion per minute and carefully observed for signs of cerebral ischemia. In the subjects with spontaneous postural hypotension, control studies were done in the horizontal position, and the subjects were then tilted 30 degrees head up, and the experimental flow was done when they developed signs of cerebral ischemia.

The manifestations of cerebral circulatory insufficiency were rather stereotyped and easily recognized. Sighing, yawning, staring, and confusion, i.e., the inability to follow simple commands, were the first indications of cerebral ischemia. When any of these signs appeared, the hexa-
methonium injection was promptly discontinued, and the second, or experimental flow was begun. A fairly steady state was maintained during the first few minutes making postural adjustments unnecessary. If during the ex-
perimental flow, the patient became either unresponsive or too alert, postural adjustments were rapidly made to restore the desired clinical state. The degree of tilt re-
quired was usually not more than 10 to 20 degrees. In this way, the clinical state of the subject could be changed in a matter of seconds from one of alertness to confu-
sion, and for the remainder of the flow, the subject was maintained in the latter state.

Schelberg and Stead's modification (3) of Kety and
Schmidt's procedure (4) for the determination of cere-
bral blood flow (CBF) was utilized in this study. The
gas mixtures utilized were those described by Kety and
Schmidt (4). Blood oxygen and CO₂ content were de-
termined by the manometric technique of Van Slyke and Neill (5). Blood pH was determined using a Beckman
pH meter and an anaerobic glass electrode at room tem-
perature and corrected for 37 degrees centigrade. The cerebral oxygen consumption (CMRO₂), cerebral vas-

1 This investigation was supported by a grant from the
United Cerebral Palsy Foundation and a grant (PHS
B-178) from the National Institute of Neurological Dis-
eas and Blindness of the National Institutes of Health,
Public Health Service.

2 Supplied through the courtesy of E. R. Squibb and Sons, New York, N. Y.
Cerebral hemodynamics in acute hypotension associated with cerebral ischemia 

<table>
<thead>
<tr>
<th>Subjects with Essential Hypertension</th>
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<tbody>
<tr>
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Mean Values

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<th>AVO$_2$</th>
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<td>62</td>
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<td>29.1</td>
<td>2.4</td>
<td>1.6</td>
<td>2.8</td>
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</table>

* See Table IA for explanation of abbreviations.  
† Significant difference, p < .01.

Cerebral hemodynamics in acute hypotension associated with cerebral ischemia 

<table>
<thead>
<tr>
<th>Subjects with Malignant Hypertension</th>
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Mean Values

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<td>40</td>
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<td>35.1</td>
<td>3.0</td>
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<td>3.5</td>
</tr>
</tbody>
</table>

* See Table IA for explanation of abbreviations.  
† Significant difference, p < .01.

The mean arterial blood pressure (MAP) was obtained directly from the femoral artery by means of a damped aneroid manometer (6) and also by the usual auscultatory method. Since the subjects were tilted, it was necessary to correct for the hydrostatic pressure differences between the femoral and carotid arteries. This pressure differential was equal to the vertical height between the two arteries which varied somewhat in individual studies. The mean arterial pressures, presented in the tables are the calculated mean carotid pressures. This correction, as well as the fact that the subjects were resting in a tilted position for approximately thirty minutes, probably accounts for the normotensive values in some of the subjects with essential hypertension (Table IC).
TABLE II

Cerebral hemodynamics in acute hypotension associated
with cerebral ischemia *

Subjects with Postural Hypotension

<table>
<thead>
<tr>
<th>Age</th>
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<td>E</td>
<td>C</td>
<td>E</td>
<td>C</td>
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<td>47</td>
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<td>79</td>
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<td>69</td>
<td>44.9</td>
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<td>0.8</td>
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Mean Values

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<thead>
<tr>
<th>Age</th>
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<th>AVO₂</th>
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<td>65</td>
<td>55.8</td>
<td>35.1</td>
<td>1.9</td>
<td>1.5</td>
<td>2.8</td>
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</tbody>
</table>

* See Table IA for explanation of abbreviations.
† Significant difference, p < .05.
‡ Significant difference, p < .01.

Electrocardiograms were taken before, during, and after the experimental procedure in 21 subjects, and the internal jugular venous pressures were recorded before and during the study in 14 subjects. The internal jugular venous pressures were measured by means of a spinal fluid manometer; the zero point was considered to be the needle level.

RESULTS

An analysis of the results obtained in the 37 subjects in whom the mean arterial pressure was reduced to levels at which signs of cerebral ischemia became manifest discloses the following: The mean arterial pressure fell from a mean value of 109 mm. Hg to 48 mm. Hg (p < .01). The rate of cerebral blood flow decreased significantly from a mean of 51 to 31.5 cc./100 Gm./min. (p < .01). The mean cerebral vascular resistance also fell significantly from 2.2 to 1.5 (p < .01). The mean cerebral arteriovenous oxygen difference increased significantly from 5.80 volumes per cent to 9.20 volumes per cent (p < .01). Despite definite signs of cerebral ischemia, the cerebral oxygen utilization did not change appreciably from control values during the experimental flow. The CO₂ content of the arterial and cerebral venous blood did not change significantly with a reduction of the mean arterial pressure. Similarly there were no significant changes in the blood pH in eleven of the subjects studied.

Tables I, A through E, present the results of the individual groups. Table II presents data on seven subjects in whom the mean arterial pressure was not lowered sufficiently to induce signs of cerebral ischemia.

Though considerable variation is seen in the level of arterial pressure at which signs of cerebral ischemia became manifest, ranging from mean values of 89 mm. Hg in the malignant hypertensive group to 29 mm. Hg in the normotensive group over 60 years of age, the value for the cerebral blood flow is not appreciably different in the individual groups studied (Tables I, A through E). The mean value for cerebral blood flow in the group of subjects in whom cerebral ischemia was not induced (Table II) is significantly higher than in any of the other groups.

TABLE II

Cerebral hemodynamics in acute hypotension without cerebral ischemia *

<table>
<thead>
<tr>
<th>Age</th>
<th>Diagnosis</th>
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<td>E</td>
<td>C</td>
<td>E</td>
<td>C</td>
</tr>
<tr>
<td>67</td>
<td>Pneumonia</td>
<td>66.8</td>
<td>38.3</td>
<td>1.2</td>
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<td>36</td>
<td>Diabetes</td>
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<tr>
<td>23</td>
<td>Dermatitis</td>
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<td>1.2</td>
<td>2.7</td>
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<tr>
<td>18</td>
<td>Rheumatic fever</td>
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<td>1.4</td>
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<tr>
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</tr>
<tr>
<td>48</td>
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<tr>
<td>43</td>
<td>Uremia</td>
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<td>2.2</td>
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<td>1.8</td>
</tr>
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Mean Values

<table>
<thead>
<tr>
<th>Age</th>
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<th>CVR</th>
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<th>AVO₂</th>
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<td>43</td>
<td>61.9</td>
<td>43.9</td>
<td>1.8</td>
<td>1.5</td>
<td>2.9</td>
</tr>
</tbody>
</table>

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† Significant difference, p < .01.
‡ Significant difference, p < .05.
The mean cerebral vascular resistance fell significantly in both the young and elderly normotensive subjects (Table I A and IB) and subjects with essential hypertension (Table IC). The cerebral metabolic rate did not change significantly from the control values in any of the individual groups. In all groups presented, the cerebral arteriovenous oxygen difference was significantly increased.

In the 14 subjects studied, the internal jugular venous pressure decreased from 83 to 47 mm. of water with an average decrease of 36. Since this represents a difference of approximately 3 mm. Hg, it would only change the cerebral vascular resistance by 0.1 units.

Of interest was the complete lack of clinical and electrocardiographic evidence of coronary insufficiency in these acute studies, particularly in the elderly subjects, many of whom had abnormal electrocardiograms. The control electrocardiograms in 15 subjects were abnormal—two subjects showed evidence of old posterior myocardial infarction, the rest showed non-specific myocardial changes. When symptoms of cerebral ischemia developed, the average heart rate was 64 per minute, a reduction of 35 per cent.

DISCUSSION

Cerebral blood flow and arterial pressure

It is evident from these studies that despite the subject's age, original level of arterial pressure, per cent reduction of arterial pressure, or original rate of cerebral blood flow, signs of cerebral ischemia developed when the mean cerebral blood flow was reduced to 31.5 cc. per min. per 100 Gm. of brain. The mean values of the experimental cerebral blood flows for the individual groups varied between 29 and 35 cc. per 100 Gm. of brain per min. The fact that in the group without cerebral ischemia (Table II) the subjects were alert despite a mean cerebral blood flow of 43.9 indicates that the critical rate of cerebral blood flow is below this value. Apparently significant reductions in cerebral blood flow from normal are possible without inducing manifestations of cerebral ischemia.

The degree of fall in arterial pressure required to produce cerebral ischemia, as might be anticipated, was related to the cerebral vascular resistance. When the cerebral vascular resistance could be significantly reduced (all groups except the postural hypotensive group and the malignant hypertensive group), the arterial pressure could be lowered markedly before signs of cerebral ischemia became manifest. When the vascular resistance could not be significantly reduced, the level of arterial pressure at which cerebral ischemia developed was higher. Only in situations where the vascular resistance remains fixed, can there be a direct relationship between per cent reduction in cerebral blood flow and mean arterial pressure. Since the mean arterial pressure at which signs of cerebral ischemia developed varied considerably (89 to 29 mm. Hg), it is evident that a critical level of arterial pressure as such does not exist.

Cerebral vascular resistance

The initial values for the cerebral vascular resistance in the individual groups varied. The finding of an increased cerebral vascular resistance in the hypertensive subjects confirms the results of Kety and others (7-10). The highest mean value for the cerebral vascular resistance was noted in the malignant hypertension group. While the increased cerebral vascular resistance in the essential hypertension group was significantly reduced with hypotension, the cerebral vascular resistance in the malignant hypertension group remained relatively fixed. It may be that the inability to overcome this increased cerebral vascular tone accounted for the development of signs of cerebral ischemia at normal levels of arterial pressure.

It was particularly interesting that the elderly normotensive subjects showed a significant reduction in cerebral vascular resistance when their mean arterial pressures were reduced. This confirms previous observations demonstrating considerable alterations in the vascular tone of elderly subjects (11, 12). In the group studied, the cerebral vascular resistance was not as high as we expected it might be. In a preliminary study (13) on elderly hypertensive subjects with a markedly elevated cerebral vascular resistance, signs of cerebral ischemia have occurred at normotensive levels. An overall decrease in cerebral vascular resistance in normotensive and hypertensive subjects with cerebral arteriosclerosis should not be taken to mean that all cerebral vessels are capable of under-
going the same degree of relaxation. It is possible
that with an acute drop in blood pressure, circula-
tion through the more rigid cerebral vessels may be
seriously impaired. This may explain why tran-
sient episodes of cerebral ischemia may sometimes
be associated with a relatively slight decrease of
the mean arterial pressure. The explanation for
the decrease in cerebral vascular resistance atten-
dant with the reduction in mean arterial pres-
sure is not apparent from these studies since there
was no change in either pH or CO₂ content.

Cerebral metabolic rate

Even though signs and symptoms of cerebral
ischemia were present in most of the subjects stud-
ied, there was no significant change in cerebral oxygen utilization between the control and induced
hypotension studies. There can be no question
that in these acute experiments the manifesta-
tions of cerebral ischemia were most likely due to a
decreased oxygen delivery to certain cerebral cells
since there was neither hypoglycemia nor any
obvious impairment of cerebral enzymatic ac-
tivity. It is suggested from the neurological signs
evoked that not all regions of the brain were
equally affected by the cerebral ischemia. The
variable sensitivity of the different areas of the
brain to reduced oxygen tensions and to depres-
sant drugs is well recognized. It may be that with
a reduction of the rate of cerebral blood flow those
areas with the highest metabolic requirements are
first affected. The failure to observe significant
changes in cerebral oxygen utilization in these
studies may be due to the fact that the method em-
ployed is not sufficiently sensitive to reflect changes
in the metabolic activity of a relatively small num-
ber of cerebral cells. In this regard it should be
mentioned that during sleep (14) and with light
Pentothal® anesthesia (15) one does not observe
significant changes in cerebral oxygen utilization
with this procedure.

Cardiovascular effects

The fact that small doses of hexamethonium
were given (average dose was 8 mg. of the ion)
and the frequent finding of bradycardia and in-
creased perspiration in the drug-induced studies
suggests that full blocking doses of the drug were
not given, and the effects observed were not en-
tirely drug-induced. The hypotensive effect of
small doses of the ganglionic blocking agent en-
hanced by tilting apparently activated vasovagal
reflexes which accounted for the bradycardia ob-
served. With the onset of collapse, cardiac output
and right ventricular pressures decreased sharply
(16). These latter observations are consistent
with the concept that the mechanism of cerebral
ischemia was due to loss of peripheral vasocon-
strictor tone which in our tilted subjects promoted
failure of venous return and hence of cardiac
output.

SUMMARY AND CONCLUSIONS

1. The effect of cerebral ischemia induced by the
intravenous administration of hexamethonium
and/or tilting on cerebral hemodynamics and
metabolism was determined in young and elderly
normotensive subjects and in subjects with es-
sential and malignant hypertension. Seven sub-
jects with postural hypotension were also studied.
2. In all subjects, signs and symptoms of cere-
bral ischemia developed when the cerebral blood
flow was reduced to 31.5 cc. per 100 Gm. of brain
per min. (mean value).
3. The degree of fall in mean arterial pressure
which resulted in cerebral ischemia varied from 29
to 80 mm. Hg.
4. Subjects with a relatively fixed cerebral vas-
cular resistance (malignant hypertension) de-
veloped cerebral ischemia at higher mean arterial
pressures.
5. Although blood pressures were lowered to
levels resulting in clinical signs and symptoms of
cerebral ischemia, no change in the over-all cere-
bral oxygen consumption was noted.
6. The development of clinical signs of cerebral
insufficiency without simultaneous clinical or lab-
oratory evidence of coronary insufficiency suggests
that the brain may be more sensitive to acute hypo-
tension than is the heart.

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