OCCLUSION OF THE MIDDLE CEREBRAL ARTERY
UNDER NORMOTENSION, AND ANEMICALLY INDUCED AND
CHEMICALLY INDUCED HYPOTENSION*

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During the past four years, there has been a growing interest in the
use of induced hypotension for surgical procedures. Whereas this was
previously accomplished by arteriotomy and retransfusion, most re-
cent work deals with the reduction of blood pressure by means of “neuro-
genic” or “ganglioplegic” mechanisms such as are available in total spinal
anesthesia and by chemical ganglionic blocking agents.

During hypotension induced by ganglionic blocking agents, the blood
pressure falls as a result of arteriolar dilatation, the pulse generally remains
stable, capillary refill time is unaltered, the skin is pink and respiration is
slow. In hypotension produced by bleeding there is associated arteriolar con-
striction leading to capillary stasis, anoxia and the increased danger of irrever-
sible tissue damage.

The clinical use of ganglionic blocking agents (mostly of the methonium
group) has now become extensive, both in the United States and abroad. A
number of complications have been reported. Among these are cerebral
artery occlusion, decerebration, and blindness. Other workers, however,
have been impressed with the increased safety with which certain major
surgical procedures can be carried out with the help of this method.

Perhaps the most important area for the application of this new method
has been in neurological surgery. Its use has markedly reduced the hazard of
operating on large vascular meningeas and some of the major vascular
anomalies of the brain. Neurosurgical reports of experiences with blocking
agents have been almost uniformly favorable. They indicate that fatalities
have been low and that those that have occurred are not generally traceable
to the hypotension.

Despite the use of methonium compounds in several thousand cases, little
has been done experimentally to check on the clinical impressions or to
study the altered vascular dynamics or to search for pathological changes in
the vascular tree. Morris et al. found in unanesthetized humans, in the
supine position, a significant decrease in cerebral blood flow following

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marked depression of the blood pressure. This occurred in the presence of diminished cerebral vascular resistance. Cerebral oxygen consumption was only slightly reduced because of a more complete extraction of oxygen from the blood. They concluded that there is apparently little danger of cerebral anoxia in the supine patient with a mean blood pressure of 55 mm. Hg when employing hexamethonium induced hypotension. Finnerty et al., obtained similar results for blood flow and found a critical rate of flow at which symptoms appeared. Flow studies by Stone, however, following administration of hexamethonium to young adults, showed no change despite reduction of mean arterial pressure of 40–50 per cent.

The objectives of this study have been to compare and to contrast, in the monkey, the degree of pathological and electrical disturbance of the brain produced by a controlled vascular lesion (permanent occlusion of the middle cerebral artery), under normotensive, anemically induced, and chemically induced hypotensive conditions.

MATERIALS AND METHODS

The middle cerebral artery of the monkey (Macaca mulatta) was permanently occluded and divided at its origin in a manner that has been well standardized and described elsewhere. There was some modification of the technique. Instead of an osteoplastic craniotomy, the procedure was carried out through a large subtemporal craniectomy. Although the artery can be satisfactorily exposed and divided through a small bony opening, a bony decompression of at least 3 cm. diameter was found necessary to prevent death of the animal from cerebral edema associated with the infarction.

All manipulations of the skin and temporalis muscle were done with the electro-surgical unit to reduce bleeding to a minimum. For EEG recording, a Type A, 8 channel Offner machine was used. Recording was carried out from both sides of the head during the operation. This was done through phonograph needle electrodes driven into the skull above the bony opening on the operated side, and from sub-galeal needle electrodes contralaterally. The disposition of these electrodes was as has been described previously. Records were made at intervals in the postoperative period, employing the subgaleal needle electrodes.

Blood pressure was measured every few minutes through a plastic cannula inserted into the femoral or common iliac artery and connected to a mercury manometer. Patency was constantly maintained by using a slow continuous high pressure drip of normal saline through the system. This was provided by a modified pressure cooker with a needle valve at the outlet. There was no need for anticoagulants. Blood was removed or infused through this cannula when necessary. An additional cannula was placed in a leg vein for the introduction of drugs. The circle of Willis was approached by an overhanging head technique, thus eliminating the need for intravenous sucrose to facilitate exposure. The middle cerebral artery was dissected free from its covering of arachnoid and cut between clips placed as close to its origin as possible.

Three groups of animals were studied:

1) Normotensive (5 animals). In this, the control group, the blood pressure was not permitted to fall, blood transfusion or dextran being given, as necessary.

2) Anemic Hypotensive (6 animals). In this group, the blood pressure was lowered
by bleeding to 60–80 mm. Hg. This was accomplished over a period of 10–20 minutes in most instances. Following varying periods of time, the blood pressure was returned to above 100 mm. Hg or to normal, by transfusion.

3) Arfonad Hypotensive (10 animals). In this group, the drug Arfonad* (RO 2–2222) was given to reduce the blood pressure. The agent, a thiophanium derivative, was chosen in preference to the methionium compounds because its effect is supposed to be more certain and transient. This allows considerable minute-to-minute control by intravenous drip and a prompt return to normal on stopping the infusion, without the use of vasodepressor substances.14 In our experience, several animals were resistant to the drug, showing a slight drop or none at all under anesthesia. This was true despite the use of doses larger than those recommended10 and after which some of the animals stopped breathing. An initial dose of 5–10 mg./kg. in 100 cc. was given as an intravenous drip and supplemental doses were given if necessary. In this group the average rate of blood pressure fall was 2.4 mm. Hg/minute.

The operating table was kept level, in order to eliminate the added effect of postural ischemia.

Following the hypotensive period, the blood pressure was returned to 100 mm. Hg or normal by stopping the drug and by giving dextran, neosynephrine, or ephedrine if necessary. The rise in blood pressure was not as prompt or controllable as in the anemic group, and, as a result, the hypotensive period was frequently somewhat prolonged.

The animals were followed in the postoperative period for from 3–21 days. Animals surviving less than 8 days were not included in the series to insure adequate time for evidence of infarction to appear. The maximum survival time permitted was 3 weeks. At death, the position of the clips was verified, the carotid arteries were perfused with formalin, and a week later the brain was sectioned. The gross extent of softening was plotted on standard diagrams and microscopic sections were taken for check.

The shorter survival time in some animals was probably caused by massive infarcts approaching the third ventricle, or by gangrene resulting from ligation of the principal artery to the lower limb. Because of the latter complication, it was felt that no accurate appraisal of the degree of hemiplegia could be made.

RESULTS

The results are discussed under two headings: pathologic and electroencephalographic. The blood pressure fall in mm. of mercury and the percentage fall this represented, as well as the duration of the hypotension is shown in Table 1.

PATHOLOGIC

A) Normotensive. The resulting infarcts were similar to those obtained previously, but were slightly less extensive. Typical examples are shown in Fig. 1. Anteriorly, the head of the caudate nucleus was only slightly involved, sometimes spared, and the cortex was involved only in its inferolateral aspect. The damage usually did not extend above the fissure of Sylvius, and at the thalamic level involved the basal ganglia not at all, or

* Supplies of Arfonad were made available by Hoffmann-La Roche Inc., Nutley 10, New Jersey.
TABLE 1

Average mean blood pressure following arterial occlusion and duration before return to normal

<table>
<thead>
<tr>
<th>Blood Pressure (mm. Hg)</th>
<th>Normotensive</th>
<th>Anemic</th>
<th>Arfonad</th>
</tr>
</thead>
<tbody>
<tr>
<td>100+</td>
<td>9-117 mm.</td>
<td></td>
<td>83-110 mm.</td>
</tr>
<tr>
<td></td>
<td>12-116 mm.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>11-105 mm.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1-104 mm.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2-100 mm.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>90-100</td>
<td></td>
<td></td>
<td>34-94 mm. (25%) - 70 min.</td>
</tr>
<tr>
<td>80-90</td>
<td></td>
<td></td>
<td>33-88 mm. (35%) - 100 min.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>31-80 mm. (24%) - 90 min.</td>
</tr>
<tr>
<td>70-80</td>
<td>13-76 mm. (41%) - 90 min.</td>
<td>36-78 mm. (38%) - 100 min.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>20-78 mm. (38%) - 110 min.</td>
<td>25-78 mm. (41%) - 90 min.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>21-70 mm. (26%) - 100 min.</td>
<td>27-73 mm. (37%) - 170 min.</td>
<td></td>
</tr>
<tr>
<td>60-70</td>
<td>17-68 mm. (40%) - 90 min.</td>
<td>24-64 mm. (40%) - 70 min.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>15-65 mm. (51%) - 80 min.</td>
<td>25-60 mm. (50%) - 130 min.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>14-64 mm. (40%) - 70 min.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

# = number of experimental animal
mm. = millimeters Hg mean blood pressure
min. = minutes
% = percentage blood pressure fall

only at their peripheral margin. More posteriorly, softening was slight or absent. In one animal (#2) the total area of infarction was only a few millimeters in extent.

B) Anemic Hypotensive (Fig. 2).

The distribution of the blood pressure responses can be seen in Table 1. The infarcts in 5 of the 6 animals were almost identical in this pressure group. They were characterized by more extensive and more severe softening than in the normotensive group. Anteriorly, there was marked involvement of the entire head of the caudate nucleus and extension of the softening to cover the whole inferior half of the frontal lobe. At the thalamic level, the infarct extended deeply to involve the basal

Fig. 1. Diagrammatic representation of area of infarction in normotensive animals. Density of stippling indicates severity of involvement. (A) Monkey #12. (B) Monkey #11.
ganglia and the structures in the vicinity of the third ventricle. There was extension of the infarction above the Sylvian fissure and a much larger and deeper involvement posteriorly in the inferior parietal region. One animal (#14) showed no infarction, despite a pressure drop to 64 mm. Hg.

C) Arfonad Hypotensive (Fig. 3). As the depressor response could not be so precisely controlled as by exsanguination, the spread of the blood pressure levels was wider and is indicated in Table 1. The areas of involvement were similar to those of the normotensive group but the softening was definitely more marked. The caudate nucleus was softened to about the same degree, but this was present in a greater percentage of animals. Only the inferolateral frontal cortex was involved at this level. At the thalamic level, the infarction did not extend deeply into this structure. There was minimal involvement above the fissure of Sylvius, and posteriorly, the parietal region was only slightly infarcted. The maximum degree of softening was obtained in one animal (#34) in which the blood pressure did not drop appreciably. It should be noted that the variability in extent and severity of the infarction in this group was comparable to that in the normotensive control group.

A direct comparison between the Arfonad and anemic groups can be made in the 60–70 mm. Hg and the 70–80 mm. Hg blood pressure range. In the 70–80 mm. Hg range the percentage blood pressure fall in the anemic group was quite comparable to that in the Arfonad group. The extent and severity of the infarction was clearly less pronounced in the

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**Fig. 2. Diagrams of typical infarcts in anemic hypotensive animals.** (A) Monkey #13: 70–80 mm. Hg pressure range. (B) Monkey #15: 60–70 mm. Hg pressure range.

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**Fig. 3. Diagrams of typical infarcts in Arfonad hypotensive animals.** (A) Monkey #36: 70–80 mm. Hg pressure range. (B) Monkey #34: 60–70 mm. Hg pressure range.
Arfonad group, but this in turn was clearly more pronounced than in the normotensive group.

**ELECTROENCEPHALOGRAPHIC**

The EEG changes were similar to those previously described. The marked lack of correlation between severity of EEG changes and extent of infarction was again noted. Records with minimal or no EEG alteration occurred in each of the three groups as did records with marked loss of normal fast activity, general decrease in amplitude and/or presence of large slow waves.

Seizure discharges were seen in only one of these 21 animals as compared with 10 of 19 monkeys in a previous series. This is of doubtful significance, however, as the total length of recording time in each animal was much less in the present series.

Levels of mean blood pressure as low as 60 mm. Hg in these monkeys did not cause any definite change in the EEG in most of the animals. In the others, the factor of the level of the anesthesia complicates the interpretation. A recent study suggests that the rate of fall of blood pressure is, within limits, more important than the final level in determining EEG changes.

**DISCUSSION**

The present study confirms the generally held impression that hypotension induced by bleeding increases the brain damage produced by occlusion of a major cerebral artery. In the case of occlusion of the middle cerebral artery of the monkey, hypotensive levels of 70–80 mm. Hg, representing blood pressure falls of 26–41 per cent, produced a maximum middle cerebral artery infarct almost identical to that associated with levels of 60–70 mm. Hg, representing blood pressure falls of 46–51 per cent.

The use of a thiophanium derivative, Arfonad, to produce similar levels of hypotension lessened the size of the infarct but did not completely compensate for the hypotension since the resulting infarcts were somewhat more extensive than in the normotensive animals.

It is of some interest, and a little surprising, that the variability in extent and severity of the infarction in the normotensive and Arfonad groups was similar to that of a previous series in which the blood pressure was not measured.

The mechanism of the protection afforded by Arfonad is not completely clear, despite the previously discussed theorizations, as there is some evidence of a considerable drop in cerebral blood flow in humans rendered hypotensive by hexamethonium, despite decreased vascular resistance. Some observers feel that this may be easily compensated for, at least in the normal. Another possible mechanism may be the blockade of pathways that contribute to vasospasm and focal ischemia.

These results may or may not have any significance as regards injury to the brain produced in other ways, such as that associated with surgical
manipulation. Further experimental investigation of this aspect seems indicated. It should be noted, however, that the benefits of increased safety provided by chemical hypotension may far outweigh the disadvantages of slight increase in local tissue damage. Further efforts to define limits of safety in regard both to blood pressure levels and duration of hypotension would seem advisable.

SUMMARY

1) The extent of cerebral damage following occlusion and division of the middle cerebral artery of the monkey under normotensive, anemically induced, and chemically induced hypotension has been compared and contrasted.

2) Whereas anemically induced hypotension resulted in a marked extension of the infarction, similar depression of the blood pressure using Arfonad, resulted in slight but definite additional damage as compared with the normotensive control group.

3) The characteristic electrical changes of infarction were seen in all groups. The changes were not proportional to the size of the infarction but tended to be less severe in the animals receiving Arfonad, as compared with the anemically induced hypotensive group.

4) It seems unlikely that the EEG will be useful in determining when the depth or duration of chemically induced hypotension begins to be hazardous to the brain.

REFERENCES


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