Failure of Prolonged Hypocapnia, Hypothermia, or Hypertension to Favorably Alter Acute Stroke in Primates

JOHN D. MICHENFELDER, M.D.,* AND JAMES H. MILDE†

SUMMARY The effects of induced hypocapnia, hypothermia, and hypertension were surveyed in a primate model of acute stroke during and following a 48-hour period of intensive care. The results were compared to a group of nine control animals previously studied. Hypocapnia (PaCO₂ = 25 torr) was examined in five animals and did not appear to alter the expected mortality, degree of neurological deficit, or frequency and size of infarction. There was, however, a suggestion that the size of infarction may be reduced. Hypothermia (29°C) in five animals had a detrimental effect in that no animals survived following the intensive care period and all had infarction with massive edema. We speculate that hypothermia caused a sufficient increase in blood viscosity as to compromise collateral flow, thereby accounting for this detrimental effect. Induced hypertension (to 20% above control levels) was abandoned after three animals because of severe systemic effects (cardiac failure and pulmonary edema) resulting in death during the period of intensive care.

Introduction
A VARIETY OF MEASURES has been proposed as possibly being therapeutic in the management of acute stroke.1 Recommendations have been variously based upon laboratory investigations, theoretic considerations, and/or clinical impression. Laboratory investigations which attempt to document the effect of such measures in acute stroke can often be criticized for any one of several reasons. Studies of acute stroke in non-primates are vulnerable to retraction, possible brain trauma, substantial disruption of the cranial vault, or insertion of a foreign body. Finally, studies which examine only the acute effects of a proposed therapeutic measure may be misleading, since any observed beneficial effects might be only transient or even ultimately detrimental if the test treatment were continued.

Recognizing the validity of these criticisms, we have studied Java monkeys after occlusion of a middle cerebral artery via a transorbital approach which requires no brain retraction and minimal disruption of the cranial vault. Thereafter, these animals have been maintained for 48 hours in a laboratory-created intensive care environment during which time the test therapeutic intervention is introduced and maintained and following which the effects are examined. Using this preparation, we previously studied the effects of 48 hours of halothane anesthesia and demonstrated a significant beneficial effect in terms of mortality, neurological deficit, and frequency and size of infarction.2 The present report details our observations in a survey of three other proposed therapeutic interventions: hypocapnia, hypothermia, and hypertension.

Methods
Thirteen Java monkeys of both sexes and weighing 1.0 to 1.9 kg were studied. The protocol for the study is summarized in table 1. The monkeys were studied in groups of two
or three and were ultimately divided into three final groups as determined by the test treatment. In all monkeys, anesthesia for the surgical preparation was induced and maintained with halothane (1%). Endotracheal intubation was accomplished following muscle paralysis with succinylcholine (40 mg). Ventilation was controlled with a small Harvard pump. A femoral artery and vein were exposed and cannulated for pressure measurements, blood samples, and drug and fluid administration. A urinary catheter and rectal thermometer were inserted and secured. The right middle cerebral artery (MCA) was exposed via a transorbital approach using the operating microscope. A miniaturized Mayfield clip was placed across the MCA just distal to the first anterior branch which supplies an anterior-inferior portion of the frontal lobe. The body of the clip remained extradural. Thereafter, halothane was discontinued and the animals were paralyzed with pancuronium (0.05 mg per kilogram), and sedated with diazepam (0.1 mg per kilogram) intravenously. The dural incision was sealed with Surgicel and glue (alpha cyanoacrylate) and the wound was closed. Streptomycin (100 mg) and penicillin (300,000 units) were administered intramuscularly. With completion of surgery, a 48-hour period of intensive care was initiated with fluids, drugs, monitors, and nursing care as indicated in table 1. The monkeys were continuously attended by two technicians under the supervision of a physician.

The test treatment was initiated 30 minutes after the MCA had been occluded. Five monkeys were maintained hypocapnic (Paco₂ = 25 torr), five hypothermic (29°C), and three hypertensive (20% above control levels) for the 48-hour period of intensive care or until death. In all other respects, the 13 monkeys were managed identically (table 1). Hypocapnia (five animals) was rapidly achieved (within five minutes) by an increase in both tidal volume and respiratory rate. Hypothermia (five animals) was induced and maintained with surface cooling techniques (ice bags, alcohol sponging) and the target temperature of 29°C was achieved within 15 to 25 minutes of initiating cooling. These animals were ventilated in a manner to maintain Paco₂ at 35 to 40 torr as measured at 37°C (thus, corrected Paco₂ values were all below 30 torr). Shivering was rigorously prevented by additional doses of pancuronium as needed. Hypertension (three animals) was rapidly achieved (< five minutes) initially with an infusion of phenylephrine (0.05%) delivered by a Harvard pump. When resistance to phenylephrine developed, levarterenol (0.05%) was next infused. This was followed by angiotensin (0.05%) and finally adrenalin (0.02%).

In the surviving monkeys, all drugs, fluids, and test treatments were discontinued after 48 hours. If spontaneous ventilation was judged adequate, the endotracheal tube was removed, all catheters were removed, and monitoring was discontinued. These monkeys were returned to their cage for observation. If spontaneous ventilation remained inadequate (despite total reversal of muscle relaxants), the monkeys were allowed to die (usually within two to three hours of discontinued intensive care measures). The remaining monkeys were observed for five days (or until death) and neurological deficits were graded daily by two independent observers. After five days (seven days following MCA occlusion...
The size of each cerebral hemisphere was measured by volume displacement before sectioning into 5-mm coronal slices. The end area of infarction in each slice was measured with a grid, and the total size of infarction was computed and then expressed as a percent of that hemisphere's volume.

The mortality, frequency, and degree of neurological deficit and frequency and magnitude of infarction were then compared in each of the three treatment groups to a control group of nine monkeys (previously reported). The monitored variables among the three groups were comparable and similar to control animals during the 48-hour period of intensive care (table 2). Differences between the groups were those accounted for by the different test treatments. Thus, in the hypothermic animals, body temperature, heart rate, and \( \text{Paco}_2 \) values (corrected for temperature) all differed significantly from the previously reported control group. In the hypocapnic animals, only \( \text{Paco}_2 \) differed significantly. In the hypertensive group, MAP was not tabulated because of the large variability that occurred in these three animals (see fig. 1).

Comparing mortality, neurological deficit, and infarction to control animals (tables 3 and 4) reveals little or no therapeutic merit for any of the test treatments. Results in the hypocapnic animals suggest a similar mortality rate, degree of neurological deficit, and frequency of infarction as seen in control animals. In two of these animals, gross infarction was not found, but edema, softening, and shift of midline structures was found in each. Each of these had a mild neurological deficit. In the remaining three, the infarcts were small despite moderate to marked neurological deficits. Compared to control animals there is a suggestion that the size of infarction may be reduced by hypocapnia.

Hypothermia and hypertension were clearly detrimental. None of the hypothermic animals survived more than three hours following the 48 hours of intensive care (one died at 39 hours) and all had cerebral infarction with massive edema. None of the hypertensive animals survived even the period of intensive care with death occurring at 15, 22, and 39 hours, respectively. Two of these animals had definite cerebral infarctions and the third had cerebral edema only. Death in the hypertensive animals resulted from pulmonary complications secondary to congestive failure. At necropsy, all showed massive atelectasis, pulmonary hemorrhagic edema, and pericardial effusions. In each case, these animals had progressive resistance to the vasopressor used. With initiation of a different vasopressor, a brief pressor effect was usually observed (fig. 1) but was evanescent with ultimate uncontrolled hypotension and death. In none of the animals

![Graph of Blood pressure record of one monkey (B3) in the hypertensive group. An initial infusion of phenylephrine resulted in the desired 20% increase in mean arterial pressure. This was maintained (with an increase in infusion rate) for about six hours. Thereafter, levaterenol had no pressor effect, while a brief response to angiotensin II was observed. Terminally (after 12 hours), adrenaline was without particular effect and a repeat infusion of phenylephrine was only briefly effective.](image-url)

**Table 2** 48-Hour Values in Four Monkey Groups (Mean ± SE)

<table>
<thead>
<tr>
<th>Group</th>
<th>No. monkeys</th>
<th>MAP (mm Hg)</th>
<th>CVP (mm Hg)</th>
<th>HR (beats/min)</th>
<th>Temp (°C)</th>
<th>Ht (g/dl)</th>
<th>( \text{Paco}_2 ) (mm Hg)</th>
<th>Paco, (mm Hg)</th>
<th>pH</th>
<th>BB.+ (mEq/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>9</td>
<td>98</td>
<td>2</td>
<td>196</td>
<td>37.1</td>
<td>10.9</td>
<td>160</td>
<td>35</td>
<td>7.55</td>
<td>53</td>
</tr>
<tr>
<td>Hypocapnia</td>
<td>5</td>
<td>102</td>
<td>2</td>
<td>216</td>
<td>37.1</td>
<td>10.8</td>
<td>151</td>
<td>23</td>
<td>7.61</td>
<td>53</td>
</tr>
<tr>
<td>Hypothermia</td>
<td>5</td>
<td>3</td>
<td>0</td>
<td>186</td>
<td>36.9</td>
<td>9.7</td>
<td>103</td>
<td>36</td>
<td>7.48</td>
<td>52</td>
</tr>
<tr>
<td>Hypertension</td>
<td>3</td>
<td>—</td>
<td>3</td>
<td>11</td>
<td>0.0</td>
<td>1.5</td>
<td>10</td>
<td>1</td>
<td>0.02</td>
<td>1</td>
</tr>
</tbody>
</table>

**Table 3** Five-Day Survival, Neurological Deficit, and Size of Infarction Following 48 Hours’ Intensive Care in Control Monkeys

<table>
<thead>
<tr>
<th>No.</th>
<th>Survived</th>
<th>Neurological deficit</th>
<th>% Infarct</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Yes</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>No</td>
<td>4</td>
<td>24</td>
</tr>
<tr>
<td>3</td>
<td>Yes</td>
<td>2-3</td>
<td>&lt;1</td>
</tr>
<tr>
<td>4</td>
<td>No</td>
<td>4</td>
<td>100</td>
</tr>
<tr>
<td>5</td>
<td>Yes</td>
<td>0-1</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>Yes</td>
<td>2-3</td>
<td>2</td>
</tr>
<tr>
<td>7</td>
<td>No</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>8</td>
<td>Yes</td>
<td>1-2</td>
<td>18</td>
</tr>
<tr>
<td>9</td>
<td>Yes</td>
<td>3</td>
<td>20</td>
</tr>
</tbody>
</table>

FIGURE 1. Blood pressure record of one monkey (B3) in the hypertensive group. An initial infusion of phenylephrine resulted in the desired 20% increase in mean arterial pressure. This was maintained (with an increase in infusion rate) for about six hours. Thereafter, levaterenol had no pressor effect, while a brief response to angiotensin II was observed. Terminally (after 12 hours), adrenaline was without particular effect and a repeat infusion of phenylephrine was only briefly effective.
was a pressure greater than 20% above control mean arterial pressure produced at any time.

Discussion

Using a similar protocol in this same stroke model we had previously demonstrated a beneficial effect of prolonged barbiturate anesthesia. In that study nine control monkeys (table 3) were compared to nine pentobarbital-anesthetized monkeys and the observed differences in mortality, neurological deficit, and infarction approached or exceeded statistical significance (p < 0.06). It is unlikely that significant differences would have been demonstrable had fewer animals been studied. In the present study, because of both the expense and the scarcity of primates for laboratory investigation, we elected to survey other possible therapeutic interventions which have been suggested (or clinically used) in the treatment of acute stroke. The hope was to be able to identify with only a relatively few animals the suggestion of either a beneficial or detrimental effect. Any strong suggestion of a beneficial effect would have warranted an expanded study. There was no such suggestion.

Hypocapnia

In 1968, Soloway et al. reported an apparent beneficial effect of hypocapnia in acute strokes in dogs. In that study cerebral infarction as produced by MCA occlusion was significantly lessened if the animals were maintained hypocapnic for several hours at the time of MCA occlusion. Several mechanisms have since been postulated whereby hypocapnia might be beneficial. These include increased flow to the ischemic brain (inverse steal effect), decreased flow to the normal brain and, hence, a decrease in intracranial pressure, partial titration of the cerebral lactic acidosis by the blood alkalosis, and a possible increased resistance of cerebral tissue to hypoxia due to hypocapnia per se. The results reported by Soloway et al. have not been consistently confirmed by other investigators working with different animal models of acute stroke. In common, however, these studies all examined the effects of hypocapnia for a period of a few hours only. In 1973, Christensen et al. reported the failure of hypocapnia in a clinical study where acute stroke patients were maintained hypocapnic for three days. As with any such clinical study, homogeneity of control and experimental groups was lacking and on that basis, the results may be questioned. In the present primate study, homogeneity existed to the degree that it is experimentally possible. A 48-hour period of hypocapnia did not appear to favorably alter the ischemic consequences of MCA occlusion. Certainly in terms of mortality and neurological deficit, no benefit is apparent. There is a suggestion that the size of infarction may be reduced by hypocapnia in that none of these animals had an infarct larger than 3% while four of nine control animals had large infarctions. To determine whether or not this suggested difference is a real one would likely require many more animals in both control and experimental groups. We elected not to pursue this question further.

Hypothermia

The consistent detrimental effect of hypothermia was unexpected. In the absence of life-support measures, all of these animals died; all had massive cerebral edema with underlying infarction. Since none of these animals survived more than 51 hours, comparison of the percent infarction to that in control animals which survived seven days is probably misleading. Had the hypothermic animals survived the full seven days, the measured infarcts would likely have been larger.

An explanation for the detrimental effect of hypothermia is not immediately apparent. These animals were hemodynamically stable during the period of intensive care and ventilation was well maintained. Acid-base balance was essentially normal and the low Paco₂ (24 torr) that we maintained was assumed to be appropriate for a body temperature of 29°C. At this temperature cerebral metabolic rate (as well as whole body) should be reduced approximately 50%. Assuming no other effects, such a reduction in O₂ requirements should have protected, at least partially, the ischemic brain.

The potential cerebral protective effect of hypothermia is well established. Total cerebral ischemia or anoxia is tolerated for increasing periods as temperature is lowered. The relationship of O₂ consumption to temperature is essentially exponential, such that for every 8° to 10°C reduction in temperature O₂ consumption is halved and tolerance to a period of anoxia is doubled. Thus, in a circumstance of temporary complete cerebral ischemia protection by hypothermia is unquestioned.

In the circumstance of prolonged incomplete focal ischemia, a protective effect of hypothermia is often assumed and has been reported in one canine study. However, differences between canine and primate collateral circulations may be sufficient to account for a different effect. In the squirrel monkey following MCA occlusion, the collateral flow is initially about 40% of the pre-occlusion flow and is maintained for at least two hours. In the absence of therapeutic intervention, infarction occurs some time after two hours, presumably secondary to progressive edema and failure of the collateral circulation. Reasonably, if the O₂ requirements of the ischemic brain could be significantly reduced so as to match the reduced oxygen

<table>
<thead>
<tr>
<th>Table 4</th>
<th>Five-Day Survival, Neurological Deficit and Size of Infarction in Monkeys Following 48 Hours of Intensive Care</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypocapnia</td>
<td>Hypothermia</td>
</tr>
<tr>
<td>No.</td>
<td>Survived</td>
</tr>
<tr>
<td>1</td>
<td>No</td>
</tr>
<tr>
<td>2</td>
<td>Yes</td>
</tr>
<tr>
<td>3</td>
<td>Yes</td>
</tr>
<tr>
<td>4</td>
<td>Yes</td>
</tr>
<tr>
<td>5</td>
<td>Yes</td>
</tr>
</tbody>
</table>
delivery by way of the collaterals, infarction should be preventable. On this basis, one would predict that a reduction in brain temperature to 29°C would prevent infarction as long as collateral flow was maintained. Since an opposite effect was observed, we conclude that collateral circulation failed, at least in part, because of hypothermia itself. We speculate that this might be accounted for by the increase in blood viscosity that accompanies a temperature reduction with a consequent reduced flow through the small collateral vessels. If this is correct, then hypothermia might only be protective if combined with hemodilution so as to maintain or even reduce the normal blood viscosity.

**Hypertension**

This protocol was abandoned after only three animals because of the disastrous systemic consequences of artificially maintained hypertension in this species. Whether such an effect might be expected in other primates is unknown. We selected an alpha agonist (phenylephrine) as our initial vasopressor on the assumption that this would have the least deleterious cardiac effects. This was effective for a period of 6 to 20 hours but “resistance” was eventually encountered and thereafter a variety of vasoactive drugs (levarterenol, angiotensin, and adrenaline) were only briefly effective. Based upon the findings at necropsy, we suspect that the development of “resistance” in fact signaled the onset of cardiac failure presumably due to the prolonged period of an artificially induced increase in peripheral resistance and, hence, in the afterload on the heart. Whether the same ultimate effect would have been seen had we initially used a mixed vasopressor, i.e., an alpha and beta agonist, is unknown.

The theoretical merit of chronic induced hypertension in incomplete focal ischemia is based upon the assumption that flow in ischemic regions is pressure-dependent. Experimentally, this is demonstrable on an acute basis and clinically transient periods of hypertension are commonly induced during such procedures as carotid endarterectomy. To our knowledge, chronic induced hypertension has not been studied experimentally and reports of clinical efficacy are anecdotal only.

The results in the three animals of this study do not permit any meaningful conclusions. Any possible beneficial cerebral effects were overwhelmed by the deleterious systemic effects. That such might be expected to occur in man is not suggested by clinical experience with prolonged vasopressor therapy. However, for the most part, such therapy has been used for the maintenance of normal blood pressure rather than the production of chronic hypertension. It is reasonable to expect the latter may introduce undesirable systemic effects.

**Conclusions**

The results of this study offer no support for the use of prolonged hypocapnia, hypothermia, or hypertension in the management of acute stroke. Whereas hypocapnia appeared to have little or no beneficial effect, both hypothermia and hypertension had detrimental effects. Among other suggested therapeutic interventions, only barbiturate anesthesia has been consistently demonstrated to favorably alter the ischemic consequences of middle cerebral artery occlusion in experimental animals.

**References**

Failure of prolonged hypocapnia, hypothermia, or hypertension to favorably alter acute stroke in primates.
J D Michenfelder and J H Milde

Stroke. 1977;8:87-91
doi: 10.1161/01.STR.8.1.87
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1977 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/8/1/87

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org/subscriptions/