Canine Cerebral Function and Blood Flow after Complete Cerebral Ischemia: Effect of Head Position

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It has been reported that animals exposed to relatively “bloodless” cerebral ischemia have improved cerebral function post-ischemia. This suggests the possibility that large variations in cerebral blood volume during complete ischemia might affect outcome following reperfusion. The purpose of this study was to determine whether changes in dog head position (and therefore cerebral blood volume) during complete cerebral ischemia produced by occluding the aorta and vena cava affect post-ischemic cerebral blood flow (CBF), cerebral metabolic oxygen requirements (CMRO₂), or neurologic outcome. Two dogs were transfused with ¹¹¹In-labeled red blood cells. Gamma camera images taken during complete cerebral ischemia showed 45-degree head-up dogs to have 50% of the cranial blood volume of a 10-degree head-down dog. CBF and CMRO₂ 90 min post-ischemia were not significantly different between the head-up and head-down groups in the 14 dogs studied. There was also no significant difference in neurologic outcome at 48 h post-ischemia between head-up and head-down dogs. The authors conclude that head position during complete cerebral ischemia has a major effect on cranial blood volume, but no effect on post-ischemic CBF, CMRO₂, or neurologic outcome. (Key words: Brain; blood flow; ischemia. Heart: cardiac arrest.)

There are several reasons to suspect that the presence of stagnant, anoxic blood within the cerebral vasculature during a period of complete global ischemia (i.e., cardiac arrest) might contribute to the resulting brain damage. Neely and Youngman produced a relatively “bloodless” ischemia in dogs and reported improved outcome following up to 25 min of such ischemia. Suppan and Olson flushed the cerebral vasculature of cats with lactated Ringer’s solution during complete ischemia and reported improved outcome. Hallenbeck et al. showed that the presence or absence of certain blood elements following complete ischemia could influence post-ischemic cerebral blood flow (CBF). We observed that the greatest concentration of histoplastic lesions following complete ischemia in primates was in the dependent (posterior) regions of the brain. Finally, Fischer and Ames suggested that gravitational pooling of stagnant blood might contribute to impaired reperfusion. All of this suggests a possible deleterious interaction between stagnant blood and the brain, which could be either mechanical, biochemical, or both acting on either the cerebral vasculature, the cerebral tissue, or both. It follows that maneuvers which might reduce cerebral blood volume during ischemia might improve neurologic recovery. Elevation of the head during ischemia should reduce cerebral blood volume and would be clinically applicable during cardiopulmonary resuscitation.

The purpose of this study was to determine whether changes in dog head position (and therefore cerebral blood volume) during complete cerebral ischemia affects post-ischemic CBF, cerebral metabolic oxygen requirements (CMRO₂), or neurologic outcome.

Methods

Twenty-seven unmedicated, fasting adult female mongrel dogs, weighing 11.0 to 18.5 kg, were studied in the prone position. The protocol was approved by the institutional Animal Research Committee. Two dogs were used to determine the effect of head position on cranial blood volume. Fourteen dogs were used to study the effect of head position on post-ischemic CBF and CMRO₂. Eleven dogs were used to study the effect of head position on neurologic function 48 h post-ischemia.

In the two dogs used to study cranial blood volume, anesthesia was induced and maintained with pentobarbital 40 mg/kg. After intubation, ventilation was controlled with a Harvard® pump. Through a right-sided thoracotomy in the fourth interspace, umbilical tapes were placed around the ascending aorta, inferior vena cava, and superior vena cava above the azygos vein. Ten milliliters of ¹¹¹In-labeled red blood cells were transfused. Ventilation was adjusted to PaO₂ 100 ± 20 mmHg (mean ± SE); PaCO₂ 40 ± 2 mmHg; buffer base 40 ± 1 mEq/l during the next 10 min. A computerized gamma camera (Siemens® Pho-Gamma V) with a 10-min image time was used to determine relative cranial blood volumes while the dog’s head was in various positions during ischemia.

Dog 1 was initially placed with the head at heart level, and a 10-min anterior image was made (control). Thereafter, the dog was placed in a 45-degree head-up position for another 10-min image. Complete cerebral ischemia was produced by simultaneously occluding the aorta and the inferior vena cava and then (5 s later) the superior vena cava. During occlusion, 10-min gamma camera images were made in the 45-degree head-up, 10-degree

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head-up, and 10-degree head-down positions. Dog 2 was initially positioned with the head at heart level, and a 10-
min image was made (control). The dog was then placed in a 10-degree head-down position for another 10-min
image. To produce complete cerebral ischemia, the su-
perior vena cava of this dog was occluded 2 s before the
simultaneous occlusion of the aorta and inferior vena cava.
During occlusion, 10-min gamma camera images were
made in the 10-degree head-down, 10-degree head-up,
and 45-degree head-up position.

Fourteen dogs were used to study the effect of head
position on post-ischemic CBF and CMRO2. Six dogs were
studied after complete cerebral ischemia in a 45-degree
head-up position. Eight dogs were studied after complete
cerebral ischemia in a 10-degree head-down position. In
all of the head-up dogs and four of the head-down dogs,
a fixed interval of 10 min of occlusion was used; in the
remaining four head-down dogs, the occlusion time was
determined by the time of onset of isoelectric electroen-
cerephalogram (EEG). Once this occurred, occlusion was
maintained for another 9 min 25 s.

In these dogs, anesthesia was induced and maintained
with 1% halothane in N2O (60–70%) and O2. Succinyl-
choline 40 mg was given before intubation and continually
infused at 150 mg/h to maintain paralysis. Ventila-
tion was controlled with a Harvard® pump. Cannulae
were placed in a femoral artery for pressure measurements
and in a femoral vein for drug and fluid administration (nor-
mal saline). Right-sided intercostal nerve blocks with
0.25% bupivacaine were performed. Through a right-
sided thoracotomy in the fourth interspace, umbilical
tapes were placed around the ascending aorta, inferior
vena cava, and superior vena cava above the azygos vein.
Heparin 3,000–4,000 U/kg was given, and the sagittal
sinus was exposed, isolated, and cannulated for direct
measurement of CBF.8,9 Arterial and sagittal sinus blood
O2 contents were calculated from measurements of oxy-
hemoglobin concentration (IL 282 CO-oximeter®) and
O2 tension. Four-lead bilateral EEG was obtained
with electrodes glued to the skull. Body temperature was
measured with an esophageal thermistor, and brain tem-
perature was measured with a parietal epidural thermistor.
EEG and intracranial pressure (Ladd® ICP monitor) were
also measured. All wound edges were infiltrated
with 0.25% bupivacaine, the ears were plugged with cotton,
and the eyes were taped shut. After all surgery was com-
pleted, the halothane was discontinued. During the next
20 min the following variables were adjusted: tempera-
ture, 37 ± 0.2°C; PaO2, 150 ± 9 mmHg; PaCO2, 38 ± 1
mmHg; and buffer base, 40 ± 1 mEq/l. Five minutes
before complete cerebral ischemia, N2 was substituted
for N2O. Pre-ischemic measurements of CBF, arterial–sagittal
sinus blood O2-content differences, and blood glucose10
were done with the dog level and again in either the head-
up or head-down position. These did not differ signifi-
cantly and, therefore, control was considered the average
of measurements taken in both positions. Normal saline
was infused as necessary to maintain normal blood pres-
sure. CMRO2 was calculated as the product of CBF and
the blood O2-content difference.

Complete cerebral ischemia was produced in the head-
up dogs by simultaneously occluding the aorta and the
superior and inferior vena cavae. The head-down dogs
had the superior vena cava occluded 2 s before the si-
multaneous occlusion of the aorta and inferior vena cava.
After occlusion the dog was ventilated with 100% O2.
Occlusion was verified by a mean arterial pressure of zero,
onset of an isoelectric EEG, and cessation of flow from
the sagittal sinus. Just prior to release of the tapes (the
caval tapes were released 15–20 s prior to the aortic tape),
the dog was placed in the level position, and 100 ml nor-
mal saline with 30 mEq sodium bicarbonate was given.
As necessary, epinephrine was given to a few dogs in each
group to maintain blood pressure after release of the
tapes. As soon as vital signs were stable (1–3 min post-
ischemia), N2 was added so that PaO2 was 135 ± 5 mmHg.
The following measurements were done at 1, 3, 15, 35,
60, and 90 min post-ischemia: mean arterial pressure,
PaO2, PaCO2, pH, buffer base, CBF, CMRO2, and blood
glucose. EEG was recorded continually post-ischemia.

Ten dogs were used for neurologic function studies
following complete cerebral ischemia. Five dogs were
studied after ischemia while in a 45-degree head-up
position, and five dogs were studied after ischemia while in
a 10-degree head-down position. With the exceptions that
no surgery was done on the head and needle electrodes
were used for EEG, the preparation of these dogs and the
production of complete cerebral ischemia for 9 min 25 s
after onset of an isoelectric EEG were the same as the
CBF study dogs. As soon as vital signs were stable (1–3
min after aortic unclamping), N2 was added so that
PaO2 was 130 ± 5 mmHg, and the thoracotomy was closed.
Ventilation was controlled until spontaneous ventilation
was adequate (PaCO2 < 45 mmHg). Blood gas measurements
were repeated 30 min following extubation and, if ade-
quate (PaO2 > 70 mmHg, PaCO2 < 45 mmHg), the
dog was returned to its cage. If necessary, intravenous
fluids were administered 12–36 h following ischemia.
Forty-eight hours after ischemia, the dogs were evaluated
neurologically and assigned to one of four groups.11
Group 1 dogs (no damage) ate and behaved normally with
fully coordinated movements. Group 2 dogs (moderate
damage) could stand alone but were ataxic or exhibited
blindness. Group 3 dogs (severe damage) could not stand
alone or were comatose. Group 4 dogs died within 48 h.
The surviving dogs were killed and examined for post-
thoracotomy complications.

The Fisher exact test was used for statistical comparison
of neurologic outcome between head-up and head-down
groups. For all other comparisons between head-up and
head-down dogs, Student's t test for unpaired data was used. For comparison between pre- and post-ischemic values in the same group, Student's t test for paired data was used. A P value of less than 0.05 was considered significant. All mean values are reported with the standard error of the mean (SEM).

Results

Effect of Head Position on Cerebral Blood Volume

In two dogs pre-ischemic gamma emissions from the cranial area while the dogs were level were similar (fig. 1). Both dogs received an equivalent amount of $^{111}$In (315 $\mu$Ci in dog 1 vs. 312 $\mu$Ci in dog 2). When either dog was placed in a 45-degree head-up position, gamma emissions during ischemia decreased to 51% of control. Dog 2 was placed in a 10-degree head-down position prior to ischemia. During ischemia its cerebral gamma emissions increased to 168% of control. Dog 1 was initially placed head-up prior to ischemia. Without release of the aortic and venae cavae clamps, it was placed in a 10-degree head-down position where gamma emissions were no different than control. Both dogs, while head-up, had 30% of the gamma emissions of dog 2 that was initially placed in the head-down position (figs. 1 and 2).

CBF and CMRO2 Studies

There were no significant differences in any variables between the head-down dogs exposed to 10 min of ischemia and those exposed to 9 min 25 s of ischemia after the onset of an isoelectric EEG. These dogs were therefore combined into one head-down group. There were also no significant differences in blood gases between the head-up and head-down groups at any time pre- or post-ischemia (table 1). Except for an increased CBF in the head-up group 15 min post-ischemia ($P < 0.05$), there were no significant differences in CBF or CMRO2 between head-up and head-down groups pre- or post-ischemia (figs. 3 and 4). CBF and CMRO2 were significantly increased in both groups at 1-min post-ischemia. By 35 min, CMRO2 and CBF were significantly decreased in both groups. There was no further change from 35 to 90 min. At 90 min CMRO2 was 84% of control in both groups; CBF ranged from 52% to 62% of control.

The EEG became isoelectric at $28 \pm 3$ s in the head-up dogs and $57 \pm 14$ s in the head-down dogs. EEG activity returned at $17 \pm 4$ min in the head-up versus $16 \pm 4$ min in the head-down dogs. These differences were not statistically significant.

Neurologic Studies

There was no significant difference in the neurologic outcome between the head-up and head-down group at 48 h post-ischemia. In addition to the animals shown in table 2, one head-down dog was excluded from study after developing a pneumothorax and dying prior to 48 h.

Discussion

The evidence which suggests that areas of the brain exposed to static blood or certain blood elements during complete cerebral ischemia sustain more damage than areas not so exposed warrants more detailed consideration. Neely and Youmans produced complete cerebral ischemia in dogs by increasing intracranial pressure above...
HEAD POSITION AND POST-ISCHEMIC CEREBRAL FUNCTION

TABLE 1. Intracranial Pressure (ICP), Mean Arterial Pressure (MAP), Blood Glucose, Arterial Blood Gases, and Sagittal Sinus Pco2 for CBF and CMRO2 Studies in Dogs (means ± SEM)

<table>
<thead>
<tr>
<th>State</th>
<th>Position</th>
<th>n</th>
<th>ICP (mmHg)</th>
<th>MAP (mmHg)</th>
<th>Glucose (mg/dl)</th>
<th>Pco2 (mmHg)</th>
<th>Pco2 (mmHg)</th>
<th>pH</th>
<th>Buffer Base (mEq/l)</th>
<th>Po2o (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-ischemia</td>
<td>Head-up</td>
<td>6</td>
<td>2 ± 1</td>
<td>153 ± 8</td>
<td>112 ± 20</td>
<td>150 ± 13</td>
<td>38 ± 1</td>
<td>7.32 ± 0.01</td>
<td>40 ± 1</td>
<td>42 ± 1</td>
</tr>
<tr>
<td></td>
<td>Head-down</td>
<td>8</td>
<td>6 ± 1</td>
<td>113 ± 7</td>
<td>108 ± 8</td>
<td>147 ± 5</td>
<td>38 ± 1</td>
<td>7.32 ± 0.01</td>
<td>40 ± 0</td>
<td>42 ± 1</td>
</tr>
<tr>
<td>5 min post-</td>
<td>Head-up</td>
<td>5</td>
<td>15 ± 7</td>
<td>108 ± 19</td>
<td>250 ± 33</td>
<td>375 ± 41</td>
<td>54 ± 7</td>
<td>7.14 ± 0.04</td>
<td>34 ± 2</td>
<td>78 ± 16</td>
</tr>
<tr>
<td>ischemia</td>
<td>Head-down</td>
<td>8</td>
<td>19 ± 3</td>
<td>110 ± 12</td>
<td>218 ± 23</td>
<td>334 ± 56</td>
<td>53 ± 4</td>
<td>7.25 ± 0.04</td>
<td>42 ± 1</td>
<td>95 ± 14</td>
</tr>
<tr>
<td>90 min post-</td>
<td>Head-up</td>
<td>6</td>
<td>2 ± 1</td>
<td>106 ± 6</td>
<td>156 ± 21</td>
<td>143 ± 15</td>
<td>38 ± 1</td>
<td>7.37 ± 0</td>
<td>43 ± 1</td>
<td>25 ± 2</td>
</tr>
<tr>
<td>ischemia</td>
<td>Head-down</td>
<td>8</td>
<td>1 ± 1</td>
<td>99 ± 10</td>
<td>148 ± 17</td>
<td>129 ± 6</td>
<td>38 ± 1</td>
<td>7.30 ± 0.01</td>
<td>39 ± 1</td>
<td>27 ± 2</td>
</tr>
</tbody>
</table>

systolic blood pressure. They found that dogs exposed to this presumed "bloodless" ischemia for less than 25 min were able to see, stand, and hear the following day. They speculated that the relative lack of blood within the brain during the period of ischemia may have a protective effect. Hossmann and Olsson9 flushed the cerebral vasculature of cats with nonoxygenated lactated Ringer’s solution during complete cerebral ischemia. These animals had a greater rate and degree of electrophysiologic recovery than animals not flushed with lactated Ringer’s. Hossmann and Kleihues10 postulated that the reversibility of ischemic brain damage may be related to the composition of blood and cerebral spinal fluid. Hallenbeck et al. 8 found that post-ischemic cerebral reperfusion could be improved by filtering blood through a glass-wool filter prior to complete cerebral ischemia. If the dogs were given Factor VIII von Willebrand Factor prior to ischemia, the enhancement of post-ischemic reperfusion was nullified. They concluded that activity deleterious to post-ischemic reperfusion primarily resides in the Factor VIII/von Willebrand Factor fraction of cryoprecipitate. We produced complete ischemia in supine primates for 17 min and evaluated the efficacy of nimodipine therapy during the post-ischemic period.4 Whether treated or not, the histopathologic findings were almost exclusively limited to the posterior (dependent) circulation. These diverse observations suggest the possibility that shifting blood away from the brain during complete cerebral ischemia may offer some cerebral protection. Changing head position during cardiopulmonary resuscitation would be a clinically applicable way of potentially changing intracerebral blood volume.

A radioisotope-labeled red blood cell method7 was used to determine relative cranial blood volume. With the gamma camera at a fixed position in relation to the head, gamma emissions detected during a fixed time period are directly related to the blood volume under the camera. The two dogs received the same dose of radioisotope and had the same number of gamma emissions from the head as control; therefore, gamma emissions obtained from the head-up dog should be directly comparable with gamma emissions from the head-down dog without applying correction factors. Head-up dogs had 30% of the gamma emissions and, thus, 30% of the cranial blood volume of the head-down dog. This methodology is not sensitive enough to detect where blood volume changes are occurring in the intracranial vasculature, and some minor extracerebral contamination also occurs. It does show that position has a major effect on cranial blood volume.

FIG. 3. CMRO2 values (means ± SEM) pre-ischemia and after complete cerebral ischemia for head-up and head-down dogs. There were no significant differences between the groups.

FIG. 4. CBF values (means ± SEM) pre-ischemia and after complete cerebral ischemia for head-up and head-down dogs. Head-up dogs had a significantly greater CBF than head-down dogs at 15 min (P < 0.05).
Table 2. Neurologic Status 48 h after Complete Cerebral Ischemia

<table>
<thead>
<tr>
<th>Grade of Neurologic Damage</th>
<th>n</th>
<th>1 (none)</th>
<th>2 (moderate)</th>
<th>3 (severe)</th>
<th>4 (dead)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Head-up</td>
<td>5</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Head-down</td>
<td>5</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

Post-ischemic CBF and CMRO₂ were followed for 90 min after aortic unclamping to determine whether head position and, thus, cerebral blood volume had an effect on these variables. We detected no significant differences in CBF or CMRO₂ between the head-up and head-down groups at 90 min. The previously described delayed post-ischemic hypoperfusion state \(^{13-16}\) was also seen in this study. At 90 min both groups had CBF and CMRO₂ values very similar to those previously reported for this model.

Head-up dogs were very consistent in the amount of time required for the EEG to become isoelectric. The head-down dogs showed more variability, but overall appeared to require more time to achieve an isoelectric EEG. Thus, in four of the eight head-down dogs, instead of a fixed interval of 10 min of aortic occlusion, a variable interval was used as determined by onset of an isoelectric EEG. A previous study in prone dogs had shown the mean time to isoelectric EEG to be 35 ± 2 s. \(^{13}\) Therefore, in these four head-down dogs, the aortic occlusion interval was set at 9 min 25 s after onset of an isoelectric EEG. This same method for timing ischemia was used in all of the dogs studied for neurologic outcome. This assumes that onset of an isoelectric EEG reflects a similar degree of cerebral ischemia in individual dogs. CBF and CMRO₂ were not different at 90 min between the two head-down subgroups.

The neurologic outcome evaluation system that we used has detected differences between various groups in prior studies.\(^ {11,14}\) In this study there were no significant differences in neurologic outcome between the head-up and head-down groups at 48 h. It should be noted that the number of dogs in both groups was relatively small. However, it was clear from the data trends after just ten dogs were studied that our hypothesis (that head-up dogs would fare better than head-down dogs) was not supported (table 2). Indeed, the opposite hypothesis is suggested.

Previous studies that suggested a detrimental effect of static cerebral blood on neurologic outcome demonstrated protection only in the presence of “bloodless” ischemia and offered no clinical application.\(^ {1,2}\) Using a clinically feasible means of altering cerebral blood volume, we produced a relative three-fold decrease in cranial blood volume with the head-up position rather than “bloodless” ischemia. If the postulated detrimental effect of blood on neurologic outcome is an “all or none” phenomenon, then the results seen here would be expected. An alternative explanation is that lack of blood within the brain did not contribute to the improved outcome noted in the previous studies.

In conclusion, head position during complete cerebral ischemia had a major effect on the cranial blood volume but had no effect on post-ischemic CBF, CMRO₂, or neurologic outcome.

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References