A Brief Episode of Severe Arterial Hypertension
Induces Delayed Deterioration of Brain Function
and Worsens Blood Flow After Transient
Multifocal Cerebral Ischemia

Andrew J. Dutka, J.M. Hallenbeck, and P. Kochanek

Transient arterial hypertension occurs sporadically following cerebral air embolism and may occur during the acute phase of stroke. This study used an animal model of multifocal cerebral ischemia induced by air embolism and reversed by recompression to assess the effect of induced hypertension on the evoked response recovery, local cerebral blood flow, intracranial pressure, and brain water in 19 anesthetized dogs (Canis familiaris). Six received 0.4 ml of air via the internal carotid artery, 8 received intracarotid air and 10 μg/kg norepinephrine to produce transient hypertension, and 5 received intracarotid saline and norepinephrine. The average evoked response recovery in the air-only group was 58.3 ± 7.7% (mean ± SEM) of control after 4 hours of recompression; the air plus hypertension group recovery was 15.4 ± 2.7% (p < 0.01). The final evoked response in the dogs receiving hypertension alone did not differ from control values. Seven of 8 dogs in the air plus hypertension group had very low blood flows; only 1 of 4 in the air-only group had very low flows. The amount of brain water and the intracranial pressure were not detectably different at the end of treatment among all 3 groups. These results support a role for endothelial damage produced by air and hypertension in potentiating the process of postischemic hypoperfusion. (Stroke 1987;18:386–395)
Materials and Methods

Anesthesia and Respiration

Twenty-three dogs (10 kg) were tranquilized by subcutaneous injection of xylazine (1.1 mg/kg) and atropine (0.05 mg/kg) prior to the insertion of a peripheral i.v. line. Anesthesia was induced with 13.5 mg/kg i.v. pentobarbital followed in 20 minutes by 6.25 mg/kg i.v. pentobarbital. Anesthesia was maintained by doses of 1.6 mg/kg pentobarbital every 20 minutes thereafter. Anesthetized dogs were intubated and ventilated with a Bird respirator connected to a built-in breathing system of a Bethlehem Steel hyperbaric chamber, modified so that flow rate and respiratory rate could be varied with the animal at depth. End-expired CO₂ was monitored continuously with a Beckman LB2 CO₂ analyzer and maintained at a fraction equivalent to 4.0 ± 0.2% at the surface.

The experiments reported were conducted according to the principles set forth in the “Guide for the Care and Use of Laboratory Animals,” Institute of Laboratory Animal Resources, National Research Council, Department of Health and Human Services, publication no. (NIH) 85-23.

Venous and Arterial Access

The left cephalic vein, right and left femoral veins, and left femoral artery were exposed, and polyethylene catheters were inserted. The right femoral artery received 2 catheters, 1 directed distally and 1 directed proximally; these were joined later with a Y-connector to externalize the circulation for rapid sampling during the [14C]iodoantipyrine blood flow study. The left cephalic vein catheter, proximal right femoral artery catheter, and left femoral vein catheter were connected to ports in the chamber wall to permit i.v. drug administration and arterial blood sampling at depth. The left femoral artery catheter was connected to a Gould-Statham pressure transducer; the output of this transducer was continuously monitored on the physiograph. In 3 dogs the CSF was tinged with blood, probably due to penetration of the brainstem by the needle; these dogs were excluded from the experiment.

Experimental Groups

The remaining 19 dogs were divided into 3 experimental groups. In Group 1 (air plus hypertension, n = 8), 0.4 ml of air was flushed with 0.6 ml of warm saline into the internal carotid catheter; this was followed by a single bolus injection of norepinephrine (10 µg/kg i.v.) as soon as therapeutic compression commenced. Group 2 (hypertension alone, n = 5) received 1 ml of warm saline injected via the internal carotid catheter and norepinephrine (10 µg/kg i.v.). Group 3 (air alone, n = 6) had 0.4 ml of air injected into the internal carotid catheter, but no norepinephrine.

Therapeutic Compression

All dogs were initially compressed to 6 atmospheres absolute (ATA) on air, reaching treatment depth in 2.5 minutes. Groups 1 and 2 received norepinephrine during the travel to depth; Group 3 received an equivalent volume of saline. All groups followed the same treatment schedule (Figure 1). After 30 minutes at 6 ATA, the dogs breathed 100% oxygen at 2.8 ATA for 3 20-minute periods with 5-minute air breaks between each period. A slow ascent to 1.9 ATA while breathing oxygen followed the exposure at 2.8 ATA. The dogs breathed air for 15 minutes at 1.9 ATA followed by oxygen for 1 hour before surfacing. The total time at depth was 214 minutes; the compression schedule is modeled closely on the standard U.S. Navy Treatment
Cerebral somatosensory evoked potentials (SEPs) were obtained every 10 minutes at depth, and a final recording was obtained at the surface after any blood or serous fluid that had accumulated around the recording electrode was removed.

**Blood Flow Study**

After the final somatosensory evoked response had been obtained, 60 μCi/kg [14C]iodoantipyrine (New England Nuclear) was injected at a constant rate for 1 minute, and approximately 0.5 ml of blood was collected at 5-second intervals by opening and closing a Y-connector installed in the femoral artery proximal-to-distal shunt. Euthanasia was accomplished within 10 seconds by injection of a saturated solution of KCl into the right ventricle via the previously placed catheter. From each blood sample, 0.2 ml was spotted on tared filter paper and weighed, and the filter paper was transferred to vials containing 10 ml of scintillation cocktail (Beckman Ready-Solv). The radioactivity of each sample was determined by a Beckman β-counter and divided by the weight of the blood; the resulting concentration curve was integrated using a computer program based on the technique of Sakurada et al. The concentration of radioactivity in selected brain areas was measured by a Macbeth photodensitometer with a 1-mm² aperture from autoradiograms prepared from 20-μm frozen brain sections (described below). The blood concentration curve and the densitometer measurements were used to calculate local blood flow.

**Preparation of Autoradiograms and Measurement of Wet and Dry Weights**

The brain was removed as rapidly as possible to a glass petri dish cover, where a roughly 0.5-mm coronal section was cut from the right frontal-parietal junction. The remaining brain was frozen in liquid Freon over liquid nitrogen at −70°C. The frozen brain was divided roughly into thirds, and the rear face of the anterior, front face of the middle, and front face of the posterior section were cut into 20-μm sections on an American Optical microtome within 1 week after the experiment. The sections were incubated in contact with Kodak SB5 film in a sealed cassette containing [14C]methyl-methacrylate standards. The data from 4 blood flow studies were lost due to accidental thawing of the brain.

The unfrozen coronal section was dissected immediately, and 2 samples of cortical gray matter and 2 samples of subcortical white matter were placed in preweighed vials, which had been dried for no less than 48 hours at 110°C and allowed to cool in a sealed container over dessicant (Drierite) before initial weighing. The vials were exposed to room air for only a minimal amount of time. All weights were measured on an analytic balance accurate to 5 decimal places (Mettler HL52). The samples were dried for at least 48 hours at 110°C. Previous experiments had shown that the brain samples continued to lose weight for up to 48 hours at this temperature. In 2 dogs the weights obtained after drying were lower than the tare weight, indicating that the vials had not been predried sufficiently. In subsequent determinations a fifth vial that did not contain a brain sample was weighed at each time, and the results of the samples were rejected if the empty vial’s weight changed by >0.1%. The wet and dry weight data of 4 more dogs were excluded by this criterion. The percent water was calculated as:

\[
\text{% brain water} = \frac{\text{wet weight} - \text{dry weight}}{\text{wet weight}} \times 100\%
\]

The values of the 2 samples of gray and white matter were averaged for each dog.
Results

The values of mean blood pressure (BP), heart rate, blood pH, \( P_{\text{CO}_2} \), \( P_{\text{O}_2} \), and hematocrit at 3 times during the experiment are displayed in Table 1. There were no significant differences among the groups for any variable at any time by repeated one-way analysis of variance (ANOVA) testing. The \( P_{\text{O}_2} \) values at the later times generally indicated that the dog was breathing hyperbaric oxygen, but probably do not accurately reflect the true values because of decompression of the sample.

Air (0.4 ml) was flushed into the internal carotid catheter of dogs in Groups 1 and 3; the average time from this embolus to the beginning of therapeutic compression was 7.9 ± 0.55 minutes (mean ± SEM) in Group 3 and 7.9 ± 0.6 minutes in Group 1, not significantly different by Wilcoxon rank sum test. Groups 1 and 2 received an i.v. bolus of norepinephrine, 10 \( \mu \text{g/kg} \), during the descent to initial treatment depth. In both groups, this produced a rise in BP within about 30 seconds to a maximum of approximately 350 mm Hg systolic over 210 mm Hg diastolic; the systolic remained above 200 mm Hg for about 2.5 minutes and above prenorepinephrine control values for about 6 minutes. The intracranial pressure (ICP) rose markedly as BP increased but then returned to prehypertension values as BP returned to normal. The cerebral perfusion pressure also increased during the hypertensive response. The mean ± SEM for the onset time, duration, maximum BP, and change in cerebral perfusion pressure produced by norepinephrine in Groups 1 and 2 are displayed in Table 2. There were no significant differences between groups for any value by one-way ANOVA. One dog in Group 1 had a brief period of hypotension (mean BP < 90 mm Hg) following the hypertension; this was corrected by volume expansion with Ringer’s lactate within 2 minutes. BP did not vary from values obtained prior to air injection during descent in Group 3.

Cerebral Somatosensory Evoked Response

The cerebral somatosensory evoked response (CSER) 2 minutes after air embolus in Group 1 was 4.3 ± 1.2% (mean ± SEM) of control evoked response; in Group 3 it was 4.9 ± 1.95%. These 2 groups did not differ significantly by Wilcoxon rank sum test, demonstrating that the level of ischemia for each group was similar. The CSER of Group 2 increased during the course of treatment but did not differ from baseline values by the end of the experiment by Wilcoxon rank sum test. Because the baseline was an average of 5 samples and the maximum and final values are 1 sample each, it is possible that the apparent increase at depth was due to sampling error. Accordingly, the 95% confidence limits on the baseline were calculated for each dog. The final CSER amplitudes were within the 95% confidence range of the baseline evoked response in all but 1 case, suggesting that any observed difference was due to sampling error. The maximum observations at depth were all above the upper 95% confidence limit, suggesting that these were not due to sampling error.

Table 3 shows the control evoked response amplitudes, maximum recovery, and final recovery for each dog and the means for each group. Statistical testing between groups was done by one-way ANOVA and

<table>
<thead>
<tr>
<th>Table 1. Heart Rate, Blood Pressure, Arterial Blood Gases, pH, and Hematocrit at 3 Times During the Experiment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time</td>
</tr>
<tr>
<td>Heart rate</td>
</tr>
<tr>
<td>C</td>
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<tr>
<td>D</td>
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<tr>
<td>F</td>
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<tr>
<td>Mean blood pressure</td>
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<td>C</td>
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<tr>
<td>D</td>
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<tr>
<td>F</td>
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<tr>
<td>pH</td>
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<tr>
<td>C</td>
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<tr>
<td>D</td>
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<tr>
<td>F</td>
</tr>
<tr>
<td>( P_{\text{CO}_2} )</td>
</tr>
<tr>
<td>C</td>
</tr>
<tr>
<td>D</td>
</tr>
<tr>
<td>F</td>
</tr>
<tr>
<td>( P_{\text{O}_2} )</td>
</tr>
<tr>
<td>C</td>
</tr>
<tr>
<td>D</td>
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<tr>
<td>F</td>
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<tr>
<td>Hematocrit</td>
</tr>
<tr>
<td>C</td>
</tr>
<tr>
<td>D</td>
</tr>
<tr>
<td>F</td>
</tr>
</tbody>
</table>

Values are mean ± SEM. Time: C, control prior to air injection; D, 2.8 ATA \( \text{O}_2 \) during treatment; F, prior to surface and blood flow study (1.9 ATA \( \text{O}_2 \)). ATA, atmospheres absolute.
Table 2. Maximum Blood Pressure, Cerebral Perfusion Pressure, and Duration of Hypertension Produced by Injection of Norepinephrine

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (n = 8)</th>
<th>Group 2 (n = 5)</th>
<th>Group 3 (n = 6)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Maximum blood pressure after injection of norepinephrine</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>346 ± 20</td>
<td>386 ± 27</td>
<td>No hypertension</td>
</tr>
<tr>
<td>Diastolic</td>
<td>204 ± 11</td>
<td>221 ± 12</td>
<td>No hypertension</td>
</tr>
<tr>
<td>Mean</td>
<td>247 ± 13</td>
<td>276 ± 16</td>
<td>No hypertension</td>
</tr>
<tr>
<td><strong>Duration of hypertensive response</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic &gt; 200 mm Hg</td>
<td>170 ± 17</td>
<td>128 ± 23</td>
<td>No hypertension</td>
</tr>
<tr>
<td>Pressure &gt; control</td>
<td>404 ± 94</td>
<td>368 ± 119</td>
<td>No hypertension</td>
</tr>
<tr>
<td><strong>Cerebral perfusion pressure</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>92 ± 7</td>
<td>99 ± 7</td>
<td>118 ± 5</td>
</tr>
<tr>
<td>At peak blood pressure</td>
<td>204 ± 36</td>
<td>234 ± 30</td>
<td>No hypertension</td>
</tr>
<tr>
<td>Final</td>
<td>100 ± 8</td>
<td>96 ± 10</td>
<td>107 ± 4</td>
</tr>
</tbody>
</table>

Values are mean ± SEM, mm Hg for blood pressure and perfusion pressure, seconds for duration. Norepinephrine injected at 10 µg/kg.

the modified t test with Bonferroni correction for multiple comparisons of the maximum (column 3) and final percent recovery (column 4). At the final time, the percent recovery of Group 1 was significantly different from the percent recovery of Group 3 (modified t = 6.37; p < 0.01). Groups 3 and 1 differed significantly from Group 2 (t = 4.92 and t = 11.27, respectively; p < 0.01). Group 1 did not recover as well as Group 3 even at maximum recovery (t = 3.49; p < 0.05).

Each dog in Group 1 failed to sustain the level of recovery achieved during recompression and deteriorated through the course of the experiment. Figure 2 plots the average recovery of CSER at each time during the experiment for Groups 1 and 3. Figure 3 shows the time at which each animal reached its maximum recovery in relation to the therapeutic compression profile. No relation between the maximum recovery point and treatment depth or partial pressure of oxygen is evident.

Cerebral Blood Flow Measurements

The method used to cut the brain yielded 3 different types of section: the anterior section included the head of the caudate, the middle section included the thalamus, and the posterior section included the hippocampus. Standard sites were selected on each type of section to represent the brain structures cited in Table 4, and the optical density of sites on 3 adjacent sections were determined and averaged to calculate blood flow. Table 4 displays the average blood flows for each area measured in the injured hemisphere. The somatosensory cortex was the only area with a significant difference in flow by one-way ANOVA; Group 1 dogs had lower flows. This result may be due to the application of multiple tests of significance; however, it correlates well with the CSER measurements, and this area is within the expected distribution of most of the air.

Table 3. Cortical Somatosensory Evoked Response

<table>
<thead>
<tr>
<th>Animal</th>
<th>Control</th>
<th>Maximum recovery during treatment</th>
<th>Final</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Group 1: Intracarotid air plus hypertension (n = 8)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3N22</td>
<td>62.5 (100)</td>
<td>12.5 (20)</td>
<td>6.9 (6)</td>
</tr>
<tr>
<td>4658</td>
<td>36.4 (100)</td>
<td>12.2 (35)</td>
<td>4.6 (12)</td>
</tr>
<tr>
<td>1636</td>
<td>20.2 (100)</td>
<td>6.4 (31)</td>
<td>3.8 (18)</td>
</tr>
<tr>
<td>8455</td>
<td>121 (100)</td>
<td>60 (49)</td>
<td>17.8 (14)</td>
</tr>
<tr>
<td>1571</td>
<td>38.5 (100)</td>
<td>15.1 (39)</td>
<td>8.1 (21)</td>
</tr>
<tr>
<td>7718</td>
<td>40 (100)</td>
<td>10.2 (25)</td>
<td>1.7 (4)</td>
</tr>
<tr>
<td>5348</td>
<td>34.4 (100)</td>
<td>15.3 (45)</td>
<td>9.6 (28)</td>
</tr>
<tr>
<td>5335</td>
<td>76 (100)</td>
<td>25 (33)</td>
<td>14 (18)</td>
</tr>
<tr>
<td><strong>Mean</strong></td>
<td>53.62</td>
<td>19.66 (34.8)</td>
<td>8.31 (15.4)</td>
</tr>
<tr>
<td><strong>SEM</strong></td>
<td>11.43</td>
<td>6.06 (3.4)</td>
<td>1.91 (2.7)</td>
</tr>
<tr>
<td><strong>Group 2: Hypertension alone (n = 5)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8906</td>
<td>39.6 (100)</td>
<td>53.6 (135)</td>
<td>41.4 (105)</td>
</tr>
<tr>
<td>2976</td>
<td>28 (100)</td>
<td>33 (118)</td>
<td>28.6 (102)</td>
</tr>
<tr>
<td>9364</td>
<td>77 (100)</td>
<td>88.9 (115)</td>
<td>75.7 (98)</td>
</tr>
<tr>
<td>8227</td>
<td>45 (100)</td>
<td>53.8 (119)</td>
<td>41.2 (91)</td>
</tr>
<tr>
<td>1163</td>
<td>33 (100)</td>
<td>37.9 (114)</td>
<td>26.7 (81)</td>
</tr>
<tr>
<td><strong>Mean</strong></td>
<td>43.84</td>
<td>53.41 (120.2)</td>
<td>42.7 (95.5)</td>
</tr>
<tr>
<td><strong>SEM</strong></td>
<td>8.86</td>
<td>9.78 (3.8)</td>
<td>8.79 (4.2)</td>
</tr>
<tr>
<td><strong>Group 3: Intracarotid air alone (n = 6)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8545</td>
<td>57.2 (100)</td>
<td>33.8 (59)</td>
<td>33.8 (59)</td>
</tr>
<tr>
<td>9667</td>
<td>87.2 (100)</td>
<td>71 (81)</td>
<td>71 (81)</td>
</tr>
<tr>
<td>2644</td>
<td>24.5 (100)</td>
<td>13.8 (56)</td>
<td>12.6 (52)</td>
</tr>
<tr>
<td>9711</td>
<td>40.5 (100)</td>
<td>18 (43)</td>
<td>16.3 (40)</td>
</tr>
<tr>
<td>8686</td>
<td>41.2 (100)</td>
<td>33 (82)</td>
<td>32 (79)</td>
</tr>
<tr>
<td>7558</td>
<td>46.3 (100)</td>
<td>17.2 (37)</td>
<td>17 (37)</td>
</tr>
<tr>
<td><strong>Mean</strong></td>
<td>49.48</td>
<td>31.12 (59.6)</td>
<td>30.48 (58.3)</td>
</tr>
<tr>
<td><strong>SEM</strong></td>
<td>8.69</td>
<td>8.69 (7.8)</td>
<td>8.85 (7.7)</td>
</tr>
</tbody>
</table>

Values are µV (percent in parentheses).
In addition to average readings for each structure, many dogs had areas of very low and very high flow within each structure. Evidence suggests that flows < 6 ml/100 g tissue/min in white matter and < 15 ml/100 g tissue/min in gray matter are associated with severe and probably irreversible neuronal dysfunction. \(^{14}\) Seven of 8 dogs in Group 1 had at least 1 area of low flow; 2 dogs had 1 area each, 3 had 2 areas, 1 had 5 areas, and 1 had 7 areas. There were no dogs with low flows in Group 2, and 1 dog in Group 3 had 1 area of low flow. The \(G\) test with a Williams correction for continuity to compensate for the small number of observations applied to these proportions showed a significant difference (6-9.06; \(p < 0.025\)) in the frequen-
Group 3 differ from Groups 1 or 2 (modified \( t = 2.02; p > 0.1 \) and \( t = 2.22; p > 0.1 \), respectively). The power of this ANOVA is >0.99.

### Wet and Dry Weights

Four dogs in Group 1, 5 in Group 2, and 4 in Group 3 had wet and dry weights measured successfully. The average ± SEM percent water in the gray matter of Group 1 was 79.7 ± 1.0%; Group 2, 81.3 ± 0.9%; and Group 3, 80.5 ± 2.25%. There was no difference among these values by one-way ANOVA (\( F = 0.391; p > 0.50 \)). The percent water in white matter was 66.1 ± 0.4% in Group 1, 68.0 ± 1.7 in Group 2, and 66.2 ± 1.3 in Group 3. There was again no difference among these groups by one-way ANOVA (\( F = 0.6977; p > 0.50 \)). The maximum difference between the grand mean of the 3 groups and an observed gray matter value was 0.9% water, and the corresponding value for white matter was 1.3% water. The power of the ability of one-way ANOVA to detect true differences of the magnitude observed is <0.1; however, the ANOVA would have detected a difference of >4.2% brain water with a power of 0.8.

### Discussion

These results indicate that a single episode of severe hypertension lasting <10 minutes worsens evoked potential outcome and cerebral blood flow measured after 4 hours of treatment. The effect of the hypertensive episode is delayed; that is, the dogs all recover to some degree initially but then deteriorate despite adequate treatment, accurately mirroring the clinical problem of secondary deterioration after air embolism. The effect of hypertension is not easily explained by an effect on ICP because there was no difference in ICP among the experimental groups at the final time. No difference in brain water was detected; however, this result was less reliable than the other findings because of a large Type II error associated with this measurement.

The major effect of norepinephrine in this model should be secondary to the hypertension produced by the injection, but it is difficult to separate this from other direct effects on brain function. Moderate doses of norepinephrine produce cerebral vasocostriction when administered i.v., but this effect wanes immediately on stopping the infusion and is therefore unlikely to contribute to delayed neuronal dysfunction. When administered after osmotic damage to the blood–brain barrier, intracarotid norepinephrine produced increased blood flow coupled with increased brain metabolism, but very little effect on BP. In the present study, the blood–brain barrier is damaged by air embolism prior to injection of norepinephrine, therefore norepinephrine may reach brain cells to potentially cause excitation. Only cells at the margin of zones rendered ischemic by air are likely to respond to this stimulus, however, and autoregulation is paralyzed in these areas. The marked increase in cerebral perfusion pressure caused by systemic norepinephrine will increase blood flow in these areas and probably more than compensate for the increased metabolic de-

### Intracranial Pressure

ICP was recorded continuously in all dogs except for 2 in Group 2 due to transducer failure at depth. The control values were not significantly different by one-way ANOVA; Group 1 controls were 11.1 ± 1.7 (mean ± SEM), Group 2 were 8.7 ± 2.2, and Group 3 were 8.2 ± 1.1 mm Hg. In the groups receiving air embolism (Groups 1 and 3), ICP rose within 30 seconds of receiving air then gradually returned to normal (Group 1, 30 seconds after air, 26.6 ± 2.1 mm Hg and Group 3, 26.5 ± 3.6 mm Hg), and, as noted previously, increased with hypertension. ICP at the end of the experiment are as follows: Group 1, 15.9 ± 1.8; Group 2, 9.6 ± 2.3; and Group 3, 18.8 ± 3.3 mm Hg. The one-way ANOVA detected no difference among the 3 groups (\( F = 2.08; 0.25 > p > 0.10 \)), and the modified Student’s t test with Bonferroni correction detected no difference between Groups 1 and 3 (\( t = 0.85; p > 0.1 \)) nor between Groups 3 and 2 (\( t = 2.06; p > 0.1 \)). The power associated with the ANOVA test was approximately 0.8. In addition, the change from control to final ICP was calculated for each dog and averaged for each group. All groups increased during the course of the experiment: Group 1 by 3.6 ± 1.8, Group 2 by 1 ± 0.6, and Group 3 by 10.6 ± 3.6 mm Hg. Again, these groups were not significantly different by one-way ANOVA (\( F = 2.97; 0.05 < p < 0.10 \)), nor does

### Table 4. Cerebral Blood Flow in Various Areas of the Embolized Hemisphere

<table>
<thead>
<tr>
<th>Area</th>
<th>Air and hypertension (n = 8)</th>
<th>Hypertension only (n = 3)</th>
<th>Air only (n = 4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Auditory cortex</td>
<td>53.8 ± 10.6</td>
<td>76.2 ± 17.7</td>
<td>53.4 ± 19.7</td>
</tr>
<tr>
<td>Caudate nucleus</td>
<td>77.5 ± 15.7</td>
<td>71.9 ± 15.4</td>
<td>80.2 ± 30.5</td>
</tr>
<tr>
<td>Hippocampus</td>
<td>57.5 ± 10.3</td>
<td>78.8 ± 36.9</td>
<td>57.5 ± 25.2</td>
</tr>
<tr>
<td>Sensorimotor cortex</td>
<td>41.6 ± 6.5</td>
<td>104.7 ± 26.8</td>
<td>73.3 ± 22.8</td>
</tr>
<tr>
<td>Thalamus</td>
<td>90.0 ± 20.6</td>
<td>111.2 ± 20.2</td>
<td>84.6 ± 23.0</td>
</tr>
<tr>
<td>Visual cortex</td>
<td>68.3 ± 12.9</td>
<td>130.0 ± 41.6</td>
<td>61.1 ± 23.2</td>
</tr>
<tr>
<td>Anterior association cortex</td>
<td>53.2 ± 11.1</td>
<td>62.1 ± 10.3</td>
<td>46.4 ± 11.0</td>
</tr>
<tr>
<td>Watershed cortex</td>
<td>43.7 ± 11.1</td>
<td>59.5 ± 26.7</td>
<td>52.6 ± 14.6</td>
</tr>
<tr>
<td>between posterior and</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>middle cerebral arteries</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Watershed cortex</td>
<td>49.5 ± 8.4</td>
<td>68.4 ± 14.6</td>
<td>46.4 ± 11.0</td>
</tr>
<tr>
<td>between anterior and</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>middle cerebral arteries</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Corpus callosum</td>
<td>19.2 ± 4.8</td>
<td>16.6 ± 2.6</td>
<td>17.6 ± 4.4</td>
</tr>
<tr>
<td>Internal capsule</td>
<td>18.1 ± 6.4</td>
<td>20.6 ± 5.6</td>
<td>15.9 ± 4.8</td>
</tr>
<tr>
<td>Middle centrum ovale</td>
<td>14.0 ± 5.1</td>
<td>19.1 ± 0.8</td>
<td>14.1 ± 2.2</td>
</tr>
<tr>
<td>Anterior centrum</td>
<td>16.7 ± 5.1</td>
<td>15.3 ± 7.6</td>
<td>14.9 ± 2.8</td>
</tr>
<tr>
<td>ovale</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Optic radiations</td>
<td>13.4 ± 5.5</td>
<td>13.3 ± 4.0</td>
<td>11.6 ± 2.5</td>
</tr>
</tbody>
</table>

Values are mean ± SEM, ml/100 g tissue/min.
Hypertension Worsens Outcome After Ischemia

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mand of these cells. This is the case in the course of
generalized seizures, where reddening of the venous
blood is observed despite huge increases in metabo-
lism. Excitatory amino acids have been postulated to
have direct toxic effects when released in excess irre-
respectively of the ability of blood flow to compensate for
increased metabolism, but it is not known if all excitatory
neurotransmitters share this effect. It seems likely
that the major effect of norepinephrine in the present
study is related to its effect on BP.

There are numerous clinical and experimental stud-
ies that address the effect of chronic hypertension on
outcome following focal cerebral ischemia; the
consensus is that preexisting high blood pressure leads	only to increased risk of stroke, but worsened prog-
nosis as well. The effect of hypertension induced in
previously normal animals in the postischemic period
on functional neuronal outcome has been studied less
often, although the stress of acute cerebral infarction
commonly produces transient hypertension. Monkeys
subjected to global ischemia and brief episodes of hy-
pertension had higher neurologic deficit scores than
animals maintained without hypertension. Rats with
focal cerebral hypoxic-ischemic insult had reduced
survival time when mean arterial pressure was main-
tained > 180 mm Hg. We have used the SEP ampli-
tude as a measure of functional neuronal outcome.
There is good evidence that a very low amplitude of the
primary cortical response is highly correlated with
poor brain function, and that changes in the evoked
response in controlled situations reflect changes in
the outcome following ischemia. In addition, we have
extensive data that demonstrates minimal effects of
hyperbaric oxygen on the amplitude of the evoked
response. Our results, therefore, support the conten-
tion that hypertension worsens the outcome following
focal cerebral ischemia.

The mechanism whereby a single transient burst of
high blood pressure causes deterioration of neurologic
response 4 hours later is unclear. Air bubbles are
pushed through the circulation until the fluid phase
of the cerebral arterial bed is exceeded, leading to
increased perfusion pressure, generally lodging in small intracerebral
arteries. Increased perfusion pressure causes more rap-
identifying of air and faster resolution of EEG changes
induced by air embolism. The clearance of air in the
present model is further aided by the reduction in bub-
ble volume with recompression. Mechanical distortion
of neurons contributing to the evoked response by
widely dilated arteries would be maximal during the
hypertensive phase and should be resolving by the time
the response begins to deteriorate in the present series
of experiments.

The levels of hypertension achieved by the dose
used in this study are probably sufficient to overcome
the upper limit of cerebral autoregulation, leading to
increased cerebral blood flow and vasodilation. This
level of hypertension is also associated with
breakdown of the blood–brain barrier as measured by
increased extravasation of Evans blue dye and horse-
radish peroxidase. Since cerebral air embolism is also
associated with the breakdown of the blood–brain bar-
rier to these substances, it is possible that hyperten-
sion simply worsens cerebral edema. However, an
increase in edema alone is not sufficient to cause neu-
ronal injury. Global cerebral perfusion pressure is not
reduced in our experiments, so the major detrimental
effect of increased brain edema is not present. Some
workers believe that there are local differences in per-
fusion pressure after ischemia, which we have not
assessed directly; the measurement of brain water in
the maximally damaged area, however, also shows no
great differences among groups, again arguing that
edema is not a major factor in the worsened outcome.
This result is consistent with previous experiments that
demonstrate no correlation between damage from ce-
bral air embolism and the amount of brain water.
The permeability increase produced by cerebral air
embolism and hypertension resolves rapidly, lasting
no longer than 3–4 hours. Instead of improving, the
evoked response continues to deteriorate during this
time, which again suggests that the permeability
change does not correlate well with neuronal function.

The permeability changes induced by hypertension
are the effect of endothelial damage in areas of vessel
dilation. The damage may be worsened by in-
creased activity of the enzymes metabolizing arachi-
donic acid, which produce highly reactive free radical
species. Endothelial damage is also marked by in-
creased pinocytosis, flattening and fenestration of en-
dotheial cells, appearance of craters in endothelial
membranes and decreased oxygen use, and
decreased negative surface charge. Leukocytes and
platelets also have negative surface charge; the
electrostatic repulsion between the vessel wall and cir-
culating cells is important in avoiding granulocyte
margination and platelet adhesion. Morphologically
similar damage to pulmonary endothelium causes
release of Factor VIII/von Willebrand factor (FVIII/vWF), which can bind to platelet receptors and promote adhesion. Endothelial tissue cultures also
respond to a variety of injurious stimuli by uncovering
Fc and C3b receptors; complement binding to these
increases granulocyte adhesion. We have shown in
previous experiments that FVIII/vWF deficiency re-
duces postischemic hypoperfusion and that platelet
and leukocyte accumulation occur in the early post-
ischemic period. We propose that hypertension im-
mediately after air embolism potentiates and extends
endothelial damage and the interaction between cellu-
ar elements of the blood, coagulation, and comple-
ment systems to produce severe limitation of reperfu-
sion. In multifocal ischemia, there are areas of
hyperemia adjacent to areas of ischemia; vasodilation
increases the endothelial damage produced by hyper-
tension. Since postischemic hypoperfusion takes some
time to develop, delayed deterioration such as seen in
this model would be expected. The high incidence of
very low flows in the dogs that developed late dete-
rion is also an expected consequence of this hy-
pothesis.

Although this study uses a relatively unfamiliar
method of inducing ischemia, the results are widely applicable. Recompression of dogs after air embolism effectively removes mechanical blockage of the arteries within an estimated 8 minutes at 6 ATA, which would mean that this model’s multifocal ischemia lasted about 15 minutes. The effects of compression and decompression on cerebral blood flow, evoked potential, brain water content, and ICP are known and are not confounding. In particular, although the recompression schedule is shorter than that used in humans, this difference should not produce decompression sickness in dogs. This study suggests that avoidance of high blood pressure in the immediate poststroke period is extremely important, even if the blood pressure elevation is as transient as those seen with endotracheal intubation. It also strongly supports the concept of the blood–damaged tissue interaction in promoting postischemic hypoperfusion and supports the notion that this interaction is an important mediator of the evolution of ischemia into infarction. Finally, this method of inducing secondary deterioration will be an important tool for examining therapies aimed at preventing this phenomenon.

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