Neurologic and Cardiovascular Effects of Hypotension in the Monkey

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SUMMARY Thirty monkeys were exposed to controlled systemic hypotension of different magnitudes and durations to determine factors leading to brain injury or cardiovascular failure. Fourteen monkeys developed brain injury. Of these, 6 survived indefinitely and 8 were sacrificed or died within 12–62 hours due to neurologic deterioration accompanied by respiratory failure. Sixteen animals did not develop brain injury, but 9 of these died within 24 hours from documented cardiovascular failure while the remaining 7 survived indefinitely. A highly reproducible threshold for the development of brain injury was found at a mean arterial blood pressure (MABP) of 25 mm Hg. Maintenance MABP was ≤25 mm Hg in 13 of 14 lesioned monkeys and >25 mm Hg in 15 of 16 non-lesioned monkeys. Maintenance MABP averaged 20.1 ± 1.1 mm Hg in lesioned and 32.1 ± 1.7 mm Hg in non-lesioned animals (p < 0.001). Among the non-lesioned animals, death from delayed cardiovascular failure ensued when MABP was maintained between 27 and 35 mm Hg for 90 min or longer. Animals exposed to this range of hypotension for <90 min or to MABP exceeding 35 mm Hg for as long as 3 h survived intact. EEG changes occurring during hypotension most accurately predicted neurologic outcome. The threshold MABP required to produce cerebral electric silence was 21–22 mm Hg. Monkeys developing marked brain injury had >25 minutes of EEG flattening, while slightly injured animals had it for 5–15 minutes and those without injury for <5 min. Changes in acid-base state, common carotid artery blood flow, and cerebral uptake of glucose and oxygen during hypotension also correlated with neurologic and cardiovascular outcome. Hypoxemia and hypercarbia were not contributory factors in the production of brain injury in this study.

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The relative contributions made by hypoxemia, systemic acidosis, hypotension associated with reduced cerebral blood flow, and altered brain intermediary metabolism to the development of brain injury as a consequence of hypoxic exposure remain uncertain. This lack of precise knowledge of the pathogenesis of hypoxic brain injury is particularly unfortunate since exposure to hypoxia constitutes one of the common causes of brain injury and death in man.

We have considered 3 questions of fundamental importance to the clinician and experimentalist alike. First, can hypotension and reduced cerebral blood flow be studied independently and assigned a role in the development of brain injury separate from the hypoxemia and systemic acidosis that commonly accompany hypotension? Second, can the threshold value of systemic hypotension that leads to brain injury be delineated with precision? Finally, why does exposure to hypotension cause brain injury in some instances and death from cardiogenic shock in others?
This last question addresses the longstanding dilemma of the relative vulnerabilities of the brain and heart to oxygen deficiency.

Norris and Pappius failed to produce brain injury by exposing cats to relatively marked levels of hypoxia, acidosis, and hypercarbia. It has been suggested that their avoidance of hypotension during these insults may have accounted for the absence of brain injury. It is the latter factor that we have attempted to isolate in order to study its role in the production of brain injury. Past experimental efforts to explore the neuropathology of hypotension have frequently been plagued by the “all or none” phenomenon in which animals either died within hours following exposure, often with brain edema, or survived without neurologic or pathologic changes. In the present study we have been able to induce cerebral injury in monkeys that survived for many hours or indefinitely following hypotensive exposure. Since the arterial blood Po2 was maintained within its normal range throughout exposure, hypoxemia itself did not play a role in the development of brain lesions.

The animals were allowed to breathe spontaneously through an endotracheal tube during the insult and recovery periods whenever possible so as not to interfere with physiologic compensatory mechanisms during hypotension. Consequently, ventilation with room air on a Harvard animal respirator was employed only if marked respiratory depression or apnea occurred and then only long enough to reestablish regular spontaneous breathing. The first 4 animals were mechanically ventilated throughout both insult and early recovery periods. In all animals, the respirator was adjusted during the control period to achieve normal blood gases.

The initial animals were used to ascertain the approximate level of hypotension at which irreversible neurologic injury occurred. MABPs of 35 to 40 mm Hg could be sustained for as long as 120 to 180 min without development of neurologic or cardiovascular sequelae. Thereafter, all animals were subjected to one of 3 ranges of hypotension: 1) marked hypotension (MABP ≤ 25 mm Hg) of short duration (<40 min); 2) less marked hypotension (MABP = 26 to 34 mm Hg) of intermediate (60 to 120 min) or long (120 to 220 min) duration; and 3) moderate hypotension (MABP ≥ 35 mm Hg) of long duration (>120 min). To increase the proportion of surviving but neurologically impaired subjects, the duration of hypotension was controlled in an inverse relation to magnitude of blood pressure lowering.

Hypotension was terminated by reinfusing the withdrawn heparinized blood and administering 100% oxygen. The interval between initiation of blood pressure lowering and the initiation of measures to restore blood pressure was taken as the duration of hypotension. Most animals were given small injections of sodium bicarbonate (8.1 ± 2.7 mEq) and digoxin (0.075 to 0.15 mg) early during recovery. A few also received intravenous epinephrine, isoproterenol, xylocaine, or calcium gluconate as needed to support control, insult, and early recovery periods, and thereafter at 30- and later 60-min intervals. All samples were analyzed for Po2, PCO2, and pH using a Radiometer-Copenhagen microelectrode unit. Additional 0.4 ml blood samples were taken at similar intervals and assayed for serum glucose concentration using a Beckman glucose analyzer. All physiologic and metabolic results are reported as mean ± standard error of the mean.

Blood pressure was lowered by withdrawing blood through the arterial catheter into heparinized syringes (15 animals) or injecting a small initial dose of the ganglionic blocking agent, trimethaphan camsylate (Arfonad, 3 or 5 mg/kg) in combination with blood withdrawal (15 animals). Head and body tilt were avoided so that systemic and cerebral blood vessels experienced similar blood pressures. The rapidity of induction of hypotension was varied as described. Once the target mean arterial blood pressure (MABP) was reached, small amounts of blood were reinfused or removed, as needed, to maintain the MABP within 1 to 2 mm Hg of the pre-selected value. Later analysis revealed that the MABP had been maintained with ± 2 mm Hg of the target pressure during greater than 90% of the insult time in most animals.

This work correlates the magnitude and duration of hypotensive exposure with the physiologic, metabolic, and neurologic changes produced. Factors that lead primarily to brain injury, on the one hand, or to delayed circulatory failure, on the other, are distinguished and analyzed.

Materials and Methods

Thirty monkeys (M. mulatta) weighing 5.07 ± 0.63 kg were exposed to episodes of hypotension of precisely determined magnitudes and durations. Animals were anesthetized with i.v. pentobarbital, 30 mg/kg. Small supplemental doses (8.3 ± 2.7 mg/kg) were given, as needed, prior to onset of hypotension. Catheters were placed in the abdominal aorta via a femoral artery, the inferior vena cava via a femoral vein, and in the jugular vein just below the jugular foramen. The former 2 catheters were attached to strain gauge pressure transducers (Hewlett-Packard 267 AC) for continuous recording of arterial and central venous pressure. The electrocardiogram (ECG) was monitored with standard limb leads. A Sanborn cardiotachometer monitored heart rate. Four lead, bipolar electroencephalographic (EEG) recordings were made using a pair of disc electrodes fixed beneath the scalp in each frontal and parietal area. An electromagnetic flow probe specially constructed for these studies was carefully positioned around one common carotid artery in 10 representative animals and flow was continuously monitored on an electromagnetic flow meter (Biotronex BL 410). A rectal thermister measured body temperature which was kept between 36.5 and 38.5°C with a water blanket. All physiologic functions were recorded on an 8-channel Sanborn model 7700 polygraph.

Simultaneous 0.4 ml blood samples were withdrawn from all 3 sample sites at 15-min intervals throughout control, insult, and early recovery periods, and thereafter at 30- and later 60-min intervals. All
cardiovascular function. All animals were given 10 to 50 ml infusions of 10% glucose starting 3 hours post-insult. Most subjects were weaned from oxygen 2 to 6 hours post-insult while a few received oxygen for up to 10 hours. Mechanical ventilation was used during resuscitation only during periods of apnea.

Seventeen animals died or had to be sacrificed by perfusion between 2 and 62 hours after hypotension. The remaining 13 survived and were electively killed after 3 to 99 days via cardiac perfusion with 10% buffered formalin. All brains were examined grossly, sectioned, and examined microscopically after thionine staining (Nissl technique).

Results

The animals were divided into 3 outcome groups. The 14 animals of Group I all showed brain injury consisting of focal parenchymal necroses of cerebrum and cerebellum in a characteristic distribution. Eight of these animals died within 12 to 62 hours following exposure while 6 survived long-term. Among the short-term survivors, grossly apparent brain swelling was almost always present. The 7 animals constituting group II all survived indefinitely and showed no brain abnormalities. The 9 animals comprising Group III also showed no brain abnormalities but all died within 24 hours of cardiovascular failure. The physiologic and pathologic findings exhibited by the animals of the 3 outcome groups are summarized in tables 1–3.

Correlation of Magnitude of Hypotension with Neuropathologic Outcome

A close correlation was found between the blood pressure level maintained during hypotension and the subsequent development of brain injury (table 4). When the MABP was maintained at or below 25 mm Hg the probability of later neurologic and neuropathologic changes was great. Thirteen of 14 monkeys (93%) with target MABP ≤ 25 mm Hg developed brain injury. The single exception (monkey 514) showed less marked reduction in its carotid artery blood flow (CABF) during hypotension than did the brain-injured animals in which this parameter was measured (see below). Maintenance of MABP above 25 mm Hg led to neuropathologic changes in only one of 16 animals. The injury in this exceptional animal (monkey 417) was minor. This monkey, 417, had the highest MABP during hypotension (31 mm Hg) but had the longest insult duration (65 min) and developed the most marked acidosis.

The mean maintenance MABP for all animals which developed brain-lesions was 20.0 ± 1.0 mm Hg compared to 32.1 ± 1.7 mm Hg for all monkeys without brain lesions (both Groups II and III) and 34.4 ± 3.4 for the animals that survived long-term without brain lesions (Group II). The differences between the animals that developed brain injury and the 2 groups that remained brain-intact were highly significant (p < 0.001) (table 5).

The duration of hypotension was a dependent rather than an independent variable in the present study. Most animals that developed neuropathologic changes were exposed to marked hypotension (MABP ≤ 25 mm Hg) for short periods, ranging from 22 to 40 min (mean: 34.8 ± 1.4 min). Within this range, 6 out of 8 animals with insult durations of 36–40 min developed moderate or marked neurologic and pathological changes and died within 3 days. On the other hand, 3 out of 4 animals that were markedly hypotensive for less than 34 min survived indefinitely with no clinical deficits but showed restricted parenchymal necrosis. Those animals with MABP maintained above 25 mm

<table>
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<tr>
<th>Animal number</th>
<th>Target MABP (mm Hg)</th>
<th>Duration (mins)</th>
<th>Time to MABP (min)</th>
<th>Insult time with flat EEG (min)</th>
<th>% Insult with flat EEG</th>
<th>Lowest blood pH</th>
<th>Neurologic findings</th>
<th>Survival time</th>
<th>Brain pathology</th>
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<td>0</td>
<td>7.01</td>
<td>Slight deficit</td>
<td>12 hr</td>
<td>R</td>
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</table>

*Animals ranked according to duration of EEG flattening during hypotension.
**Animals electively killed.

Key: Brain pathologic findings: S = brain swelling; R = restricted necrosis in predilection areas; E = extensive necrosis in predilection areas.
For details of neurologic and neuropathologic findings, see text.

TABLE 1 Physiologic and Pathologic Findings in 14 Monkeys that Developed Brain Lesions*

*NEUROLOGIC & CV EFFECTS OF HYPOTENSION/Selkoe & Myers
Hg during hypotension generally tolerated such exposures for long periods without developing brain injury. Among 12 animals exposed to MABPs of 26-34 mm Hg, only one developed brain lesions though many died of cardiovascular complications during the first 24 hours (see below). All animals with blood pressure above 35 mm Hg survived intact.

Although most animals which developed brain lesions experienced marked hypotension of rapid onset, some Group I animals had intervals to achievement of target pressure as long as 6, 9.5, and 25 min (table 1), while some animals without brain lesions had intervals as short as 3.6, 5.5, and 6 min (tables 2 and 3). Thus, though hypotension of rapid onset was frequently associated with brain injury, it cannot be concluded from this study that rapid induction of hypotension per se is causally related to development of brain injury.

Changes in EEG Activity during Hypotension and Brain Injury

Of all parameters monitored, changes in the EEG during hypotension most accurately predicted neuropathologic outcome. Slowing and diminished amplitude of the EEG appeared in almost all animals when their MABP fell below 28-32 mm Hg. The EEG changes progressed as blood pressure was lowered from 28 to 22 mm Hg. Episodes of cerebral electric silence almost invariably appeared at blood pressures below 21-22 mm Hg. The duration of EEG change varied directly with the time that MABP was below this level. Isoelectric intervals were never seen when the MABP was maintained above 27 mm Hg, irrespective of duration of hypotension or acid-base state of the animal.

Both the duration of electric silence and the percent of the insult period during which the EEG was flat correlated significantly with neuropathologic outcome (table 5). Animals which developed brain-lesions (Group I) experienced cerebral electric silence for 17.8 ± 3.3 min and the mean percent of insult time showing an isoelectric EEG was 50 ± 9%. The corresponding values for all the animals without lesions (Group II and III) combined were 3.3 ± 2.3 min and 7 ± 3% (differences significant at \( p < 0.001 \)). Within the group with brain-lesions the severity of the neurologic deficit and the extent of parenchymal necrosis correlated with the duration of the isoelectric silence.
EEG. The 7 animals with moderate or marked brain injury and clinical deficits all experienced 25 min or longer (mean 29.4 ± 3.5) of cerebral electric silence, representing more than 70% (mean 76 ± 13%) of the total hypotensive period. Among the remaining 7 animals with slight neuropathologic changes and minor or no clinical deficits, all had EEG flattening for 13 min or less, with a mean duration of 6.1 ± 4.8 min and a range of 5 to 60% of the total hypotensive period.

Animals with prolonged electric silence during hypotension usually showed some return of EEG activity within 10–20 min after their blood pressure was restored, but the frequency and voltage remained depressed. Those animals which later had marked brain injury often failed to achieve full recovery of the EEG as late as 10 hours post-insult, while their mildly lesioned co-subjects recovered normal EEGs or showed only slight voltage depression by 3 to 5 hours.

The arterial blood Po2 remained between 85 and 110 mm Hg throughout exposure to hypotension in the majority of animals and remained above 70 mm Hg in all animals. Oxygenation was well maintained even though 20 of the 30 monkeys averaged only 15% of their hypotensive period on the respirator and 6 others required no mechanical ventilation. (The first 4 animals were ventilated on room air throughout exposure. Thus, a decreased Po2 played no role in causing brain injury.

An increased respiratory effort associated with transient hypocarbia accompanied the initiation of hypotension (table 6). Changes in PCO2 were similar in lesioned and non-lesioned animals and significant hypercarbia (PCO2 > 44 mm Hg) was not observed in either group. No differences in the pH of jugular venous blood were found.

Changes in Cerebral Oxygen and Glucose Extraction

Hypotension caused tissue extraction of oxygen in both the cerebral and systemic circuits to rise markedly (table 6). Almost all animals increased their Po2 from control values near 90 mm Hg to 105–110 mm Hg, presumably as a result of their greater...
respiratory efforts. Simultaneously, the arterial-jugular venous (A-JV) and arterial-systemic venous blood Po2 differences rose nearly 2-fold. The oxygen difference across brain, which was similar in all animals at rest, consistently rose more during hypotension in those animals that developed brain lesions than in those that did not (table 6). Thus, the A-JV O2 difference increased by 107% in the Group I animals compared to 80% in Group II (p < 0.05) and 60% in Group III (p < 0.01). Furthermore, cerebral oxygen extraction increased more in those animals that developed marked brain injury than in those that showed only slight injury. The A-JV difference returned to values at or slightly higher than control in all animals during recovery.

Changes in the arterial, mixed systemic venous, and jugular venous serum glucose concentrations were monitored in 13 of the 30 monkeys. Exposure to hypotension caused a several fold increase in the arterial serum glucose level and A-JV glucose difference (fig.). Among all animals tested, the arterial level increased from 65.6 ± 31.3 mg% during the control period to 146.3 ± 22.2 mg% at 15 min and 178.4 ± 36.0 mg% at 30 min into hypotension. The level then fell to control values within 30–60 min post-insult. This 3-fold rise in glucose level greatly exceeded the 25% increase noted in an earlier study in which blood pressure was lowered less markedly.2 Our brain-lesioned and brain-intact animals showed no differences either in the rise of arterial glucose concentration during hypotension or in its levels monitored up to 3 hours post-insult.

During hypotension, as the arterial level rose the glucose difference across brain increased 4-fold by 15 min (mean 32.5 ± 3.6 mg%) and remained in this range throughout exposure. The A-JV glucose difference increased in both lesioned and non-lesioned animals (fig.) but the rise was greater in 6 markedly injured animals (mean at 30 min: 49.2 mg%) than in 5 slightly lesioned (mean 19.3 mg%) or in 2 non-lesioned animals (mean 8.0 mg%) (differences significant at p < 0.01). After blood pressure was restored, the A-JV glucose difference declined rapidly during the first 15 min to or below control values in all categories of animals.

**Common Carotid Artery Blood Flow**

Reproducible artifact-free recordings of common carotid artery blood flow (CABF) were obtained in 8 animals. The mean control CABF was 27.6 ± 2.2 ml/min, a value agreeing with reported studies.3 4 The magnitude and duration of the subsequent decreases in CABF brought about by hypotension correlated well with depression of the EEG and neuropathologic outcome. Of the 8 animals monitored, 4 showed marked decreases in CABF coincident with the fall of MABP below 25–30 mm Hg and the slowing of the EEG. A close temporal relation existed between maintenance of CABF at <10 ml/min and periods of EEG flattening. For example, monkeys 512 and 513 reduced their CABF below 10 ml/min for 73% and 92% and showed isoelectric EEG's for 70% and 90%, respectively, of the hypotensive period. The 4 monitored subjects that underwent the most marked and sustained reductions in CABF developed the most marked neurologic and pathologic changes.

Two monkeys that developed only slight or moderate brain injury were also monitored. In one (507), the duration of isoelectric EEG (18.7%) correlated well with the duration of CABF <10 ml/min (20%) while in the other (505), the CABF remained this much longer (95% of insult time) than the EEG remained flat (60%). Finally, 2 animals without lesions either showed no change (416) or reduced CABF to <10 ml/min for only 10% of the insult time (514).

During the early recovery period, CABF increased in all animals but reached only 40 to 60% of control values by 60 min post-insult in animals with severe brain injury, and it approached control levels by 15 min in those with mild or no injury. In animals with marked lesions, the CABF remained at 50–60% of

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**Figure** Changes in mean serum glucose concentration during and following exposure to hypotension: (a) arterial serum glucose concentration (all monkeys); (b) arterial-jugular venous serum glucose concentration difference. Time Scale: C = pre-hypotensive control period, I = insult period and R = recovery period.
control as late as 4 h post-insult. It appears from these limited data that failure of CBF to return to values greater than one-half of control by 60 min post-hypotension correlates with a poor neurologic outcome.

**Recovery from Hypotension**

A close correlation was found between rapid restoration of blood pressure to near normal levels and long-term survival whether with or without brain injury. When the MABP rose to values >80 mm Hg by 15 min post-insult, long-term survival was likely. Conversely, when the MABP remained at values <75 mm Hg at 15 min post-insult, death in the early hours from cardiopulmonary dysfunction was likely. When all animals that survived indefinitely are considered together, whether or not they were brain-lesioned, 12 of 13 achieved a MABP > 80 mm Hg by 15 min post-insult. Among the 17 non-surviving animals, all of which died within 4 days, 14 exhibited MABPs of 75 mm Hg for less at 15 min post-insult. While MABP at 15 min into recovery thus correlated well with later cardiovascular performance, blood pressure rose steadily thereafter in both groups so that by 2 and 4 hours post-insult, all subjects exhibited MABPs of 85–105 mm Hg regardless of eventual survival. The therapeutic modalities employed during resuscitation did not differ significantly between the lesioned and the non-lesioned or between the surviving and the non-surviving monkeys.

**Cardiovascular vs Neurologic Injury as a Function of Hypotension**

Among the monkeys that failed to develop changes in the brain, 9 died early, 7 within 12 hours and 2 between 12 and 24 hours after hypotensive exposure (table 3). These animals constitute a highly important outcome group since they all died without clinical or pathologic evidence of brain injury. A detailed analysis of their records, most of which were monitored physiologically until the moment of death, showed that each died of cardiovascular complications rarely seen in the brain-intact animals (Group I) and never seen in the brain-intact animals that survived indefinitely (Group II).

Some physiologic comparisons between the surviving (Group II) and non-surviving (Group III) brain-intact animals are listed in table 7. The maintenance pressures of all the brain-intact monkeys dying in the early hours (Group III) fell in the "intermediate" range of 26 to 34 mm Hg. However, the magnitude of hypotension did not differ significantly between Groups II and III, since 3 of the Group II long-term survivors also sustained pressures within or below this range. Rather, the important feature distinguishing the 2 groups was the duration of exposure to these intermediate pressures. The 2 brain-intact long-term survivors with blood pressure maintained between 25 and 34 mm Hg had hypotensive period durations considerably less than 90 min (60 and 83 min, respectively) and 8 of the 9 brain-intact animals that died early were exposed for 90 min or longer (mean 161.0 min).

The more prolonged exposures to an intermediate level of hypotension among the non-survivors were associated with a higher incidence of cardiovascular complications. Thus, all Group III animals developed ECG changes generally beginning after 45 to 60 min of hypotension. These changes included ST segment elevation, increase in amplitude and peaking of T waves, slight or moderate decrease in voltage of QRS complex and, occasionally, deep Q waves. ECG changes were often associated with brief periods of bradycardia or supraventricular tachycardia. Furthermore, marked respiratory depression and apnea requiring brief mechanical ventilation developed more frequently among the Group III animals. The brain-intact short-term survivors (Group III) averaged 16.3 min of assisted ventilation during hypotension compared to 5.1 min in the brain-intact long-term survivors and 4.2 min in the lesioned animals (differences significant at p < 0.01). These additional periods of respiratory depression occurred late in the insult and were often associated with progressive declines in blood pressure requiring small reinfections of withdrawn blood.

Animals dying within 24 hours post-insult also

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**TABLE 7 Comparison of Physiologic and Metabolic Parameters in Brain-Intact Monkeys that Survived Indefinitely and that Died within 24 hours of Cardiovascular Failure**

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<thead>
<tr>
<th></th>
<th>Group II (Indefinite survival)</th>
<th>Group III (Survival &lt;24 hrs)</th>
<th>p Value</th>
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<td>Number of animals</td>
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<tr>
<td>Body weight</td>
<td>4.8 ± 0.5</td>
<td>4.7 ± 0.7</td>
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<tr>
<td>MABP during hypotension (mm Hg)</td>
<td>34.0 ± 3.5</td>
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<tr>
<td>Duration of hypotension (mins)</td>
<td>105.0 ± 17.4</td>
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<td>Duration of flat EEG (mins)</td>
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<td>—</td>
</tr>
<tr>
<td>Lowest arterial blood pH</td>
<td>7.20 ± 0.04</td>
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<td>Maximal base deficit</td>
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<td>21.4 ± 1.5</td>
<td>&lt;0.01</td>
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<tr>
<td>Lowest arterial blood P02</td>
<td>94.6 ± 3.3</td>
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<tr>
<td>Lowest arterial blood Pco2</td>
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<td>20.5 ± 1.1</td>
<td>&lt;0.01</td>
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<tr>
<td>Time on respirator (mins)</td>
<td>5.1</td>
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</table>

NS = not statistically significant.
developed significantly greater acidosis during hypotension than did their surviving co-subjects. Group III animals experienced a mean lowest arterial blood pH of 7.07 ± 0.04 compared to 7.20 ± 0.04 among Group II animals (p < 0.05). The corresponding highest base deficit values averaged 21.4 and 12.9 mEq/l, respectively (p < 0.01). These changes in pH and base deficit were maximal at the end of exposure or early during recovery and usually improved to near-normal values by 60 min post-insult. Thus, the differences described reflect in part differences in the duration of hypotension.

The ECG returned to normal shortly after blood pressure was restored in almost all animals. Continuous monitoring for up to 10 hours showed that all long-term survivors, including those that developed brain injury, suffered no further ECG changes and their MABPs remained above 85 mm Hg. In contrast, those animals that died during the first 24 hours usually became tachycardic during the post-insult period. Typically, the discontinuation of supplemental oxygen in these animals 3 to 5 hours post-insult led within minutes to ST-T segment changes, multiple premature ventricular contractions, or brief runs of ventricular tachycardia. These early abnormalities generally responded to therapy with oxygen and lidocaine, but episodes of falling blood pressure or ventricular arrhythmia occurred with increasing frequency and ultimately became unresponsive to therapy.

The Group III animals displayed no neurologic impairments during survival. They regained consciousness within 5 hours and then remained fully reactive except for transient somnolence or stupor during brief episodes of hypotension or arrhythmia. They were usually alert, vocalizing, and able to perform high level tasks such as visual following, chewing or biting an offered object, taking liquids by mouth and displaying aggression. Their pupillary and corneal reflexes remained intact and they showed no motor deficits. Their EEG's became normal and remained so during brief episodes of hypotension or arrhythmia. They generally remained alert right up to the time when a terminal decline in MABP led to death or sacrifice. Postmortem brain examination showed no gross or microscopic changes. Thus, all available evidence indicates that the Group III animals died from cardiovascular collapse brought about by cardiogenic shock and not from any manifest injury to the central nervous system.

Neurologic Findings

Of the 14 animals with brain injury, 4 survived indefinitely and showed no neurologic deficits. Three animals showed slight or moderate sensory and motor deficits but died of documented cardiovascular failure and ventricular tachycardia after 12-15 hours. Two other monkeys showed slight (503) or marked (512) sensorimotor deficits but survived for many days with intensive nursing care and were electively killed. The remaining 5 animals developed marked sensorimotor deficits and died after 1-3 days. All of the animals with moderate and marked motor deficits showed a spastic quadriparesis with generalized hyperreflexia, abnormal posturing of the limbs, and inability to stand, walk, or climb. The more severely affected animals also demonstrated loss of righting reflexes, disinterest in food, and, occasionally, ophisthotonus. Some monkeys developed stimulus-evoked myoclonic seizures that often evolved into generalized convulsions. Brain stem reflexes were intact.

The exact cause of death of the 5 markedly brain-damaged animals that survived 1-3 days remains unclear since they were not monitored physiologically in the hours just prior to death. However, their clinical cardiopulmonary status was characterized by regular, slightly labored respirations, normal pulse rate or mild tachycardia, and good limb perfusion. Terminally, these animals became bradycardic, dilated one or both pupils, and showed irregular breathing associated with increasing apneic spells. The mode of exit in these subjects suggested failure of cerebral function or development of brain edema leading to brain stem compression. The cause of death appeared to differ from that seen among the Group III animals, which died of cardiovascular complications alone.

Neuropathologic Findings

The neuropathologic changes produced by exposure to controlled hypotension are summarized in table 1. The brains of all 14 Group I animals showed characteristic areas of parenchymal necrosis which could often be seen grossly as well as microscopically. Such lesions varied only in extent between monkeys with milder or more severe insults. The focal cerebral necrosis noted both in short and long term survivors affected specific areas, including cortex of the middle paracentral region, the posterior parietal cortex, particularly in the depths of the intraparietal sulcus, the anterior occipital and posterior temporal regions and immediately adjacent areas. Orbitofrontal cortex and superior temporal cortex were relatively free of lesions. These foci of cortical necrosis were extensively present throughout the involved zones in animals with marked or moderate clinical deficits, while their extent was restricted in monkeys showing slight or no neurologic changes. Many of the monkeys also showed focal necrosis affecting the hippocampus, particularly Sommer's sector, as well as cerebellar cortex, which was affected to a greater or lesser extent in 12 of 14 lesioned animals. In a few severely injured animals, areas of necrosis in globus pallidus, caudate nucleus or thalamus were seen. Brain stem and hemispheric white matter were unaffected. Morphologic changes indicative of brain swelling were common among the animals dying early. These changes included convolutional flattening, grooving of the uncus by the tentorial edge and herniation of the cerebellar tonsils and vermis. A detailed discussion of the patterns of cerebral injury and their pathogenesis will be presented separately.

Discussion

Several previous studies have failed to produce focal brain lesions in animals exposed to marked hypoten-
sion or have demonstrated such lesions but found poor correlation between the magnitude of hypoten-
sion and presence or extent of injury. Most of these
studies had a high mortality during the early hours
following hypotension whether or not brain lesions
were produced. The present study had 3 major
goals: 1) to produce focal or diffuse brain injury in
monkeys exposed to hypotension in the absence of
significant hypoxemia, hypercarbia, or acidosis, 2)
to attain survival for intermediate or prolonged periods,
and 3) to correlate various parameters of the hypoten-
sive insult with outcome with respect to the brain and
the cardiovascular system.

The mean arterial blood pressure below which brain
injury occurred was 25 mm Hg. This threshold value
was highly reproducible: brain lesions developed in 12
of 13 monkeys exposed to a MABP at or below this
level but in only 1 of 16 maintained at a higher
MABP. Brierley and associates produced neuro-
pathologic changes in monkeys by reducing the mean
cerebral perfusion pressure (MABP minus cerebral
venous sinus pressure) to a value of 22 mm Hg or
lower. This threshold value is similar to ours since the
external auditory meatus in our animals was
positioned level with the right atrium and right atrial
and jugular venous pressures were 3–5 mm Hg.

Moreover, Gamache and Myers found that reduc-
tions of MABP to between 25 and 30 mm Hg
produced brain edema but no focal brain lesions in
rhesus monkeys.

The duration of hypotension also determined
whether the brain was injured. The duration of ex-
posure among the 14 brain-lesioned animals ranged
from 22 to 65 minutes. Three-fourths of the brain-
lesioned monkeys subjected to marked hypotension
for 33 min or less showed only minor neuropathologic
changes and no neurologic deficits, whereas three-
fourths of lesioned animals exposed for longer than 35
days developed marked clinical and neuropathologic
changes.

Our finding of a close correlation between severity
of hypotension and neuropathologic outcome con-
trasts with the experience of Brierley et al. who found
no significant differences in mean maintenance blood
pressures and insult durations between brain-lesioned
and brain-intact monkeys made hypotensive by
trimethaphan and hemorrhage. Their variable
employment of intermittent head and body tilt during
hypotension may have accounted for the lack of con-
sistent correlation. This additional maneuver may
result in a more complex insult by provoking
hemodynamic alterations that activate cardiac and
pulmonary physiologic reflexes as well as by affecting
cerebrospinal fluid dynamics.

The narrowness of the range within which the
MABP is maintained may also affect the correlation
between magnitude of hypotension and pathologic
outcome. We made particular efforts to maintain the
MABP within ±2 mm Hg of the stated target pressure
throughout exposure. Analysis of polygraph records
confirmed maintenance of the pressure within this
range during more than 90% of the hypotensive inter-
val in most animals. Those animals whose outcome
coincided less well with the magnitude of hypotension
e.g., monkey 514) experienced wider and more
prolonged fluctuations in their maintenance pressures.

Although barbiturate anesthesia decreases cerebral
metabolic rate and protects the brain against oxy-
geen deprivation, the cumulative mg/kg pentobar-
tal doses utilized in our study did not differ between
lesioned and non-lesioned animals. The mean
cumulative dosage given (38.5 ± 0.9 mg/kg) was
considerably lower than that used in most previous studies
of hypotension.

Changes in cerebral electric activity during
hypotension best predicted neuropathologic outcome.
A hypotensive insult sufficient to cause cerebral elec-
tric silence for longer than 25 min almost invariably
caused marked sensorimotor deficits and severe brain
injury. An exposure that caused EEG flattening for a
shorter time (6–13 min) resulted in restricted brain
injury. An exposure that produced little (<5 min) or no
EEG flattening generally caused no neurologic or
pathologic changes. Only 4 exceptions to these
generalizations occurred among 30 monkeys. Monkey
408 experienced 39 min of cerebral electric silence but
showed no brain lesions. However, this animal sur-
vived only 3 hours, a length of time often insufficient
for appearance of definite brain edema and tissue
necrosis. The 3 other exceptional animals (503, 417, and 502)
experienced brief or no EEG flattening
and showed restricted cortical necrosis. The oc-
currence of lesions in 2 of these animals (417 and 502)
may be due to the fact that they experienced the
longest insults (75 and 65 minutes, respectively) and
lowest pH's (7.01 and 7.13) among the lesioned sub-
jects.

The present study demonstrates that hypotension,
accompanied by only a slight acidosis (with a lowest
pH as high as 7.32) and no hypoxemia or hypercarbia,
may cause parenchymal brain injury provided the
blood pressure is lowered sufficiently to abolish the
brain's electric activity for longer than 5 min. When
these circumstances obtain, the magnitude of brain in-
jury tends to vary directly with the duration of EEG
flattening. Hypoxemia did not occur in this model
despite the fact that assisted ventilation, employed less
in the present study than in previous studies, was
utilized for <10% of the hypotensive period in most
animals.

In an earlier study using rhesus monkeys, lowering
of MABP to 25 mm Hg for 15 or 30 min reduced the
amplitude and frequency of the EEG but failed to
produce flattening. Despite the absence of flattening,
many animals in that study developed brain edema
and died after many hours. However, none showed
any focal parenchymal lesions. Brierley and
associates noted EEG flattening when the cerebral
perfusion pressure fell below 22–23 mm Hg. In their
study, animals that developed minor brain injury ex-
perienced isoelectric EEG's for 14–32 min while those
that developed extensive injury experienced EEG
flattening for 17–46 min. The prolonged electric
silence that several of their animals experienced may
account for the much shorter survival times (4–8
hours) of their markedly injured animals and the
development of widespread lesions throughout cerebral cortex. This is in contrast to the restricted lesions that many of the present animals showed.

The highly reproducible threshold of 20-21 mm Hg for EEG flattening in our study contrasts with the findings of Wiederholt et al., who observed flattening in dogs when the MABP was reduced to 30-50 mm Hg by continuous trimethaphan infusion whereas EEG rhythms were depressed but never abolished when the same level of hypotension was produced by blood withdrawal alone. These authors suggested that trimethaphan may directly depress cortical electric activity. The difference in findings may result from the lower trimethaphan doses employed in the present experiments (range = 10-30 mg/animal) as compared with those utilized by others.2128t9>20

A major finding of this study was the distinction in the nature of the hypotensive insult that caused brain injury versus that which caused early death from cardiovascular failure in the absence of brain injury. Cerebral injury almost never developed in animals maintained above 25 mm MABP. On the other hand, all animals that died in cardiogenic shock without brain injury after a delay of several hours had been exposed to MABP's between 27 and 34 mm Hg. Whether exposure to this “intermediate” range of hypotension led to death from cardiogenic shock or not depended on its duration: “intermediate” hypotension for less than 90 min usually resulted in intact survival while such pressures for longer than 90 min invariably led to death within 24 hours from documented progressive hypotension and cardiac arrhythmias. Since maximum acidosis always occurred at the end of hypotensive exposure, the more marked acidosis in the non-survivors largely reflects their longer insult durations.

Most animals that died of cardiovascular decompensation recovered a normal EEG, were alert, had no neurologic abnormalities when monitored until death, and showed no cerebral lesions. Thus, our data indicate that most, if not all, animals that die in shock during the 24 hours following exposure to hypotension do not develop these circulatory changes as a result of nervous system damage. The delayed recovery of MABP despite full resuscitative efforts in monkeys that die early after hypotension, as well as the later appearance of irreversible cardiovascular collapse, provide compelling evidence that death is due to failure of the heart as a pump irrespective of the state of the nervous system.

Several conclusions can be drawn from the present study:

1. Focal cerebral and cerebellar cortical necrosis and brain swelling can be produced in monkeys by exposing them to profound systemic hypotension in the absence of hypoxemia, hypercarbia, or marked acidosis.

2. The threshold MABP required to produce such brain injury approximates 25 mm Hg. Exposure to a MABP lower than this value for longer than 30 min almost invariably causes brain injury while hypotension above this value rarely leads to neuropathologic changes even after exposures as long as 3 hours.

3. Hypotensive exposures that lead primarily to central nervous system injury or to delayed cardiovascular failure can be distinguished as follows:
   a. Brief (<40 min) periods of profound hypotension (MABP ≤ 25 mm Hg) result in neurologic and neuropathologic changes generally without associated cardiovascular or pulmonary complications.
   b. Hypotension of 25-35 mm Hg rarely causes nervous system injury under the conditions of this study. However, when maintained for longer than 90 min, it leads to death during the first post-insult day from irreversible cardiovascular failure; when maintained for less than 90 min, it usually results in intact survival.
   c. Exposure to hypotension of >35 mm Hg may be tolerated for prolonged periods (up to 3 hours) with neither neurologic nor cardiovascular sequellae.

4. Reduction of the MABP below 22 mm Hg almost invariably results in cerebral electric silence.

5. Of the parameters monitored, neuropathologic outcome correlates best with duration of EEG flattening. Animals that developed marked brain lesions sustained >25 min of isoelectric EEG while those that developed mild lesions usually experienced 5-15 min and those that developed no lesions <5 min of cerebral electric silence.

6. The cerebral arteriovenous differences for glucose and oxygen increase markedly during exposure to hypotension in all animals. This increase is significantly greater in animals that become brain-lesioned than in those that remain intact and in those that develop severe lesions than in slightly lesioned animals.

7. The use of low doses of barbiturate anesthetics and of trimethaphan coupled with hemorrhage allows the production of a hypotensive insult requiring only minimal ventilatory assistance yet resulting in a significant proportion of lesioned animals that survive for intermediate or prolonged periods.

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