Changes in local cerebral blood flow following profound systemic hypotension

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The authors studied local cerebral blood flow in monkeys rendered hypotensive by infusion of a ganglionic blocking agent. Application of the ¹⁴C-antipyrine method demonstrated that the blood flow: 1) normally varies reproducibly from one structure to another within the brain; 2) appears at its lowest level in all structures during the early minutes of a rapid-onset hypotension; 3) maintains the same general rank order of blood flow rate during hypotension as was present during normotension; and 4) returns to supranormal levels immediately following the rapid restoration of blood pressure. The values for local cerebral blood flow remain close-to-normal in some animals and diminish significantly in others during late recovery from hypotension. The close-to-normal values accompany uncomplicated recoveries while the diminished values appear in those animals which became neurologically depressed. Areas of the brain considered predisposed to hypotensive injury did not exhibit depressions in blood flow rate during hypotension more markedly than did other brain areas. The present results are interpreted as strong evidence against the "border zone" hypothesis.

KEY WORDS  
• cerebral blood flow  
• hypotension  
• hypotensive brain injury

ALTHOUGH episodes of spontaneous or controlled hypotension are familiar to all clinicians, little is known about the changes that occur in the overall cerebral blood flow (CBF) or in the blood flow to specific brain regions either during or after such episodes. The local cerebral blood flow (L-CBF) refers to that which is distributed to individual neuroanatomic structures as compared to regional blood flow which is most commonly measured by determining the washout curves of gamma emitters detected by probes placed on the surface of poorly delimited, three-dimensional anatomic sites. While preliminary measurements of regional CBF have been carried out during episodes of hypotension,¹⁴ no quantitative data have been reported on L-CBF.

Previously, we have described the physiological and neuropathological effects of episodes of profound lowering of blood pressure on a rhesus monkey.⁷,⁸ During 15- and 30-minute episodes of hypotension, the heart rate decreased by an average of 33% while the electrocardiogram (EKG) showed only a slight depression of the T wave in most animals. The impedance of the cerebral cortex tissue increased while the electro-
encephalogram (EEG) decreased in amplitude. These latter electrophysiological changes rapidly reverted to normal soon after normal blood pressure was restored.

Fifty percent or more of animals showed signs of severe neurological depression during the recovery period when the episode of hypotension had lasted as long as 30 minutes. These animals exhibited breathing irregularities and could not be removed from the ventilator. Later they became hypotensive and required infusion of phenylephrine to maintain blood pressure. The development of cardiorespiratory abnormalities in these neurologically depressed animals contrasted with the behavior of the surviving animals that showed no neurological deficits. The latter animals were able to maintain their blood pressure within normal limits after 5 to 6 hours without further vasopressor support. Edema of the brain appeared in the majority of animals with neurologic depression. As the brain edema evolved, the electrical impedance again augmented and the EEG flattened.

This study seeks to complement our previous studies with the rhesus monkey by determining:

1. The changes in L-CBF induced in various brain structures both during hypotension and after rapid restoration of blood pressure.
2. Whether brain areas exist where the blood flow ceases altogether or where the reduction in blood flow is out of proportion to that observed in other brain areas during hypotension.
3. If such areas of disproportionate blood flow reduction do exist, whether this reduction might account for the distribution of tissue injury seen after recovery from hypotension.
4. Whether differences in blood-flow rate occur between those animals which recover rapidly to normality (following restoration of blood pressure) and those which later develop neurological abnormalities.

Materials and Methods

The identical model and methods were used as previously described. Twenty-one late juvenile rhesus monkeys were used in the present study. After each animal was anesthetized with intravenous pentobarbital, 30 mg/kg, it was intubated and mechanically ventilated with a Harvard respirator.* Mechanical ventilation continued from the beginning of the control period until the animal's recovery from hypotension was well under way. PE 90 polyethylene catheters† were placed into a femoral artery and vein through an inguinal cutdown. The arterial catheter was attached to a Statham pressure transducer;‡ the blood pressure and heart rate were continuously recorded, and the arterial blood was periodically sampled. Blood samples of 0.4 ml were directly analyzed for pO₂, pCO₂ and pH. The venous catheter served for the injection or infusion of any pharmacological agents or fluids.

Each animal was monitored for at least 90 minutes before the initiation of hypotension. During this time control arterial blood samples were collected for analysis at 30-minute intervals. During the ensuing episodes of regulated hypotension, samples were collected at 15-minute intervals and, during the recovery period, again at 30-minute intervals to record any alterations in respiratory gas or acid-base state of the animal. The pO₂ of the arterial blood was maintained at all times between 85 and 100 mm Hg by regulating the oxygen content of the inspired gas mixture. The pCO₂ was adjusted to and maintained in the range 26 to 36 mm Hg by adjusting the rate or stroke volume of the respirator. The pH was maintained between 7.35 and 7.45 either by respirator adjustments as described above, or by 3 to 5 ml injections of sodium bicarbonate (0.892 mEq/ml). The respirator was briefly halted at various times to evaluate the animal's ability to breathe spontaneously.

Hypotension was induced and regulated by infusing trimethaphan. During the hypotensive episode, mean arterial blood pressure was maintained approximately at 25 mm Hg. The episode was terminated by rapidly

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*The Harvard respirator is made by Harvard Apparatus Company, 150 Dover Road, Millis, Massachusetts 02054.
†PE 90 polyethylene catheter made by Clay Adams, Division of Becton and Dicksons, Parsippany, New Jersey 07054.
‡Statham pressure transducer made by Statham Instruments Company, 2230 Statham Boulevard, Oxnard, California 93030.
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elevating and maintaining the blood pressure near the control level by infusing phenylephrine. All animals were decapitated at specified times before, or during the hypotensive episode (maximum length = 30 minutes), or after the restoration of blood pressure. The times of decapitation were selected to coincide with critical changes in the physiological state as observed in the serum and cisterna magna glucose, in the cisterna magna pressure, or in the cerebral electrical activity.\textsuperscript{7,8}

Continuous recordings of the EKG and the EEG were made during each experiment. Normal body temperature and the arterial pH, \(pO_2\), and \(pCO_2\) were maintained. A \(^{14}\text{C-antipyrine}\) modification of the autoradiographic method was employed to measure the L-CBF.\textsuperscript{9,10} One minute prior to decapitation, 200 \(\mu\) Ci/kg \(^{14}\text{C-antipyrine}\) (specific activity, 15.5 mCi/mm) was infused intravenously with a Harvard infusion pump.\textsuperscript{*} The hematocrit and specific gravity of the blood were recorded just prior to antipyrine infusion. Throughout the period of infusion sequential droplets of arterial blood were collected and weighed. The concentrations of tracer in the droplets were determined by liquid scintillation counting.\textsuperscript{†} Representative samples were also counted following the addition of an internal standard. A curve which depicted the changes in concentration of the tracer in the arterial blood throughout the 1-minute infusion period was then plotted. Immediately after decapitation, the brain was removed from the skull and frozen in a solution of cooled (70° to 90° C) isohexane-isopentane (1:3). The frozen brain was then embedded in 3% cellulse and sectioned at 30 \(\mu\)M with an A-O sliding microtome.\textsuperscript{‡} After drying, each tissue section was apposed to Kodak SB-54 x-ray film in cassettes and stored for 4 days in the dark. The tissue concentrations of antipyrine were determined by quantitative autoradiography from the developed photographic films by an optical densitometer.\textsuperscript{§}

Ten measurements of optical density (OD) were made for each of 55 neuroanatomic structures in each brain as sampled from multiple sections. A mean value and standard deviation were then computed for each of the selected structures for each brain.

The aperture size and the light source intensity of the densitometer limited the accuracy of the resolution of the optical density of very small structures. This factor, together with the variation in blood flow rates which frequently are found between different portions of individual structures did not permit an accurate calculation of the blood flow rates through small structures although approximations were made for a few.

It was not always possible to differentiate the anatomic subdivisions of the thalamus from the autoradiographic sections. Even so, a number of thalamic nuclei examined in individual brains generally showed similar flow rates. Therefore, the dorsomedial nucleus was selected as representative of the thalamus as a whole and references to the thalamus generally refer to values obtained for this region.

Several previously calibrated plastic standards which corresponded in OD to various concentrations of tracer in tissue cut at 30 \(\mu\)M in thickness were included on each film. Sections 30 \(\mu\)M thick from the same brain but cut with two different microtomes were compared to verify the results obtained from the above-mentioned calibration standards. With these standards, the concentration of tracer could be estimated in each structure in the section. A graphic solution to the relation:

\[
\text{arterial conc of tracer} = \frac{\text{conc of tracer in specific structure}}{\text{permitted calculation of local cerebral blood flow}}
\]

The animals were grouped into control; 5-minute hypotension (H5); 30-minute hypo-

\textsuperscript{*} \(^{14}\text{C-antipyrine}\) supplied by International Chemical and Nuclear Corporation, 2727 Campus Drive, Irvine, California, 92644. Harvard infusion pump, model 940, manufactured by Harvard Apparatus Company, 150 Dover Road, Millis, Massachusetts 02054.


\textsuperscript{‡} A-O model 860 sliding microtome manufactured by American Optical, Instruments Division, Buffalo, 15 New York.

\textsuperscript{§} Photovolt model 501A densitometer, model 52 window unit with 87 mm circular aperture, manufactured by Photovolt Company, 1115 Broadway, New York, New York 10010.
tension (H30); 5-minute recovery (R5); and complicated and uncomplicated recovery groups. The flow rate was determined from the 10 OD measurements carried out on each structure in each animal. The mean values for the L-CBF of the 55 different neuroanatomic structures were then calculated for each of the experimental groups and compared (structure by structure) to the values obtained for the control group. Similar comparisons were also carried out for significant levels of group differences by analysis of variance (F test) followed by Scheffe’s multiple comparison procedure.\(^{20}\)

The mean value for each structure in each group was also tested for its own level of significance of difference from: the average total CBF rate for that group (approximated by averaging the flow rates of all 55 structures examined in each group, although the relative contribution of the blood flow of each component structure to the overall blood flow was not known); and the flow rates of the two structures which were ranked immediately above and below its own flow rate. The paired \(t\) test\(^{13}\) was used to rank the flow rates to component structures within each brain since other statistical methods were not generally applicable to the sample size used.

Results

Physiological and Pathological Data

The pH of the arterial blood was maintained within the control range of 7.35 to 7.45, the \(pO_2\) between 85 and 125 mm Hg, and the \(pCO_2\) between 26 and 36 mm Hg throughout the episodes of hypotension and the recovery period. The physiological and neurological alterations observed as a consequence of the hypotension followed the same patterns as described previously\(^7,8\) and are summarized in Table 1.

Bradycardia developed in all during the period of lowered blood pressure. The (EKG) showed, however, only slight ST or T-wave changes. Respiratory slowing also developed after about 15 minutes of hypotension\(^8\) and persisted for up to 60 minutes into the recovery period. The EEG frequency and amplitude diminished slightly to moderately during hypotension but recovered rapidly following restoration of blood pressure. During the recovery period distinct neurological abnormalities appeared in a number of animals. These animals often showed disturbed patterns of breathing which included Cheyne-Stokes breathing, hyperpnea, and apnea. They also became flaccid and lost their responsiveness to stimulation. One animal, Monkey R120, developed dilated and fixed pupils and multiple cranial nerve impairments approximately 60 minutes into recovery. It also became apneic and bradycardic. This animal was treated with intravenous epinephrine (.05 ml, 1:1000 USP single injection), intravenous furosemide (5 mg single injection \(\times\) 2), and urea (50 ml infusion). Thereafter, the animal improved until decapitated after 120 minutes of recovery. Although this was the only animal to exhibit such marked signs of deterioration among the present recovery group, reactions of this type have been observed in earlier studies.\(^7,8\) The blood flow values obtained with this animal lie well within the range of values observed for other animals in the depressed group and are included in the present study despite the measures which were taken in treatment.

When its brain was removed, this animal showed only a mild tenting of the dura and no distinct signs of brain swelling. Gross brain swelling was suspected clinically in two other animals (Monkeys R150, R240) but was confirmed on postmortem examination in only one (Monkey R240).\(^8\)

General Patterns of Blood Flow Before and After Hypotension

The L-CBF in the three control animals varied from one structure to another over a wide range. Figure 1 depicts the L-CBF values for a limited number of structures among the 55 examined at the different times before, during, and after the hypotensive episodes. The ranking of structures with respect to their blood flow rates were similar for the three time periods examined. However, the magnitudes of the differences in blood flow rates from one structure to another in the sequence was greatly diminished during hypotension. Thus, during this period, many more structures exhibited similar flow rates than before or afterward. Yet, minor differences did appear in the ranking of structures with respect to blood flow rates during the three time periods. These changes in rank order are summarized in Table 2, and usually amounted to one or more changes in the position of structures.
Systemic hypotension and local CBF

**TABLE 1**

*Effects of 30-minute episodes of hypotension (mean blood pressure = 25 mm Hg)*

<table>
<thead>
<tr>
<th>Group Sampled</th>
<th>No. of Animals</th>
<th>Vascular Status</th>
<th>EEG Activity</th>
<th>Respiratory Activity</th>
<th>General Neurologic Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>3</td>
<td>no vp</td>
<td>primarily delta</td>
<td>spont</td>
<td>reactive</td>
</tr>
<tr>
<td>H-5</td>
<td>4</td>
<td>trimethaphan</td>
<td>mild D</td>
<td>spont</td>
<td>moderately depressed</td>
</tr>
<tr>
<td>H-15</td>
<td>1</td>
<td>trimethaphan</td>
<td>mild D</td>
<td>spont</td>
<td>depressed</td>
</tr>
<tr>
<td>H-30</td>
<td>3</td>
<td>trimethaphan</td>
<td>mild to mod D</td>
<td>apneic</td>
<td>depressed</td>
</tr>
<tr>
<td>R-5</td>
<td>3</td>
<td>vp</td>
<td>improved to mild D</td>
<td>apneic</td>
<td>depressed</td>
</tr>
<tr>
<td>R-15</td>
<td>1</td>
<td>vp</td>
<td>improved to mild D</td>
<td>apneic</td>
<td>depressed</td>
</tr>
<tr>
<td>R-30</td>
<td>1</td>
<td>vp</td>
<td>essentially normal</td>
<td>apneic</td>
<td>depressed</td>
</tr>
<tr>
<td>R-60</td>
<td>1</td>
<td>vp</td>
<td>essentially normal</td>
<td>spont</td>
<td>moderately reactive</td>
</tr>
<tr>
<td>R-120</td>
<td>1</td>
<td>vp</td>
<td>iso at R-60, improved later</td>
<td>apneic</td>
<td>depressed with brsw</td>
</tr>
<tr>
<td>R-150</td>
<td>1</td>
<td>vp</td>
<td>improved to mild D</td>
<td>Cheyne-Stokes</td>
<td>depressed</td>
</tr>
<tr>
<td>R-180</td>
<td>1</td>
<td>very little vp</td>
<td>return to normal</td>
<td>spont since R-90</td>
<td>fully reactive</td>
</tr>
<tr>
<td>R-240</td>
<td>1</td>
<td>vp</td>
<td>mild to mod D</td>
<td>hyperventil since R-60</td>
<td>depressed with brsw</td>
</tr>
</tbody>
</table>

* brsw = brain swelling confirmed at necropsy, D = decrease in wave amplitude and frequency, iso = isoelectric, spont = spontaneous respirations, vp = required vasopressors.

along the ordered continuum. The most prominent change was that the entire cortex and the caudate nucleus, and putamen all developed the highest blood flow rates when the tissues were sampled at 5 minutes into recovery. Thus, these structures disproportionately increased their blood flow rates during the period of posthypotensive hyperemia (Fig. 1 D). Those animals that rapidly and fully recovered from exposure to hypotension, as, for example, Monkeys R60 and R180, returned to a rank order sequence which closely approximated that observed in the control animals (compare Fig. 1 A and F, and Table 2 A).

When the arterial blood pressure was

**TABLE 2**

*Rank order of volumes of blood flow through various specific brain structures*

**A: General rank order of flow rates as characterized by control animals**

IColl > Gen > Put, Vermis > Caud, Cortex > DM, PHypo > PRS > Hippo > AHypo, MRS > Gl.Pal > Wht exceptions to above pattern observed in animals demonstrating essentially the same rank ordering:

animal R60: PRS > DM, PRS > PHypo > AHypo > Wht R180: Caud > Cortex > PRS > DM > PRS, Hippo >

**B: General rank order observed in hypotensive and post-hypotensive recovery animals**

IColl > Gen, Put, Caud, Cortex > DM, PHypo, PRS > Hippo, MRS > Gl.Pal > Wht exceptions to above pattern observed in animals demonstrating essentially the same rank ordering:


* All structures are listed in order of descending L-CBF as indicated by >. H and R designate the sample times for which exceptions to the rank order of control animals appeared (in minutes). IColl = inferior colliculus, DM = dorsomedial nucleus of thalamus, PRS = pnotine mesencephalalic reticular substance, Caud = caudate nucleus, MRS = mesencephalic reticular substance, Gen = geniculate nucleus, Gl.Pal = globus pallidus, Hippo = hippocampus, AHypo = anterior hypothalamus, PHypo = posterior hypothalamus, Put = putamen, Wht = white matter.

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rapidly depressed to 25 mm Hg, the blood flow to all structures in the brain diminished. These decreases were most prominent 5 minutes after the onset of blood pressure lowering and were significantly less when tested after 15 and 30 minutes. For example, after 5 minutes of hypotension the cortex diminished its blood flow by 68% while after 30 minutes it decreased it by only 55%. The comparable percentage decreases for the

![Graph showing rank order of blood flow rates for different brain structures](image-url)

**FIG. 1.** Rank order of blood flow rates for different brain structures as sampled before, during, or after exposure to hypotension. A = Control group, B = After 5 minutes of hypotension, C = After 30 minutes of hypotension, D = After 5 minutes of recovery, E = Neurologically depressed (complicated) animals (Monkeys R15, R30, R120, R150, R240), F = Neurologically reactive animals (Monkeys R60, R180). The rank order of blood flow to various brain structures is similar in all population groups except for that sampled after 5 minutes of hypotension (B) where the alterations in order are designated in parentheses. The values described for thalamus and cortex are averages of values obtained in various anatomical subdivisions (that is, VA, DM, VPL, VPM, pulvinar; prefrontal, precentral, postcentral, occipital, and superior temporal gyri). The thick horizontal lines designate where the significance of differences in flow rates to successive structures reaches a value of p < 0.05 (as determined by the paired t-test). The flow rates to all structures which lie between successive thick lines fail to differ significantly from one another; exceptions are marked: S > s indicates structure “S” differs significantly from “s,” as in B and E. “NS” indicates two structures in the late hypotensive animals (C) which do not differ significantly from one another although separated by thick horizontal lines. The vertical lines mark the borders (upper and lower) of the average flow for all 55 structures examined together in each brain for the different brains in each group; structures characterized by values which do not fall between these two lines are significantly (p < 0.05) above or below the group mean as determined by the paired t-test. VA = ventral anterior nucleus of thalamus; DM = dorsomedial nucleus, VPL = ventral posterior lateral nucleus; VPM = ventral posterior medial nucleus.
other 55 structures taken separately were all highly significant (> 95%). Five minutes after
the arterial blood pressure was rapidly re-
stored to its prehypotensive level, the L-CBF
to the various individual structures aug-
mented to values significantly higher than the
control values (> 95% confidence). Excep-
tions to this degree of blood flow increase
were the fastigial nucleus, globus pallidus,
hippocampus, hypothalamus, red nucleus,
reticular substance, spinal gray, subthalamic
nucleus, superior colliculus, superior olive,
thalamus (general), anterior commissure, s.
cerebellar peduncle, corpus callosum, optic
tract, and cerebellar white matter. Further-
more, the L-CBF to the geniculate nuclei,
substantia nigra, inferior colliculus, and those
cranial nerve nuclei examined were slightly
but significantly (> 95%) lower than that
observed in the same structures in the control
animals. During the later stages of recovery,
the L-CBF to all structures examined was
significantly below normal (> 95%) among
the depressed animals, and was close to nor-
mal in those animals which appeared neurolo-
gically intact (p >> 0.1).

Flow to Specific Structures

Stasis of blood flow was never observed in
any of the structures examined. While the
blood flow to the so-called “border zones” of
the cortex (which lie in the territories farthest
removed from the main stems of the cerebral
arteries) occasionally was lower than that in
adjoining cortex, the results from multiple
samplings of these areas in numerous animals
gave no suggestion that these regions differed
significantly (p >> 0.1) in their blood flow
rates from the neighboring cortex. The blood
flow to such border zone areas was satisfac-
torily described by specifying the blood flow
rates to neighboring or other cortical areas.
The changes in the mean values of the blood
flow to the cortex as a whole before, during,
and after the hypotensive episodes are sum-
marized in Fig. 1.

The effects of lowered blood pressure on
blood flow was not entirely uniform
throughout the brain (see the vertical bars in
Fig. 1). Those structures at the extreme ends
of the flow spectrum (for instance, the white
matter or globus pallidus, on the one hand,
and the geniculate nuclei or inferior colliculi,
on the other) consistently remained below and
above the mean cerebral blood flow values, as
calculated from the values of all brain struc-
tures taken together, during as well as after
the episodes of hypotension, regardless of the
animal's clinical status. The structures which
manifested the highest blood flow rates nor-
manly (the inferior colliculi and the geniculate
nuclei) also experienced the highest percent-
age decreases in blood flow during the period
of hypotension. At the same time, those areas
often considered to be predisposed to injury
during hypotension, namely, the putamen,
caudate nucleus, “border zones” of cere-
bellum and cerebrum, hippocampus, and
globus pallidus, all maintained absolute blood
flow rates which remained at or above the
calculated mean cerebral blood flow rates in
all animals examined (Fig. 1). Only the hip-
pocampus deviated in that, during the period
of supranormal flow at 5 minutes after
restoration of blood pressure, its blood flow
rate remained below the average of all other
brain structures summed (see Fig. 1 D). The
relative proportion of the blood flow which
was accorded to a few structures increased
significantly (p < 0.05) relative to the mean
of all other brain structures taken together
during the episode of hypotension. These
structures included amygdala, reticular for-
mation, and both hypothalamic areas. The
percentage decreases in blood flow to these
structures thus remained less than the average
percentage decrease observed for all the other
brain structures taken together.

Cerebral Blood Flow in Relation to Clinical
Status.

Those animals which required the infusion
of phenylephrine to maintain blood pressure
for a long period of time during recovery and
which exhibited slight to moderate depres-
sions of the EEG, abnormal respiratory
patterns, and depressed levels of conscious-
ness could be distinguished from those
animals which recovered fully by differences
in cerebral blood flow as shown in Fig. 1 E
and F. Among those animals which showed
signs of neurological and circulatory
deterioration, the blood flows to various
specific brain structures decreased generally
by 30% to 40%. More depressed still was the
blood flow to the anterior and posterior hypo-
thalamus, spinal gray matter, pontine
reticular substance (PRS), superior temporal
gyrus (STG), and amygdala in these animals.
On the other hand, the reactive or responsive animals showed mean levels of blood flow to various brain structures of 85% to 130% of normal. Generally, the rank order of L-CBF to various brain structures in the reactive animals was similar to that observed in the control animals (Fig. 1 A and F) while the rank order exhibited by the depressed animals more clearly resembled that obtained during the hypotensive periods (Fig. 1 B, C and E).

Some animals which showed signs of developing neurological depression late in recovery showed, for the first time, disproportionate reductions in blood flow to specific regions of the cortex, such as, the region of the postcentral gyrus, superior temporal gyrus, and anterior cerebellar gray matter. These alterations were observed among those animals which generally showed clinical or pathological evidence of edema of the brain.

Discussion

Antipyrine has been shown to be limited as to diffusion.6 Thus, those values which have been obtained with radioactively labeled antipyrine underestimate the actual blood flow rates. This error is greatest for those structures which show the highest blood flow rates where the underestimation may be as great as 30%. However, because the present study focuses primarily on alterations in blood flow during and after recovery from hypotension, the method’s limitation in this respect does not detract from its usefulness. Another limitation of the method is that, because the animals are decapitated, measurements of L-CBF can be carried out only with respect to a single point in time. Thus, the different time points studied with respect to the episodes of hypotension represent values obtained using several series of animals. Despite this, the alterations in blood flow which were delimited seem to reflect the alterations which would have taken place if corresponding measurements could have been obtained in the same animal at the various sample periods. Indeed, the L-CBF values obtained for various brain structures in the present study in the lightly anesthetized (control) animals were, although slightly lower, still in close agreement with the values observed in unanesthetized primates (Kennedy, personal communication).

Trimethaphan is not known to exert a direct vasodilatory effect on cerebral blood vessels.8 Therefore, the reductions observed in CBF result primarily from the reduction in blood pressure. Phenylephrine, which is reported to increase CBF to a slight degree,9 is thought to affect cerebral blood vessel caliber only negligibly.21 Therefore, a considerable part of the changes in both directions observed in L-CBF may result from the marked changes observed in blood pressure rather than from the direct effects of the drug treatment on cerebral blood vessel caliber.

Although the general rank order of L-CBF to various structures of the brain was largely preserved during and after exposure to hypotension, the normally high magnitudes of the differences in L-CBF observed from structure to structure were greatly reduced. However, some structures, such as the hypothalamus, reticular formation, caudate nucleus, and posterior cerebellar gray matter showed disproportionately slight changes in L-CBF. Since the blood flow to various brain structures is generally adjusted to their state of activity as recently demonstrated by the 14C-deoxyglucose method,4 the relatively small decreases in blood flow to these structures during hypotension may well result from their active participation in the response to the hypotensive stress itself.

The observation that the L-CBF of all brain structures was less depressed after 15 to 30 minutes than after 5 minutes of hypotension, despite the fact that the mean arterial blood pressure was maintained at 25 mm Hg throughout, suggests that some autoregulation persists even at this low blood pressure. This interpretation seems particularly likely since the respiratory gas tensions and pH of the arterial blood were maintained within their normal ranges at all times in the present study.

No animal showed any areas of cessation of blood flow in the brain during exposure to hypotension. This finding confirms the report of Ames, et al.,2 with regard to the effects of hypotension on no-reflow. In addition, no differences in the reactions of the blood flow rates to blood pressure lowering were observed between those areas of cortex which correspond to the so-called “border zones” and those areas of cortex which are located closer to the arterial stems (p > 0.1). This finding, which has been observed earlier using less precise methods,14 is of particular importance since much speculation has been
focused on the supposed tendency of the "border zones" to show disproportionate decreases in blood flow during hypotension. This tendency, in turn, has been suggested as the basis for the supposed predilection of these areas to injury during blood pressure lowering.

Neuropathological changes have been observed in the cerebral cortex and cerebellum of the human following hypotension of slow onset. Microscopic changes have also been demonstrated following hypotension of rapid onset in animals. Some investigators have suggested that a sudden reduction in blood pressure is necessary for the occurrence of lesions in the "border zones." While no pathological analysis could be carried out on the brains of the present animals due to the techniques of handling, previous studies which used the identical animal model have failed to demonstrate pathological changes other than a diffuse brain edema. The present study supports the earlier finding of an absence of focal brain pathology following hypotension when all experimental parameters have been carefully controlled. These studies taken together also suggest that the focal pathology which has been observed by others after exposure of animals to hypotension, probably resulted not from the abruptness of onset of the episodes but rather from differences in the conditions under which the hypotension was maintained.

The structures which manifested the highest blood flow rates and which also showed the largest percentage decrease in blood flow during and following the hypotensive episodes (that is, the inferior colliculi and the geniculate nuclei), failed to exhibit any pathological abnormalities after recovery despite their relatively greater diminutions in blood flow. This finding is the more unexpected since the inferior colliculi and the superior olives (another structure which is supplied with a high rate of blood flow) are among the structures the most sensitive to the effects of anoxia. However, since the respiratory gas tensions and pH were carefully maintained, and since no brain structure showed blood flow stasis, it can be concluded that no area of the brain experienced any actual anoxia during the hypotensive episodes. The fact that the present animals were mechanically ventilated and never allowed to remain apneic suggests that the oxygen levels may have been better maintained in the present study than in others where extensive neuropathological sequelae were reported. If this interpretation is correct, it would underscore the role of oxygen deprivation in producing what has been generally regarded as hypotensive brain injury. The present results also suggest that the mean CBF must decrease to levels as low as 30% of normal (and indeed probably lower) for as long as 30 minutes in order to produce the conditions which lead to brain edema. Indeed, a blood flow of 40% of normal has been suggested as being sufficiently low as to cause metabolic injury.

The mean L-CBF of various brain structures was found to be depressed to approximately 20% and to 40% of normal during the early and late stages of hypotension respectively. Yet some structures such as the hippocampus, globus pallidus, caudate nucleus, putamen, and various regions of the cortex sustained blood flow reductions expressed as percentage values which always were either equal to or less than the mean value calculated for all brain structures together. Since areas which have been described as predisposed to injury with hypotension are not characterized by greater reductions in blood flow generally than are other areas during hypotension, it seems likely that the pathology observed in these areas is related to effects other than to disproportionate underperfusion during hypotension.

The observation of a significant increase in blood flow during the first 5 minutes of recovery, a process similar to what Lassen has called "luxury perfusion," might be interpreted as reflecting an impaired autoregulation. However, the hypothalamus, hippocampus, reticular substance, and thalamus all exhibited blood flow rates at 5 minutes into recovery which were not significantly different from corresponding control values. In view of the relation between L-CBF and cerebral metabolism and functional activity, the present observation of smaller proportionate decreases in blood flow to the reticular substance and the hypothalamus during hypotension, as well as the marked increases in flow to hypothalamus in those animals which had satisfactory recoveries provides the first evidence that changes in blood flow to these anatomic structures may
reflect an animal's status with regard to its autonomic and respiratory reactivity (its overall bodily homeostasis). That these structures may play a role in cerebral autoregulation has already been suggested though changes in blood flow in these structures with altered states of autoregulation have never before been quantitated.\textsuperscript{15,16}

The CBF may return to normal when the blood pressure is restored by the infusion of a vasopressor agent as evidenced by the data obtained from the recovering animals. However, the degree of recovery of the CBF is not necessarily proportional to the level to which the blood pressure has been restored as has been suggested in recent discussions of this subject.\textsuperscript{19} In the present study, despite the recovery of blood pressure to preinsult levels in all animals, a variety of posthypotensive blood flow levels was observed. Animals in which the CBF remained close to normal made satisfactory clinical recoveries; those in which the CBF was consistently retarded showed a depressed neurological state. The specific reductions in blood flow which were noted in the anterior cerebellar gray matter and in certain zones of the cerebral cortex (the postcentral and superior temporal gyri)\textsuperscript{1} to several hours following restoration of blood pressure may be attributed to compression of small blood vessels within areas of tissue edema.\textsuperscript{17} Alternatively, these zones of diminished blood flow may result from distortions of conformation of the hemispheres caused by swelling of the brain.\textsuperscript{18}

The bulging of cortex out of burr holes which often developed several hours following an episode of hypotension could often be reduced by pharmacological treatment.\textsuperscript{9} A single animal in the present study was so treated for such a presumed brain edema. However, the brain of this animal when examined later showed no gross evidence of brain swelling. Nonetheless, the various structures in the brain of this animal manifested a decreased blood flow as measured at the time of decapitation. On a preliminary basis only, this finding suggests that the pharmacological reduction of brain swelling, although it may improve cerebral circulation, does not necessarily lead to its return to normalcy.

We have described the changes in blood flow which occur in various anatomic areas of the brain before, during and after episodes of hypotension. During the episodes of hypotension, the blood flow diminishes more or less diffusely throughout the brain and spinal cord without evidence of specific zones which show any blood flow stasis or inordinate reductions in blood flow. However, circumscribed areas, of the hypothalamus, thalamus, and reticular formation, show lesser alterations in blood flow depending on the animal's response to stress. These effects suggest a relationship between the changes in blood flow to these sites and the pattern of response of the animal to lowered blood pressure. As long as the respiratory gas tensions and pH of the arterial blood are maintained close to normal, episodes of marked cerebral ischemia of rapid onset and of 30-minutes duration do not lead to disproportionate ischemia to "predilection areas," no reflow, and/or animal death when rapidly reversed. When brain abnormalities develop in relation to carefully regulated episodes of profound hypotension they consist of disturbed cerebral metabolism and brain swelling.

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