Effects of Acutely Induced Hypertension in Cats on Pial Arteriolar Caliber, Local Cerebral Blood Flow, and the Blood-Brain Barrier

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SUMMARY Acute hypertension was induced in 19 anesthetized cats by the intravenous administration of angiotensin. The caliber of pial arteries was measured by a television image-splitting technique and local cerebral blood flow by the hydrogen clearance technique. As the blood pressure was increased, pial arterioles constricted and cerebral blood flow remained relatively constant, showing that autoregulation of cerebral blood flow was intact. At mean arterial pressures of more than 170 mm Hg arteriolar dilation appeared. In smaller arterioles (initial diameter less than 100 μm) a segmental dilation (the “sausage-string” phenomenon) frequently preceded uniform dilation. This arteriolar dilation was associated with a marked increase in local cerebral blood flow indicating that the upper level of autoregulation had been breached. In no cat was vasospasm or a decrease in blood flow observed during induced hypertension. Hypertension also caused dysfunction of the blood-brain barrier since, in 17 of 19 of the cats examined, there was extravasation of protein-bound Evans blue into brain tissue. In only one of the 19 cats subjected to neuropathological analysis was ischemic brain damage identified and this was restricted to minimal ischemic cell change. The results indicate that severe, induced hypertension in cats produces cerebral arteriolar dilation, an increase of cerebral blood flow, and dysfunction of the blood-brain barrier. These observations may be of importance in understanding the pathogenesis of hypertensive encephalopathy.

METHODS

The experiments were carried out on 19 anesthetized cats of either sex, weighing between 1.7 and 4.5 kg. The rapidly metabolized combination of alphaxalone, 67.5 mg/kg, and alphadoline acetate, 22.5 mg/kg (Saffan), was administered intravenously to induce anesthesia quickly. After endotracheal intubation, both femoral veins and one femoral artery were cannulated to administer fluids and drugs, and to measure mean arterial blood pressure, respectively. Positive pressure ventilation with 100% O₂ was used to maintain normocapnia (arterial PCO₂ ≈ 32 mm Hg) throughout the experiment. Anesthesia was maintained with α-chloralose (6 ml/kg of a 1% solution, iv); and muscular relaxation was achieved by intravenous injection of gallamine (10 mg). End-tidal PCO₂ was monitored continuously, and arterial pH, PCO₂, and PO₂ were measured frequently. Body temperature was maintained at 37–38°C by a heating blanket.
MEASUREMENT OF PIAL ARTERIOlar CALIBER

Each cat was placed in a stereotaxic head-holder and a unilateral craniotomy (2.0 × 1.0 cm) was performed in the parietal region with a saline-cooled dental drill. After removal of the bone flap, the dura was bathed in warmed mineral oil before being incised and reflected. By varying either the temperature or the flow rate of the mineral oil the brain surface temperature was kept close to 37.5°C as measured by a thermistor thermometer. The cut dural edges were sealed by bipolar diathermy.

Arteriolar caliber of 43 vessels was measured by the television image-splitting technique as modified by Wahl et al. in 10 of the 19 cats. The vessels were observed with a Bausch and Lomb stereomicroscope at magnifications of either 40x or 70x. To measure vascular diameter, the image was passed through an image-splitting eyepiece (Vickers). The split image was viewed using a television camera (Grundig FA 70) and a video monitor. The shearing screw of the eyepiece, which controls the degree of image-splitting, was connected to a sensitive potentiometer and, in turn, a pen recorder. Thus frequent measurements of shear (which is directly proportional to vessel caliber) could be obtained. The system was calibrated against monofilament nylon sutures of known uniform diameter before each experiment and allowed calculation of vessel diameter in micrometers. The surface of the brain was illuminated with a cold light source (Schott fiber optic system).

The pial arterioles studied were selected randomly, although an attempt was made to include both the largest arterioles that could be detected (resting diameter = 187 μm) and the smallest arterioles that could be measured accurately (resting diameter = 16 μm).

The coefficient of variation for repeated measurements of vessels under steady state conditions of arterial pressure and arterial gas tensions was found to be less than 1%.

MEASUREMENT OF LOCAL CEREBRAL BLOOD FLOW

Local cerebral blood flow was measured by the hydrogen clearance technique as modified by Pasztor and his co-workers. The electrodes were made of insulated platinum (200 μm in diameter) with a bare tip length of 1.0–1.5 mm, sharpened and then coated with platinum chloride. In eight cats electrodes were introduced through small burr holes into the superior parietal cortex, contralateral to the craniotomy, and fixed in place with dental cement. In four additional cats without craniotomy, electrodes were placed bilaterally. The electronic system used to amplify and display the currents from the platinum electrodes was similar to that described by Pasztor et al. After placement of the electrodes and application of the polarizing voltage, a stabilization period of approximately 1 hour was allowed before desaturation recordings were made. For each determination of cerebral blood flow, 10% hydrogen in oxygen was inhaled by the cats for approximately 10 minutes and then discontinued. The clearance of hydrogen was recorded for 8–10 minutes. The first 40 seconds of each clearance period were discarded to avoid arterial recirculation artifacts.

BLOOD PRESSURE ELEVATION

The blood pressure was elevated gradually in steps of approximately 20 mm Hg by the slow intravenous infusion of angiotensin II amide (Hypertensin, CIBA). This drug has no known pharmacological action on the cerebral circulation. Each new level of blood pressure was maintained steady for at least 5 minutes before a measurement of cerebral blood flow was made. At the highest blood pressure attained in each cat tachyphylaxis to angiotensin occasionally developed. In these cats blood pressure was maintained by adding metaraminol (Aramine, Merck, Sharp and Dohme) to the infusion. Metaraminol was only required for two cats before the measurements of cerebral blood flow and pial vessel caliber had been completed. In a few other cats metaraminol was used to maintain the systemic arterial pressure prior to perfusion and fixation of the brain for subsequent neuropathological examination. A period of between 90 and 180 minutes elapsed between the start of the angiotensin infusion and the termination of the experiment by perfusion-fixation.

![Figure 1](http://circres.ahajournals.org/). The effect of increasing mean arterial blood pressure (MABP) on pial arteries with a resting caliber greater than 100 μm in eight cats. Vessel caliber was calculated as a percent change from the caliber of each vessel at a MABP of 135 mm Hg. The mean arteriolar caliber was 146 ± 23 μm (X ± SD).
BLOOD-BRAIN BARRIER AND NEUROPATHOLOGY

At least 30 minutes before the end of the experiment, a 2% solution of Evans blue (3.0 ml/kg, iv) was injected slowly to identify areas of damage to the blood-brain barrier. These were then subjected to a neuropathological examination. Five cats without either craniotomy or electrode placement were studied following the induction of acute hypertension to serve as controls for the neuropathological examination.

Prior to perfusion-fixation the cats were removed from the stereotaxic head-holder and placed in the supine position. After heparinization (1,000 IU/kg), a thoracotomy was performed and a cannula with a short lip was introduced into the ascending aorta via the left ventricle and secured by clamping. Physiological saline was infused (at the same pressure as the elevated mean arterial blood pressure) for 15-20 seconds after incising the right atrium and clamping the thoracic descending aorta. This was followed immediately by 1,000 ml of FAM fixative (40% formaldehyde-glacial acetic acid-absolute methanol = 1:1:8) at the same pressure. This method of perfusion-fixation is based on that of Brierley et al. After perfusion the cats were decapitated and the head was stored in fixative at 4°C for at least 2 hours. The brain then was removed. The hindbrain was detached by a cut through the midbrain and the cerebral hemispheres were cut into coronal slices 6-7 mm thick. The brainstem was cut perpendicular to its long axis into slices 6-7 mm thick and the cerebellum into two slices perpendicular to the folia of the dorsal surface of each hemisphere. Large representative bilateral blocks of brain were embedded in paraffin wax and sections (7-8 μm thick) were stained by a method combining cresyl violet and Luxol fast blue, by hematoxylin and eosin and by the Martius scarlet blue method for fibrin. The sections were examined by conventional light microscopy.

DELINEATION OF THE ARTERIAL BOUNDARY ZONES

In two additional cats, the boundary zones between the territories of the major cerebral arteries were delineated through a craniotomy window by immediate postmortem perfusion of Colorpaque (Pilot) via a carotid artery. Results

PIAL ARTERIOULAR CALIBER

Measurements of vessel caliber were obtained at 43 fixed positions on 32 arteries and arterioles prior to and during the induction of hypertension. Resting mean arterial blood pressure varied between 70 and 135 mm Hg (mean, 115 ± 19 mm Hg) in this group of 10 cats. The mean arterial blood pressure closest to 135 mm Hg was chosen as an arbitrary reference pressure. The measurement of caliber of a given vessel at a fixed position was expressed as percentage change from the values obtained at pressures closest to 135 mm Hg. For ease of presentation, the vessels studied were subdivided into three groups: 17 arterioles less than 50 μm in diameter, 11 arterioles between 50 and 100 μm in diameter, and 15 arteries and arterioles greater than 100 μm in diameter.

As hypertension was induced, the arteries and arterioles constricted progressively up to a mean arterial pressure of approximately 160 mm Hg (Figs. 1-3). This arterial and arteriolar narrowing was uniform throughout the pial circulation although arterioles less than 50 μm in resting diameter showed the greatest reactivity (percent change in diameter per mm Hg increase in mean arterial pressure). At this stage of induced hypertension the cortex was noticeably paler than it was in the normotensive state; presumably this was due to the vasoconstriction associated with cerebral autoregulation in response to induced hypertension. At pressures greater than 160 mm Hg, pial arteriolar caliber either remained constant or increased slightly. At pressures around 180 mm Hg, the majority of arterioles with a resting diameter less than 100 μm displayed the sausage-string phenomenon (Fig. 4). At pressures in excess of 180 mm Hg there was a marked and uniform increase in pial arteriolar caliber which was accompanied, or slightly preceded, by an obvious reddening of the pial veins.

![Figure 2](http://circres.ahajournals.org/)

**Figure 2.** The effect of increasing mean arterial blood pressure (MAP) on pial arterioles with a resting caliber between 50 and 100 μm in seven cats. Vessel caliber was calculated as a percent change from the caliber of each vessel at a MAP of 135 mm Hg. The mean arteriolar caliber was 74 ± 13 μm (X ± SD).
On seven occasions measurements of caliber were obtained throughout the blood pressure range at positions that eventually developed into the narrowed segments of the sausage-string phenomenon. A detailed description of the changes in these narrowed segments was the subject of a previous short communication. The reference diameter (at a mean arterial blood pressure of 135 mm Hg) of these seven vessels was 50 ± 21 μm (x ± SD).

As blood pressure was increased these vessels constricted normally, but when the sausage-string phenomenon was first noted—at pressures of 180 mm Hg—no further constriction was observed. Thus, although these segments were the narrowed portions of the sausage-string phenomenon, the vessel calibers were not excessively reduced, the vessel diameters being the same as, or slightly greater than, at the upper limit of autoregulation.

On 10 further occasions, measurements were taken at sites that later became the dilated portions of the sausage-string phenomenon. Again the reference diameters of these vessels all were less than 100 μm. Upon development of the sausage-string appearance, these portions of the vessel underwent a large and rapid increase in caliber. From a constriction of 20–40% at mean arterial pressures of approximately 160–170 mm Hg they dilated to as much as 50–100% of their resting calibers (at 135 mm Hg) following the development of the sausage-string effect. Vessels that were neither the dilated nor the narrowed portions of sausage-string showed a comparatively moderate dilation at pressures around 180 mm Hg and further increased in diameter with increasing mean arterial pressure.

It should be emphasized that the sausage-string always was found to be a transient phenomenon. As blood pressure was increased further the narrowed segments gave way gradually until their calibers were the same as those of the contiguous dilated segments. These vessels, which previously had displayed the sausage-string, then were uniformly dilated. On a few occasions blood pressure either was held constant at around 180 mm Hg, or was reduced slightly; the sausage-string effect always disappeared and the vessels eventually became markedly distended. The sausage-string phenomenon never lasted longer than 20 minutes at these extreme levels of blood pressure. At arterial pressures in excess of 180 mm Hg, pathological constriction (defined as a constriction greater than that noted at the upper limit of autoregulation) never was identified, as shown in Figures 1–3.

LOCAL CEREBRAL BLOOD FLOW

Measurements of local cerebral blood flow were obtained from 19 electrodes in eight cats with a craniotomy and from 19 electrodes in four additional cats without a craniotomy. Cerebral blood flow was calculated both by the initial slope method and by compartmental analysis. Of the 38 electrodes, nine were considered to be unsatisfactory as a result of a failure to demonstrate an autoregulatory plateau; presumably this was due to local tissue damage.

The baseline values for blood flow obtained at a mean arterial blood pressure of 131 ± 11 (mean ± SD) mm Hg are...
Local Cerebral Blood Flow at Normotension*  

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$F_r =$ fast component of clearance; $F_s =$ slow component of clearance; ISI = initial slope index. All units are in ml/100 g per min. * Mean arterial blood pressure (MABP) = 131 ± 11 mm Hg.

Local Cerebral Blood Flow at Extreme Hypertension  

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$F_r =$ fast component of clearance; $F_s =$ slow component of clearance; ISI = initial slope index. All units are in ml/100 g per min. * Mean arterial blood pressure (MABP) = 205 ± 29 mm Hg.

Extreme hypertension resulted in significant overall increases in blood flow derived from the biaxponential fast component (37%; $P < 0.001$), the initial slope index (75%; $P < 0.001$) and the monoeaxponential clearance rate (147%; $P < 0.001$). There was, however, no significant increase in the slow component of the biaxponential clearance (16%; $P > 0.2$). As the mean arterial blood pressure was increased, many of the clearances that had been monoeaxponential at baseline systemic arterial pressures became biaxponential. For this reason, the initial slope index was adopted and used to examine the variation of blood flow with mean arterial blood pressure, as shown in Figure 5. Cerebral blood flow was calculated as a percentage of the value obtained by each individual electrode at the mean arterial blood pressure closest to 135 mm Hg, as for measurement of pial arteriolar caliber.

Flow was relatively constant over the pressure range from 90 to 160 mm Hg with a slope of 0.45%/mm Hg as determined by linear regression analysis ($r = 0.70; S_x, r = 7.99$). At systemic arterial pressures above 160 mm Hg, cerebral blood flow increased markedly with increasing mean arterial blood pressure. The pressure-passive electrodes also showed a large increase in cerebral blood flow at pressures in excess of 160 mm Hg (Fig. 6). Over the pressure range from 90 to 160 mm Hg local cerebral blood flow increased with increasing blood pressure in the pressure-passive electrodes to a greater extent than it did for electrodes in areas showing autoregulation (slope = 0.97%/mm Hg, $r = 0.49; S_x, r = 35.0$). Therefore, all electrodes demonstrated a...
large increase in local cerebral blood flow at high arterial pressures and on no occasion was a reduction in blood flow noted during extreme hypertension. Cerebral blood flow always was slightly increased prior to the development of the sausage-string phenomenon which occurred at pressures around 180 mm Hg in the eight cats in which blood flow and vessel caliber were measured simultaneously.

**BLOOD-BRAIN BARRIER**

There was extravasation of Evans blue in 17 cats. The amount varied from cat to cat. Extravasation was accentuated at the craniotomy and burr hole sites but also was seen in areas of cortex remote from these areas and in the brains of cats with closed skulls. The Evans blue staining was seen predominantly in the cerebral cortex, often in its full thickness, and occasionally spread to the subcortical white matter (Fig. 7). When a large amount of staining was seen the extravasation was accentuated in the arterial boundary zones between the territories of the anterior and middle cerebral arteries. In only one cat was there extravasation within deep hemispheric structures, in the brainstem, and in the cerebellum. In two of the five control cats (without a craniotomy or electrode insertion) extravasation of Evans blue albumin was not observed.

**DELINEATION OF THE ARTERIAL BOUNDARY ZONES**

The boundary zone between the anterior and middle cerebral arteries was seen to lie in the sides and depths of the intraparietal sulcus posteriorly, but in the precentral and frontal regions it lay superficially and more laterally (4-7 mm from the midline). The majority of our cerebral blood flow electrodes therefore were located in the region of the major hemispheric arterial boundary zones.

**NEUROPATHOLOGY**

**Macroscopic.** At the end of the procedure a slight degree of brain swelling usually was seen through the craniotomy, and after perfusion-fixation the external cerebral hernias were more obvious. There was no evidence of internal herniation even in cats in which there was a considerable extravasation of Evans blue, in which craniotomy had not been performed, and in the one cat that developed an intracerebral hematoma.

**Microscopic.** As judged by the uniform hardening of the specimens and by the absence of blood in the vessels, perfusion fixation appeared to be good in all cats. The cytological artifacts, the "dark cell" and "hydropic cell or water change," were not seen.

Histological examination showed small foci of ischemic damage in the superficial cortices of the 14 cats with a craniotomy, electrode insertion, or both. From the distribution and pattern of the damage it was clear that the ischemic foci were related to brain herniation at the sites of surgery. In only one case was there an ischemic focus remote from such sites and this was in the inferior part of the lateral cortex of the anterior occipital lobe. The lesion appeared as
Changes in Cerebral Blood Flow

The cerebral circulation is autoregulated over a fairly wide range of perfusion pressures. In normotensive man and the baboon the lower limit of autoregulation is between 40 and 70 mm Hg. In primates, including man, the upper limit of autoregulation is approximately 140 mm Hg.

In baboons with experimental renovascular hypertension the limits of autoregulation are shifted to higher absolute levels of mean arterial pressure. This phenomenon might explain why the upper limit of autoregulation observed in the present study (approximately 160–170 mm Hg) was at a higher absolute level of mean arterial pressure than the upper limit for normotensive man and monkey. The anesthetized cats in the current study had a mean resting arterial pressure of approximately 115–130 mm Hg so that, when compared to man or the baboon, the cat could be thought to be relatively hypertensive.

In the majority of the studies for which the upper limit of autoregulation has been demonstrated cerebral blood flow was measured by nonfocal techniques. It thus might be argued that a decrease in blood flow could exist in small circumscribed areas of the brain along with the generalized flow increase. Evidence favoring such localized flow decreases in the arterial boundary zones of the brain during acutely induced hypertension has been found by Dinsdale et al.

The results of local cerebral blood flow measurements in the current investigation show that slight increases in cerebral blood flow occurred prior to the appearance of the sausage-string phenomenon. This evidence favors the concept that generalized vasodilation, rather than vasospasm, is the cerebrovascular response to extreme hypertension. Many of the hydrogen electrodes, as subsequently confirmed post mortem, were within the arterial boundary zones. Not one of these electrodes, nor any of the electrodes placed elsewhere within the cortex, demonstrated a decrease in local cerebral blood flow at arterial pressures above the upper limit of autoregulation. Thus our results concerning cerebral blood flow differ substantially from those of Dinsdale and his co-workers, and therefore it is not surprising that—in this high flow state—there was neuropathological evidence of ischemic brain damage in only one of the cats in the present study.

Häggendal and Johansson demonstrated that blood-brain barrier damage was one consequence of an abrupt, massive increase in arterial pressure; but barrier damage did not occur when similar levels of arterial hypertension were reached in stages over 20–30 minutes. The results of our study contrast with those of Häggendal and Johansson in that extravasation of Evans blue invariably was noted with the stepwise increase in systemic arterial pressure.

Changes in Pial Arteriolar Caliber

In the present study there was a maintained constriction of the pial arterioles up to pressures of approximately 180 mm Hg. However, at pressures greater than 160 mm Hg the ability of the arterioles to constrict decreased. The first increases in cerebral blood flow occurred at lower pressures (~160 mm Hg) than the arterial pressure at which the maximum vasoconstriction was noted (~180 mm Hg). This suggests that the failure of autoregulation is due to the inability of the cerebral resistance vessels to counteract the rising perfusion pressure.

At pressures equal to, or greater than, 180 mm Hg two types of vascular response were noted. Vessels greater than 100 µm dilated without having passed through the sausage-string phenomenon. This evidence favors the concept that generalized vasodilation, rather than vasospasm, is the cerebrovascular response to extreme hypertension. Many of the hydrogen electrodes, as subsequently confirmed post mortem, were within the arterial boundary zones. Not one of these electrodes, nor any of the electrodes placed elsewhere within the cortex, demonstrated a decrease in local cerebral blood flow at arterial pressures above the upper limit of autoregulation. Thus our results concerning cerebral blood flow differ substantially from those of Dinsdale and his co-workers, and therefore it is not surprising that—in this high flow state—there was neuropathological evidence of ischemic brain damage in only one of the cats in the present study.

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string phase: in contrast, vessels less than 100 μm usually displayed the sausage-string phenomenon. These changes were accompanied by massive increases in local cerebral blood flow. Measurements made from segments of vessels that subsequently became the constricted segments of the sausage-string showed that, with the development of the sausage-string, they never constricted further. Indeed, they appeared to dilate slightly. Parts of vessels that subsequently became the dilated segments of the sausage-string became massively dilated at the onset of the alternate constriction and dilation pattern. Therefore, it may be concluded that the narrow segments of the sausage-string are the remnants of autoregulatory constrictions, whereas the dilated segments are those which have given way to the overwhelming intraluminal pressure. In support of this, the sausage-string was found to be a transient phenomenon in our experimental model. It did not matter whether blood pressure was further increased, was kept constant at the pressure at which the sausage-string was first observed, or was unintentionally reduced slightly. In all instances the comparatively constricted segments gave way to dilation, and the longest period during which the sausage-string persisted in any of the vessels was 20 minutes. The pial arteriolar responses to increasing systemic arterial pressures are summarized diagrammatically in Figure 8.

NEUROPATHOLOGY

The immediate effects of a severe and sudden elevation of systemic arterial pressure are best seen in the syndrome of hypertensive encephalopathy. Byrom found that a high or rapidly rising blood pressure was an essential prologue to encephalopathy in rats. The clinical features often consisted of epileptiform convulsions, weakness, and apathy leading to coma and death within 6–48 hours. Focal arterial necrosis, recent infarcts, and precapillary or larger hemorrhagic lesions were found in more than 50% of the rats. More recently Robertson et al. and Dinsdale et al. have produced areas of focal ischemic damage in the brains of hypertensive experimental rabbits. These studies showed that significant cerebral ischemia occurred preferentially in the boundary zones between the territories of the major cerebral arteries. The tendency for the lesions to cluster in the boundary zones remains unexplained, particularly since ischemic lesions in these areas traditionally are associated with hypotension in man and in the experimental primate. As ischemic lesions have been found in the arterial boundary zones in experimental hypertension it has been suggested that the vessels in the boundary zones may possess a capacity for increased reactivity in response to a sudden rise in the systemic arterial pressure.

In contradistinction to the neuropathological findings of others, the present study has revealed a remarkable paucity of brain damage, for in only one cat was there ischemia similar to that previously described for the rat and monkey brain. However, its pathogenesis is not clear since there was no evidence of vascular occlusion, of necrosis of vessel walls, or of extravasation of Evans blue in the affected regions.

Extravasation of Evans blue was found principally in the cerebral cortex, although in some cats it extended into the white matter. As previously described, such lesions were most prominent in the cerebral arterial boundary zones. It was, however, not possible to determine the exact site of the leakage of protein-bound dye. With forced vasodilation the arterial pressure might be partially transmitted to capillaries and venules and it is possible that some extravasation of Evans blue occurred at these distal segments of the cerebrovascular bed. It is also widely recognized that ischemia, per se, will only disturb barrier function to large molecules such as protein-bound Evans blue after prolonged periods of critical hypoperfusion. Even then, it takes several hours of reperfusion before barrier lesions are detected.

In this study no evidence was found to support the concept of cerebral vasospasm as a consequence of induced hypertension. On the contrary, the universal increase in pial arteriolar diameter, the increase in local cerebral blood flow, the absence of ischemic cell damage, and the extravasation of plasma proteins at extreme arterial pressures lead to the opposite conclusion; namely, that pronounced, acute hypertension causes an overdistention of the cerebral resistance vessel. The present observations substantiate the hypothesis advanced by Lassen and Agnoli for the pathogenesis of hypertensive encephalopathy.

Acknowledgments

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References


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