Increased Venous Pressure Causes Myogenic Constriction of Cerebral Arterioles during Local Hyperoxia

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SUMMARY. The responses of cerebral (pial) arterioles to increased venous pressure were examined in anesthetized cats equipped with cranial windows for the observation of the cerebral microcirculation. Increased venous pressure was induced by occlusion of the superior vena cava. Intracranial pressure was kept constant. Increased venous pressure when the window was filled with stationary cerebrospinal fluid caused 9–12% arteriolar dilation. Cerebral arteriolar dilation of equal magnitude (8–12%) was also seen when the space under the cranial window was perfused with fluorocarbon FC-80 equilibrated with 100% nitrogen. Increased venous pressure when the cranial window space was perfused with fluorocarbon equilibrated with 100% oxygen caused a small (5%) but significant arteriolar constriction. These results show that the dominant mechanism of autoregulation in the cerebral arterioles is metabolic, and that it involves an oxygen-sensitive mechanism. Myogenic vasoconstriction is unmasked during venous hypertension when the dominant metabolic mechanism is eliminated by increased local supply of oxygen. (Circ Res 55: 249–252, 1984)

THE responses of precapillary vessels to increased venous pressure provide information that may reveal the dominant mechanism of autoregulatory adjustments in the caliber of these vessels (Johnson, 1964). When a pressure-dependent myogenic mechanism predominates, one would expect arteriolar constriction during increased venous pressure because of the associated increased transmural pressure. On the other hand, when a flow-dependent metabolic mechanism predominates, one would expect vasodilation during increased venous pressure because of the expected accumulation of vasodilator metabolites secondary to the decrease in blood flow. Increased venous pressure causes dilation of pial arterioles in cats (Wei and Kontos, 1982) and monkeys (Raisis et al., 1979), suggesting strongly that the predominant mechanism of autoregulation in these vessels is metabolic. We emphasized earlier that these findings do not exclude the possibility that myogenic mechanisms play a significant role in the autoregulatory adjustments of pial arterioles to changes in arterial blood pressure (Wei and Kontos, 1982). If myogenic mechanisms are active concurrently with the dominant metabolic mechanisms, it is conceivable that under different experimental conditions, their relative influence may be altered, and one may identify conditions under which the myogenic mechanisms would predominate.

In earlier experiments, we found that the dominant metabolic mechanism responsible for the dilation of cerebral arterioles in cats to reductions in arterial blood pressure involved reduction in oxygen tension within the tissue (Kontos et al., 1978b) and postulated secondary release of vasodilator metabolites. This mechanism could be eliminated by increased local supply of oxygen via topical application of fluorocarbons equilibrated with high concentrations of oxygen (Kontos et al., 1978b). It appeared possible, therefore, that if one eliminated the dominant metabolic mechanisms, via local increased supply of oxygen, the presence of myogenic mechanisms in response to alterations in perfusion pressure might be unmasked. This paper reports experiments in which this was attempted by studying the responses of cerebral arterioles to increased venous pressure with and without topical hyperoxia induced via the topical application of fluorocarbons.

Methods

Experiments were carried out in six cats anesthetized with sodium pentobarbital, 30 mg/kg, iv. After tracheostomy, each animal was ventilated with a positive pressure respirator and received 5 mg/kg of gallamine triethiodide, iv, for muscle skeletal paralysis. The end-expiratory CO₂ of the animals was monitored continuously with a Beckman infrared CO₂ analyzer, and was maintained at a constant level of about 30 mm Hg. Arterial blood pressure
was measured with a Statham pressure transducer connected to a cannula introduced into the aorta via the femoral artery. Arterial blood samples were collected for determination of arterial oxygen and CO₂ partial pressures, pH, and hematocrit at appropriate intervals during the experiment. Blood gas tensions and pH were measured with Radiometer electrodes. Hematocrit was measured by a micromethod.

The microcirculation of the parietal cortex was visualized through a cranial window, acutely implanted in the skull caudal to the coronal suture, so that it overlay the ectosylvian and suprasylvian gyri. The cranial window technique has been described in detail previously (Levesque et al., 1975). The space under the window was filled with artificial cerebrospinal fluid (CSF), identical in composition to that of CSF for cats. The window has three openings. Two of these could be used as inlet and outlet for filling the window with CSF or for perfusing various solutions through the space under the cranial window. The third outlet was connected to a Statham transducer for measurement of intracranial pressure. The outlet of the window was connected to a plastic tube filled with CSF. The free end of this tube was set at a predetermined height to give a constant intracranial pressure of 5 mm Hg. Vessel caliber was measured with a Leitz Ultropak microscope equipped with a dry objective lens and connected to a Vickers image-splitting device.

Increased cerebral venous pressure was induced by pulling a snare placed around the superior vena cava, thereby occluding the vessel. Venous pressure was measured with a Statham pressure transducer placed into the jugular vein. To maintain the increased venous pressure at an easily controllable high level, a catheter was introduced into the superior vena cava via the brachial vein and connected to a reservoir filled with 0.9% sodium chloride solution. This reservoir was set at a predetermined height to give a constant level of elevated venous pressure equal to about 20 mm Hg during the period of occlusion of the superior vena cava. Increased venous pressure was maintained for 5 minutes to achieve a steady state in the associated changes in cerebral vessel caliber. The reduced venous return to the heart during superior vena cava occlusion resulted in reduced CO₂ input into the lungs. Since ventilation was constant, this resulted in arterial hypocapnia. The latter was corrected by introducing CO₂ into the inspired air from a tank.

The experimental design was as follows: A small (<100 μm in diameter) and a large (>100 μm in diameter) cerebral arteriole were selected for observation in each of five animals. In the sixth animal, the diameter of two small arterioles was measured. The responses of these vessels to arterial hypocapnia were first tested to ascertain that they were responsive to physiological stimuli. After restoration of the CO₂ level to the control value and return of vessel caliber to the baseline, the venous pressure was increased to about 20 mm Hg and maintained at that level for 5 minutes in three successive periods: (1) with the window filled with stationary CSF, (2) with fluorocarbon FC-80 equilibrated with 100% oxygen flowing through the space under the cranial window at a rate of 2 ml/min, and (3) with fluorocarbon FC-80 equilibrated with 100% nitrogen flowing through the space under the cranial window at the rate of 2 ml/min. The order in which the three venous occlusions were carried out was randomized. The equilibration of fluorocarbons with gases was carried out in a water bath at 37°C. Perfusion of fluorocarbons under the cranial window was carried out with a Harvard pump at a constant rate. The fluorocarbon perfusion began 5–10 minutes before the induction of venous hypertension to allow a steady state to be established. FC-80 equilibrated with 100% oxygen contains 0.455 ml oxygen per ml (Navari et al., 1977). The diffusion coefficient of oxygen in FC-80 equilibrated with 100% oxygen is 5.71 × 10⁻⁵ cm²/sec (Navari et al., 1977). Thus, the flux of oxygen into the brain, when FC-80 equilibrated with 100% oxygen was flowing over the brain surface, would be 40 times that expected from CSF equilibrated with 100% oxygen.

Statistical analysis of the results was carried out by analysis of variance followed by t-tests modified for multiple comparisons by Bonferroni's method (Wallenstein et al., 1980).

**Results**

The results are shown in Figures 1–3. In the absence of fluorocarbons (Fig. 1), both small and large arterioles dilated in response to increased venous pressure, a finding consistent with our earlier results (Wei and Kontos, 1982). This dilation was seen in every vessel in every animal. In the 5th minute of venous hypertension, the dilation averaged 13 ± 1.8% and 9 ± 1.6% of the control diam-

![Figure 1](http://circres.ahajournals.org/)

**Figure 1.** Time course of mean arterial blood pressure (MABP), jugular venous pressure (VP), end-tidal PCO₂, end-tidal CO₂ tension (PCO₂), and diameter of small and large arterioles during venous occlusion with the cranial window filled with stationary CSF. The mean ± se of the control diameter of cerebral arterioles is indicated. The number in parentheses after the se is the number of vessels studied. Note that both small and large arterioles dilated during venous hypertension.
eters in small and large arterioles, respectively. The administration of fluorocarbon equilibrated with 100% nitrogen did not influence this dilation. In the 5th minute of venous hypertension, small arterioles were 12 ± 3.6% and large arterioles 8 ± 1.8% larger than control (Fig. 2). All vessels in all animals dilated. Because of bleeding under the window in one animal, this period of venous hypertension was recorded in only five cats. In contrast, in the presence of fluorocarbon equilibrated with 100% oxygen, increased venous pressure caused reduction in arteriolar diameter (Fig. 3). This decrease averaged 5 ± 0.7 and 5 ± 1.9% of the control diameter of small and large arterioles, respectively, recorded during fluorocarbon administration at normal venous pressure. These changes in arteriolar diameter during venous hypertension in the presence of FC-80 equilibrated with 100% oxygen were significantly different from those seen with CSF or with FC-80 equilibrated with 100% nitrogen.

After the onset of venous hypertension, there was a small but consistent decrease in mean arterial blood pressure, followed by gradual recovery. In the 5th minute of venous hypertension, mean arterial blood pressure was 3.7 ± 5.5 mm Hg lower than the corresponding control value in Figure 1, 4.8 ± 3.3 mm Hg lower than the corresponding control value in Figure 2, and 2.2 ± 1.9 mm Hg lower than the corresponding control value in Figure 3. None of these changes were significantly different from zero. Changes in arterial blood pressure of this magnitude do not cause alterations in caliber of arterioles of the size we studied in these experiments (Kontos et al., 1978a).

Discussion

The observation of significant arteriolar constriction in response to increased venous pressure in the presence of local hyperoxia supports the hypothesis that a myogenic mechanism is operative in the autoregulatory responses to venous hypertension. The present findings and our earlier results (Kontos et al., 1978b; Wei and Kontos, 1982) demonstrate that changes in transmural and perfusion pressure initiate both metabolic and myogenic mechanisms. Under normal conditions, the metabolic mechanisms predominate. Under these normal conditions, therefore, increased venous pressure causes arteriolar dilation. The presence of the weaker myogenic mechanisms which tend to cause vasoconstriction during increased venous pressure is unmasked by preventing the dominant metabolic mechanism from operating by the induction of local hyperoxia.
The demonstration of the presence of myogenic mechanisms should not be viewed as having only theoretical interest. As we pointed out earlier (Wei and Kontos, 1982), it is possible that the expression of myogenic and metabolic mechanisms might be altered under different conditions. One may, therefore, conceive of abnormal circumstances under which the operation of the metabolic mechanisms might be eliminated or otherwise compromised and allow the expression of myogenic mechanism.

The relative contributions of myogenic and metabolic mechanisms in autoregulatory responses of arterioles in various vascular beds have been a subject of considerable investigation. Studies by others in the mesentery (Burrows and Johnson, 1983) and in skeletal muscle (Morff and Granger, 1982) have shown that both myogenic and metabolic mechanisms participate. In these vascular beds, under normal conditions, the myogenic mechanisms are more influential than we found in the brain. Burrows and Johnson (1983) found that, in the mesentery of the cat, the fraction of the arteriolar responses to increased intravascular pressure that could be attributed only to a myogenic mechanism varied from 20 to 56%, and the largest fraction of the response attributable to a myogenic mechanism varied from 50 to 93%. The fraction of the responses attributable only to metabolic mechanisms varied from 0 to 23%, and the largest fraction attributable to this mechanism varied from 18 to 73%. Morff and Granger (1982) observed vasoconstriction in response to increased venous pressure in arterioles of the cremaster muscle of the rat, indicating that the predominant mechanism of autoregulation was myogenic. The vasoconstriction in response to elevated venous pressure was more pronounced when the cremaster bath PO$_2$ was high, indicating that metabolic mechanisms were also operative. One may speculate that the difference between the brain and these other vascular beds may be related to the intensity of tissue metabolism. It is possible that the greater influence of metabolic mechanisms in the brain might be related to the higher level of metabolism of this tissue. If this is correct, one may speculate that the contribution of myogenic mechanisms in cerebral vascular responses might become more evident under conditions of low metabolism.

Recently, Wagner and Traystman (1983) measured cerebral blood flow and cerebral vascular resistance in anesthetized dogs in response to increases in venous pressure and found consistent vasodilator responses during venous hypertension. These results show that the predominant autoregulatory mechanisms in the cerebral circulation of the dog, considered in its entirety, are metabolic, a finding consistent with what we found in the pial arterioles of the cat (Wei and Kontos, 1982). It would be of interest to examine the responses of the cerebral circulation in its entirety to venous hypertension under conditions of hyperoxia to determine whether or not myogenic mechanisms also play a role.

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