Evidence of Myogenic Vascular Control in the Rat Cerebral Cortex

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SUMMARY. The potential presence of myogenic regulation in the cerebral microvasculature of the rat was investigated using a method which alters intravascular pressure without appreciably changing cerebral perfusion pressure (arterial minus venous pressure). The entire rat was placed in a sealed box, with the cranial cavity open to the atmosphere and prepared for in vivo microscopy. By increasing the ambient pressure in the box, both systemic arterial and venous pressure could be changed by nearly equal amounts (±20 mm Hg). Heart and respiratory rates were not influenced by changing ambient pressure by ±20 mm Hg. At elevated ambient pressures, cortical arterioles constricted in linear proportion to the ambient pressure, whereas subatmospheric ambient pressures caused vasodilation whose magnitude was about equal at ambient pressures of -6 to -18 mm Hg. The calculated vessel wall tension typically remained within about ±10-15% of control during changes of transmural pressure of ±20-40%. In all cases, arteriolar responses to changes in ambient and intravascular pressure reached a new steady state within 10-15 seconds and were sustained for up to 30 minutes. These data are interpreted to indicate the presence of a myogenic vascular response in the brain vasculature of the rat. (Circ Res 55: 554-559, 1984)

MYOGENIC control of the cerebral vasculature has been suggested by various studies either to be poorly developed (Wei and Kontos, 1982; Raisis et al., 1979) or to be a possible and potentially important component (Jacobson et al., 1963; Ekstrom-Jodal, 1970; Symon et al., 1971; Gourley and Heistad, 1983) of vascular regulation. In view of the sensitivity of the cerebral vasculature to blood flow changes (Siesjo et al., 1980), it could be argued that even if myogenic control exists, local metabolic and blood flow conditions would dominate vascular regulation. However, it is possible that myogenic and metabolic control mechanisms act in concert in the regulation of cerebral vascular behavior. As an example, Gourley and Heistad’s (1983) observation that reductions in cerebral blood flow by 50% or more caused the rapid and equal development of peak reactive hyperemia, whether blood flow was reduced for 5 seconds or much longer. Blood flow was reduced by inflating a cuff around the animal’s neck to compress arteries and, at the pressures used, collapse all veins. Therefore, the peak reactive hyperemia observed by Gourley and Heistad (1983) should reflect rapidly occurring changes in vascular resistance in under 5 seconds, and not a transient refill phenomenon of the vasculature. Dacey and Duling (1982) have provided evidence that individual arterioles isolated from the rat cerebral cortex are also capable of exhibiting vascular responses consistent with myogenic regulation. However, whether the individual arterioles of the intact cortex of the rat can exhibit myogenic behavior is unknown.

An approach to the study of the potential presence of myogenic behavior in the cerebral vasculature would be to change arterial and venous pressure by equal amounts and thereby maintain a constant perfusion pressure. In this way, there is no hydrostatic alteration to change blood flow, and any vascular dimension response opposite to the change in intravascular pressure should be in part, or totally, of myogenic origin. A method developed by Wied-erhielm et al. (1979) for simultaneous and virtually equal changes in mean arterial and venous pressure in the bat was adapted to the present study. In brief, the vasculature to be studied, such as the brain, is at all times exposed to atmospheric pressure, but the remainder of the animal is placed in a sealed box whose ambient pressure can be elevated or decreased relative to the atmospheric pressure. The results obtained with this approach indicate that myogenic control of the cerebral vasculature is present under circumstances where both arterial and venous pressure are altered by equal amounts.

Methods

Male Wistar rats in the weight range of 275–350 g were anesthetized with Inactin (100 mg/kg, ip) (Byk Gulden Kontanz). The trachea was cannulated and the left femoral artery and vein were cannulated to measure systemic arterial and venous pressure. The cerebral cortex beneath the parietal bone was exposed by a mid-line skin incision and removal of the parietal bone, the details of which are presented elsewhere (Harper et al., 1984). The dura was removed and, thereafter, an artificial cerebral spinal fluid (Harper et al., 1984)
equilibrated with 5% CO₂, 5% O₂, and 90% N₂ and heated to 37–38°C was suffused over the tissue (3–5 ml/min). We maintained the body temperature at 37–38°C by placing a heating mat at a constant temperature of 35°C beneath the animal.

The suffusion solution Po₂ was maintained at 45–50 mm Hg to within 100 μm of the tissue surface. However, as the oxygen microelectrode (Whalen et al., 1973) was moved to within 20–30 μm of the tissue, the suffusion solution Po₂ approached that of the tissue Po₂ (10–20 mm Hg). The Po₂ gradient of approximately 20 mm Hg in the suffusion solution is assumed to reflect consumption of oxygen from the suffusion solution by the tissue. The tissue Po₂ recorded just within (approximately 5–10 μm) the brain surface is less than 2 mm Hg if the microelectrode is used to stop flow intentionally in a single capillary or small arteriole. Therefore, even though the tissue did extract oxygen from the suffusion solution, the contribution of suffusion solution oxygen to tissue Po₂ was very small. If the suffusion flow was stopped until the solution Po₂ began to increase (2–4 minutes), the resting vascular tone or vascular response in progress did not change. Suffusion Po₂ (measured about 100 μm above tissue) greater than about 60 mm Hg or lower than about 30 mm Hg cause vasoconstriction and vasodilation, respectively. At suffusion Po₂ of 40–50 mm Hg, the tissue Po₂ at a depth of 5–10 μm to more than 150–200 μm is very similar (±3 mm Hg), unless the electrode tip passes near a microvessel.

The animal was placed in a stainless steel and plexiglass box with sealed connections for arterial and venous catheters. A stereotaxic device held the head of the rat, and a metal cover was placed over the animal such that the surgical site on the head was open to the atmosphere. The skin at the surgical site was pulled through a hole in the metal cover and used as a gasket to seal the box. At all times, a minimum air flow of 200–300 ml/min was maintained through the box. To elevate the ambient pressure in the box, the air flow was increased. To create subatmospheric ambient pressures, air was drawn through the box and, thereafter, change the ambient pressure in steps of ±2 mm Hg.

We maintained the body temperature at 37–38°C by placing a heating mat at a constant temperature of 35°C beneath the animal. For the range of ambient pressures, the change in mean systemic arterial pressure (ΔPsys) was defined by: ΔPsys = 0.92P + 1.27 (r = 0.89). For an identical range of ambient pressures, the change in mean systemic venous pressure (ΔPv) was: ΔPv = 0.96P + 0.6 (r = 0.95). In effect, the changes in both systemic arterial and venous pressure were typically 90% or more of the change in ambient pressure. For the range of ambient pressures used, perfusion pressure would remain within ±2 mm Hg of the control perfusion pressure.

The suffusion solution Po₂ was maintained at 45–50 mm Hg, the heart rate was within ±15 beats/min of the resting heart rate (275–325 beats/min). The change in mean systemic arterial pressure (ΔPsys) as a function of the ambient pressure (P) from −20 to 20 mm Hg was defined by: ΔPsys = 0.92P + 1.27 (r = 0.89). For an identical range of ambient pressures, the change in mean systemic venous pressure (ΔPv) was: ΔPv = 0.96P + 0.6 (r = 0.95). In effect, the changes in both systemic arterial and venous pressure were typically 90% or more of the change in ambient pressure. The animals would tolerate changes in ambient pressure from −18 to +15 mm Hg for at least 30 minutes and then return to a normal arterial blood pressure and vascular dimensions when atmospheric pressure was restored. Ambient pressures which elevate systemic venous pressure to 20–25 mm Hg cause a slight swelling of the brain, and cerebral venules often develop hemorrhages which can be severe. Very similar problems develop in normal rats at arterial pressures above about 190 mm Hg when cerebral venular pressures exceed about 25 mm Hg. These problems during elevated intravascular pressures occur only in the exposed portion of the brain.

Pressures measured in the individual arterioles (Pm) during changes in ambient pressure were consistently nearly linear with respect to systemic arterial pressure (Pm = 0.26 Psys + 17, r = 0.76). The pressure in the largest cerebral venules changed by 70–80% at the venous pressure. In no case did a large increase in venous pressure or stagnation of venous flow occur at the ambient pressures used. Therefore, venous outflow disturbances were not present at ambient pressures of ±20 mm Hg. However, subatmospheric ambient pressures caused a partial collapse of venules, and ambient pressures substantially (>10 mm Hg) above atmospheric pressure caused venous dilatation. At subatmospheric pressures of about −25 mm Hg and below, the brain
retracted sufficiently to apparently compress vessels because venous outflow was obviously impeded and the venular pressure increased above 40–50 mm Hg.

Figure 1 presents the percent change in inner diameter of arterioles at various intervals of ambient pressures above and below atmospheric pressure. Arterioles with a resting inner diameter of 30–60 μm were used for these studies. The percent change in diameter with ambient pressure alteration was independent of resting diameter. In previous studies, we have shown that cerebral arterioles (30–60 μm, i.d.) of the rat exhibited comparable proportional changes in diameter as arterial pressure is altered (Harper et al., 1984; Harper and Bohlen, 1984). As previously mentioned, the changes in systemic arterial (Psys) and venous (Pv) pressure are very similar to the change in ambient pressure such that the perfusion pressure (Psys minus Pv) would be nearly constant for the ambient pressure range depicted in Figure 1.

As the ambient pressure increased, arteriolar diameter decreased in almost linear proportion to the increased ambient pressure. In sharp contrast, decreasing the ambient pressure below atmospheric pressure caused vasodilation whose magnitude did not vary significantly (P > 0.05) across an ambient pressure range of –6 to –18 mm Hg. The lines fitted to the data in Figure 1 are from linear regression for increased ambient pressure and a second order polynomial equation for decreased ambient pressure (equation values in Fig. 1). In every case, the change in diameter shown in Figure 1 occurred within 10–15 seconds after the ambient pressure change, which required 2–5 seconds. The diameter was essentially constant after the initial response, with occasional slight vasomotion about the new steady state diameter. The vessel response, be it constriction or dilation, undoubtedly occurred in less than 10–15 seconds. This much time was required to recenter the vessel in the optical field and adjust the optical focus due to movement of the head and brain as the ambient pressure was changed.

Figure 2 presents the percent of control vessel wall tension (T = Pr) plotted vs. the change in arteriolar pressure during alterations of ambient pressure. As a frame of reference, a 4–5 mm Hg change in arteriolar pressure represented approximately a 10% change in transmural pressure. In view of the resolution of the microscopic and video system and microvascular pressure measurement system, a wall tension within ±15% of control was considered as a reasonable preservation of wall tension for transmural pressure changes greater than 4–5 mm Hg (about 10%). In this context, ±20–40% changes in transmural pressure (±8–12 mm Hg) did not substantially alter wall tension.

Blood flow was measured in the largest arterioles on the brain surface. An extensive network of surface collateral vessels interconnects these large arterioles. At normal and reduced ambient pressures, the point of interaction of flow from both ends of the collateral vessels was infrequently moved. However, during the vasoconstriction associated with elevated ambient pressures, the pattern of flow distribution was altered such that a collateral vessel could perfuse its parent large arteriole from an adjacent large arteriole. As a consequence, the blood flow, expressed as percent of control in Figure 3, appeared to increase in about half of the large arterioles at elevated ambient pressures and decreased in the remainder. In view of the vasocon-

![Figure 1](image1.png)

**Figure 1.** The percent change in diameter from control at 0 (atmospheric) ambient pressure is presented for various changes in ambient pressure. The numerical data are the equation parameters for the least squares regression curve fits. The x and y axis error bars represent standard errors of the means. The numbers beside data points represent both the number of vessels and animals.

![Figure 2](image2.png)

**Figure 2.** The percent change in vessel wall tension of cortical arterioles for various changes in arterial pressure measured in cortical arterioles when ambient pressure was altered. The average resting arteriolar pressure was 40–50 mm Hg at a normal mean arterial of 100–115 mm Hg. Twenty-one of the 28 measurements of wall tension are within ±10–15% of control, with the majority of these at transmural pressure changes of ±20–40%. Similar symbols at elevated and decreased arteriolar pressures represent the same vessel; each vessel represented is from a different animal.
striction which invariably accompanied elevated ambient pressures (Fig. 1) and the maintenance of perfusion pressure, a decrease in blood flow should be the expected response. At subatmospheric ambient pressures, depicted on the left side of Figure 3, blood flow increased in every animal tested, as would be expected from the vasodilation at subatmospheric ambient pressures (Fig. 1). The maximum blood flow increase in cerebral vessels after topical application of adenosine (0.04 M) was typically 100-150%.

**Discussion**

The purpose of the present study was to determine whether, at the level of individual cerebral arterioles, a change in intravascular pressure independent of a change in perfusion pressure is an adequate stimulus to initiate a myogenic-like response. As shown in Figure 1, vasconstriction occurred at elevated ambient pressures, and vasodilation was associated with decreased ambient pressures. In both cases, vessel wall tension remained within 10-15% of control, even at arteriolar pressure changes of up to ±20-40% (Fig. 2). Unfortunately, vascular trauma at ambient pressures above ±20 mm Hg limits comparisons of our data to those previously reported for other vascular beds subjected to much larger changes in intravascular pressure. However, the magnitude of cerebral arteriolar constriction is comparable to that reported by Morff and Granger (1982) for cremasteric muscle arterioles (20-50 μm, i.d.) during elevations of venous pressure similar to those in the present study. Bouskela and Wiederhielm (1979) have used the whole body change in ambient pressure, as originally described by Wiederhielm et al. (1979), and report relatively minor changes in arteriolar diameters in the bat wing for ambient pressures of ±25 mm Hg. The vessels apparently maintained a nearly constant diameter despite whatever change in intravascular pressure occurred at ambient pressures of ±25 mm Hg. Burrows and Johnson (1981, 1983) have used increases in both arterial and venous pressure to evaluate the response of mesenteric arterioles of the cat to increased transmural pressures. For increased arteriolar pressure changes comparable to those which occurred in the present study, Burrows and Johnson (1981, 1983) observed a 10-20% constriction for those vessels which constricted. However, they reported that there was no apparent relationship between the magnitude of constriction and increase in intravascular pressure, using either increased arterial or venous pressure. In effect, the cerebral arterioles responded to increased intravascular pressure as previously observed in skeletal muscle (Morff and Granger, 1982) and mesenteric (Burrows and Johnson, 1981, 1983) arterioles, and all three vascular beds appear to constrict more than do bat wing arterioles to small increases in pressure.

The change in vessel wall physical forces rather than vessel diameter is of potentially greater importance to evaluate the presence of myogenic behavior. For example, in the present study, increases or decreases in intravascular pressure of more than ±8-16 mm Hg corresponded to a ±20-40% change in pressure for the vessels depicted in Figure 2. At ambient pressures of ±20 mm Hg, vessel wall tension typically remained within ±10-15% of control. At ambient pressures of ±25 mm Hg, Bouskela and Wiederhielm (1979) calculated that the wall tension remained within ~32% to ±28% of control, which is somewhat greater than found in the present study for a similar range of ambient pressures. Mesenteric arterioles which constricted as intravascular pressure was increased, in the study by Burrows and Johnson (1983), demonstrated only a 3.8% increase in wall tension for a 10% pressure increase. By comparison, cerebral arterioles at both increased and decreased intravascular pressures change wall tension by about 5% per 10% change in pressure. These data from arterioles of the bat wing (Bouskela and Wiederhielm, 1979), cat mesentery (Burrows and Johnson, 1983), and rat cerebral cortex indicate that, under appropriate conditions, a myogenic-like mechanism does attempt to maintain vessel wall tension within a relatively narrow range. An issue raised in a study of isolated rat brain arterioles by Dacey and Duling (1982) is that, even if vessel wall stress and tension dramatically change as intravascular pressure is altered, a myogenic mechanism may be active. In their study, vessel diameter of the isolated vessels changed very little at transmural pressures from
about 15 to 150 mm Hg. This pressure range corresponds to that reported for cortical arterioles of the rat (Harper et al., 1984, Harper and Bohlen, 1984) and cat (Shapiro et al., 1971; Stromberg and Fox, 1972). The issue of a small change in vessel diameter as transmural pressure changes is raised to emphasize that preservation of a relatively constant vessel wall stress or tension is but one facet of myogenic regulation.

In the present study, we expected that, if a myogenic response occurred, the cerebral vascular response would occur rapidly and then gradually dissipate, as suggested by the observations of Gourley and Heistad (1983) and Symon et al. (1971). Virtually all the responses were at a new steady state within 10–15 seconds after the change in ambient pressure was completed. In our previous studies of cerebral vascular behavior in the rat as arterial pressure is altered (Harper et al., 1984; Harper and Bohlen, 1984), a new steady state required a minimum of 30–60 seconds to develop after an increase or decrease in arterial pressure had reached steady state. Apparently, changes in perfusion pressure evoked a mechanism, presumably metabolic feedback control, which required a greater time period to adjust vascular tone than did the mechanism which responded to a simple change in transmural pressure in the current study. Two additional factors are present in the current study which should have had some effect on the rapidity and sustained nature of the myogenic response. First, the suffusion solution PO₂ was maintained at 45–50 mm Hg to mimic the cerebral spinal fluid PO₂. This PO₂ is substantially higher than tissue PO₂ (10–20 mm Hg) and may have exaggerated the myogenic response by suppressing metabolic control. However, as described in Methods, it is unlikely that a major contribution of suffusion solution oxygen to tissue oxygenation was present. Second, the myogenic responses caused a mild hyperemia in all cases during subatmospheric ambient pressures and a reduction in blood flow in about half the animals at ambient pressures above atmospheric pressures (Fig. 3). In both situations, local metabolic control of the vasculature should have blunted the myogenic vascular responses by causing opposite changes in blood flow. We suspect that this, in fact, occurred. During both the sustained responses to increased and decreased ambient pressures, the arterioles developed low amplitude vaso-motion as if several control mechanisms were attempting to regulate vessel caliber. The sustained vasodilatation or vasostriction at altered ambient pressures is somewhat surprising because, as shown in Figure 2, vessel wall tension is near normal (± 10–15%) at steady state conditions, particularly for transmural pressure changes of ±8–16 mm Hg. In effect, one of the proposed stimuli for a myogenic response, a change in wall tension, was substantially blunted by the vascular response after a change in pressure. Had the vessels maintained a diameter similar to that at rest with increased or decreased transmural pressures, this would suggest the presence of myogenic regulation primarily in response to changes in wall tension. Vessel wall tension at a nearly constant diameter would essentially be a direct function of transmural pressure and, as such, a sustained stimulus for a myogenic response. Such a situation has been observed by Bouskela and Wiederhielm (1979) for bat arterioles at ambient pressures of ±25 mm Hg and by Dacey and Duling (1982) for isolated arterioles of the rat cerebral cortex. The potential for sustained myogenic responses has been recently reviewed by Johnson (1980). It is important to note that reasonable and sustained preservation of vessel wall tension occurred as both arteriolar pressure and vessel diameter changed. Perhaps a myogenic stimulus related to transmural pressure changes through both vessel wall length and tension changes helped sustain the vascular response (Johansson and Mellander, 1975).

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References


Johansson B, Mellander S (1975) Static and dynamic components
in the vascular myogenic response to passive changes in length as revealed by electrical and mechanical recordings from the rat portal vein. Circ Res 36: 76–83

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