Regulation of Large Cerebral Arteries and Cerebral Microvascular Pressure

Frank M. Faraci and Donald D. Heistad

Resistance of large arteries appears to be greater in the cerebral circulation than in other vascular beds. Large arteries contribute importantly to total cerebral vascular resistance and are major determinants of local microvascular pressure. Recent studies have shown that resistance of large arteries and cerebral microvascular pressure are affected by several physiological stimuli, including changes in systemic blood pressure, increases in cerebral metabolism, activity of sympathetic nerves, and humoral stimuli such as circulating vasopressin and angiotensin. Stimuli such as sympathetic stimulation and vasopressin produce selective responses of large arteries and, thereby, regulate microvascular pressure without a significant change in cerebral blood flow. These findings lead to the new hypothesis that the brain may be sensitive to changes in cerebral microvascular pressure, resulting in activation of compensatory neurohumoral mechanisms. Important changes occur in large cerebral arteries under pathophysiological conditions. Chronic hypertension increases resistance of large cerebral arteries, which protects the microcirculation against hypertension. Atherosclerosis potentiates constrictor responses of large cerebral arteries to serotonin and thromboxane, which may contribute to vasospasm and transient ischemic attacks. (Circulation Research 1990;66:8-17)

A major concept in vascular physiology has been that large arteries are conduit vessels and that arterioles regulate vascular resistance. This concept requires revision in light of a considerable body of evidence that large arteries play a major role in regulation of blood flow, especially in the cerebral circulation. It is important to specifically examine regulation of large arteries, because large arteries may respond selectively to some stimuli. Small arteries and arterioles may be either unresponsive or their response may oppose that of large arteries. The role of large arteries is also important because normal regulatory mechanisms that affect large arteries may be altered by disease states, such as chronic hypertension and atherosclerosis.

A recent concept is that neurohumoral stimuli, by affecting primarily large arteries, can modulate cerebral microvascular pressure without altering cerebral blood flow. Evidence for selective regulation of cerebral microvascular pressure leads us to formulation of the hypothesis that an important consequence of neurohumoral regulation of resistance of large arteries and of cerebral microvascular pressure may be modulation of central baroreceptors within the brain. The possibility that baroreceptors may be present in the central nervous system is a new concept.

The purpose of this review is to summarize recent concepts concerning regulation of large cerebral arteries and microvascular pressure, to define some of the functional differences between cerebral and noncerebral vessels, to discuss changes that occur under pathophysiological conditions, and to point out some unanswered questions in understanding of mechanisms that regulate these blood vessels. Finally, we will speculate about potential functional consequences of selective changes in cerebral microvascular pressure. Our discussion will focus on microvascular pressure only in small cerebral arteries or arterioles, because little information is available concerning regulation of cerebral capillary pressure.

Physiology

Segmental Resistance and Distribution of Microvascular Pressure

Traditionally, physiologists have considered small arteries and arterioles to be the major site of vascular resistance. Recent publications state that the greatest pressure drop occurs in vessels less than 100 μm in diameter.
diameter and that large and small arteries provide little resistance to blood flow. For blood vessels that supply the brain, this view is not entirely correct.

Pressure (measured with micropipettes) in the largest intracranial vessels, such as the basilar artery, is approximately 80% of aortic pressure, and pressure in pial arteries approximately 200 μm in diameter on the cerebrum is only 50–60% of systemic pressure. Thus, large intracranial and extracerebral vessels, such as the carotid or vertebral arteries, are a major site of resistance to blood flow in the cerebral circulation and contribute significantly to total cerebral vascular resistance. McRitchie has previously emphasized the importance of the carotid and vertebral arteries in regulation of cerebral blood flow. Because it is assumed that pressure in the basilar artery is the same as pressure in vessels of the circle of Willis, these findings also suggest that large cerebral arteries from the circle of Willis to pial arteries of approximately 200 μm in diameter contribute 20–30% of cerebral vascular resistance.

The relation of microvascular pressure to vessel diameter differs in several tissues (Figure 1). These selected data are all from the same species, the cat, to facilitate comparison without having to account for large differences in animal size. For an artery or arteriole of a given diameter, microvascular pressure is lower in the brain than in the heart, mesentery, or skeletal muscle. These measurements suggest that resistance of large arteries is greater in the brain than in other organs.

A marked fall in pressure along large cerebral arteries is not unique to the cat. For example, pressure in pial arterioles approximately 100 μm in diameter in the rabbit is about 50% of aortic pressure. In primates, approximately 25% of total cerebral vascular resistance is accounted for by arteries larger than 350 μm in diameter. In the same primate model, arteries greater than 270 μm in diameter account for only about 10% of total coronary vascular resistance, which again suggests that resistance of large arteries in the brain is greater than in other organs. Although a similar trend was seen in several species, the large differences in animal size make it difficult to establish a single definition for large arteries and small vessels in the cerebral circulation.

In the rat, the microvascular pressure profile in the brain is similar to that observed in the intestine and skeletal muscle. These findings are in contrast to results obtained in the cat and monkey in which resistance of large arteries in the brain appears to be greater than in other organs. This species difference may relate to differences in animal size, because the range of caliber of vessels present in small species such as the rat is relatively narrow compared with larger species. Differences between organs may be less apparent when, as is the case for the rat, most of the vessels studied are small and less than 100 μm in diameter.

There are regional differences in microvascular pressure within the brain. Pressure in similar-sized arteries and arterioles is greater in the brain stem than in the cerebrum. Differences in the relative diameter and length of large arteries as well as the branching pattern may contribute to differences in resistance of large arteries in the cerebrum and brain stem.

**Determinants of Microvascular Pressure**

A major determinant of pressure in a vessel is the ratio of upstream to downstream resistance; changes in the relative contribution of these resistances may alter microvascular pressure. For example, if large arteries constrict and arterioles dilate, pressure in small arteries where the measurement is made will decrease without any change in blood flow. In contrast, if resistance of both large arteries and arterioles increases or decreases by a similar magnitude, blood flow will change, but pressure in small arteries will remain constant. For example, hypocalcemia constricts both large and small cerebral vessels and decreases cerebral blood flow, but it does not change pressure in small arteries. Hypercapnia decreases the resistance of both large and small vessels, but because the dilator response is greater in arterioles than in large arteries, hypercapnia reduces pressure in small arteries.

During focal increases in blood flow that occur during local changes in metabolism, changes in resistance of large arteries are potential major determinants of microvascular pressure. This concept is illustrated by the hypothetical example in Figure 2. Under control conditions (panel A), blood flow to two adjacent regions of the cerebrum is the same, and microvascular pressure or the local input pressure is 50 mm Hg. Panel B illustrates the effect of an increase in metabolism and blood flow in one region when resistance of large arteries is fixed at the control levels. Under these conditions, a marked fall in microvascular pressure will occur during a twofold increase in blood flow to one of the two regions. Such a fall in microvascular pressure represents a decrease in the local driving pressure and would tend to...
reduce blood flow to the adjacent region in which metabolism and vascular resistance were unchanged. Under these conditions, the increase in blood flow to one region tends to divert blood flow away from the second region. In contrast, if the focal increase in blood flow in one region is also accompanied by a decrease in resistance of large arteries of 33%, microvascular pressure would be maintained at control levels preventing the possibility of a vascular "steal" phenomenon (panel C).

Thus, changes in resistance of large arteries during focal increases in metabolism may be a major determinant of local perfusion pressure. This concept, which also has been proposed to occur in skeletal muscle, may be particularly important in the brain, because discrete focal increases in blood flow may occur commonly and resistance of large arteries is great.

Effects of Changes in Systemic Blood Pressure

It is clear that the brain autoregulates effectively to maintain its normal rate of blood flow during changes in perfusion pressure. Cerebral microvascular pressure, however, changes in response to a number of stimuli, including aortic pressure, which are outlined in Figure 3 and will be addressed separately. Thus, although cerebral blood flow is regulated at or near control levels over a wide range of systemic pressures, microvascular pressure in small arteries and arterioles is not as constant. During moderate increases in systemic pressure, resistance of large arteries in the cerebrum increases, which attenuates but does not prevent increases in cerebral microvascular pressure. In contrast to pressure in small arteries, it seems likely that capillary pressure in the brain is relatively constant during moderate changes in systemic pressure.

Changes in microvascular pressure during changes in systemic pressure are not uniform throughout the brain. Microvascular pressure is higher in the brain stem than in the cerebrum under control conditions, and during increases in systemic pressure, pressure in small arteries rises more in the brain stem. These findings were surprising, because the brain stem autoregulates more effectively than the cerebrum during increases in aortic pressure. The greater increase in pressure in small arteries of the brain stem occurs because, unlike the cerebrum, resistance of large arteries to the brain stem decreases during even moderate increases in systemic pressure. Thus, large arteries of the brain stem respond passively during increases in blood pressure. These findings suggest that, in contrast to responses in the cerebrum, autoregulation of blood flow to the brain stem during acute hypertension is accomplished exclusively and very effectively by small vessels.

Effects of Metabolic Stimuli

Effects of changes in cerebral metabolism on blood flow have been widely studied, but effects on microvascular pressure have received little attention. Induction of seizures with bicuculline produces profound global increases in cerebral metabolism and blood flow. When aortic pressure is maintained at control levels, seizures increase blood flow more than three-fold, due to a decrease in resistance of both large arteries and small vessels. Because the greatest effect of seizures is on small vessels, however, pressure in

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

**Figure 2.** Schematic illustrating the concept that resistance of large cerebral arteries is an important determinant of microvascular pressure during focal increases in blood flow. Panel A: Control conditions. Panel B: Vascular "steal" produced by a focal increase in blood flow to one region with fixed resistance of large arteries. Panel C: Maintenance of microvascular pressure and blood flow at control levels during dilatation of large arteries.

![Figure 3](http://circres.ahajournals.org/)

**Figure 3.** A summary of the effects of changes in aortic pressure, cerebral neuronal activity and metabolism, activity of sympathetic nerves, and humoral stimuli on cerebral blood flow and arteriolar pressure. These diagrams are an extrapolation based on a limited number of actual measurements under each condition.
small arteries decreases substantially (Figure 3).17 These data again illustrate the importance of changes in resistance of large arteries, because microvascular pressure would decrease much more if large arteries did not dilate during increases in blood flow.

The observed decrease in microvascular pressure during seizures17 suggests the possibility that a fall in microvascular pressure may contribute to the increase in systemic pressure that occurs during seizures. At the onset of seizures, resistance of small pial or parenchymal vessels may fall and, thus, tend to reduce microvascular pressure in large arteries upstream. We speculate that increased sympathetic drive may be initiated in part by activation of central baroreceptors during reductions in cerebral microvascular pressure and that the consequent increases in systemic pressure would tend to restore microvascular pressure to normal. This may contribute to maintenance of cerebral perfusion during a metabolic stimulus.

It is not known to what extent, and through what mechanisms, cerebral microvascular pressure is maintained near control levels during focal increases in metabolism and blood flow, in contrast to the global change that occurs during seizures. Several mechanisms are possible. Endothelial cells may play a major role in coordinating an integrated response within the vasculature.31 In other organs, ascending dilatation may occur through a mechanism that is dependent on increases in blood flow32 and may33,34 or may not35 be endothelium dependent. In addition, a mechanism of ascending dilatation in the microcirculation of the hamster cheek pouch has been described.36 This mechanism is independent of blood flow and appears to involve a conducted response through cells in the vessel wall. Changes in the production and release of endothelium-derived relaxing factor may also play an important role in modulation of tone in the microcirculation.37

**Neural Effects on Microvascular Pressure**

Cerebral blood vessels are densely innervated by sympathetic nerves that originate primarily from the superior cervical ganglia.36,39 The density of sympathetic innervation is greatest in large arteries and perhaps in vessels of the anterior cerebral circulation (anterior and middle cerebral arteries).36,39 Stimulation of sympathetic nerves increases the resistance of large arteries and decreases microvascular pressure in the cerebrum in the absence of changes in systemic pressure (Figure 3).9 Cerebral blood flow does not change during sympathetic stimulation, despite constriction of large arteries, because resistance of small downstream vessels decreases.9 Dilatation of small vessels is presumably a response to the fall in microvascular pressure. We cannot exclude the possibility, however, that dilatation of small vessels during sympathetic stimulation is a direct neural effect. It is also possible that autoregulatory dilatation of small vessels in response to the decrease in pressure overrides constrictor effects of sympathetic nerves.

During acute hypertension, activation of sympathetic nerves and increases in pressure within small arteries may work concordantly to produce constriction of small vessels. As a consequence of these related mechanisms, sympathetic stimulation has little effect on cerebral blood flow during normotension, because dilatation of small vessels opposes constriction of large arteries. In contrast, during acute hypertension, both large arteries and small vessels constrict, resulting in important effects on cerebral blood flow.5,40,41

Large cerebral arteries are richly innervated by cholinergic and peptidergic nerve fibers that contain neuropeptide Y, vasoactive intestinal peptide, substance P, and calcitonin gene-related peptide.42-45 This innervation is not exclusive to large arteries, because parenchymal vessels receive a cholinergic innervation as well.46 The vasoactive peptides may be released by sympathetic nerves (neuropeptide Y),44 cholinergic nerves (vasoactive intestinal peptide),44 or sensory nerves such as the trigeminal nerve (substance P and calcitonin gene-related peptide).44,47

Although cerebral blood vessels are innervated by cholinergic nerves, it has been difficult to demonstrate effects of cholinergic nerves on cerebral blood flow, even when cholinergic effects on blood flow to noncerebral tissues are clearly present.48,49 It is possible that activation of cholinergic or parasympathetic nerves, like activation of sympathetic nerves, primarily affects large cerebral arteries and alters microvascular pressure but not blood flow. Cholinergic activation may decrease resistance of large arteries and increase microvascular pressure without changing blood flow, if small vessels autoregulate in response to the increase in pressure in small arteries. The rich innervation of large arteries suggests a potential role for peptidergic neural mechanisms in regulation of cerebral microvascular pressure.

**Humoral Effects on Microvascular Pressure**

Humoral stimuli such as circulating catecholamines and vasoactive peptides have little effect on cerebral blood flow. The small magnitude of responses has been attributed to the endothelial blood-brain barrier, which limits the ability of hormones to reach cerebral smooth muscle.50-52 The traditional view that humoral stimuli have little effect on cerebral blood vessels probably needs to be modified in light of recent studies that indicate that several circulating hormones may have important effects on large cerebral arteries and cerebral microvascular pressure without changing blood flow.

Vasopressin, at plasma concentrations in the range observed during hypoxia, hemorrhage, or intracranial hypertension, decreases the resistance of large cerebral arteries and increases microvascular pressure.4 During infusion of vasopressin, resistance of small vessels increases as an autoregulatory response to the increase in pial artery pressure, so that cerebral blood flow does not change. The dilator response of large arteries to vasopressin was surprising, because
vasopressin has been generally considered to be a constrictor of cerebral blood vessels. However, two studies have described relaxation of large cerebral arteries to vasopressin through an endothelium-dependent mechanism in vitro. Thus, we speculate that circulating vasopressin may activate receptors on cerebral endothelium to release an endothelium-derived relaxing factor and dilate large cerebral arteries, without penetrating the endothelial blood-brain barrier. Responses could be selective for large arteries if small vessels lack similar receptors for vasopressin.

Angiotensin produces constriction of cerebral arteries in vitro and, when applied topically, in vivo. It has been suggested that circulating angiotensin has little or no direct effect on cerebral vessels, because it does not readily cross the blood-brain barrier. We have found, however, that angiotensin has a direct effect on cerebral vessels; it increases the resistance of large cerebral arteries and decreases pial microvascular pressure with little effect on blood flow.

In other vascular beds such as the limb, vasopressin and angiotensin generally increase vascular resistance by an effect primarily on small vessels. Thus, the preferential effects of these peptides on large arteries of the brain are unusual.

Intracranial cerebral arteries have a comparatively low receptor number and affinity for norepinephrine. Norepinephrine produces constriction of large cerebral arteries in vitro, but responses are much smaller than those of extracerebral arteries. When aortic pressure is maintained at control levels, intravenous infusion of norepinephrine has no effect on the diameter of cerebral vessels, cerebral blood flow, resistance of large cerebral arteries, or microvascular pressure. Thus, in contrast to responses of large cerebral arteries to vasopressin and angiotensin, large arteries do not respond to circulating norepinephrine.

Studies of cerebral vessels in vitro and in vivo indicate that cerebral arteries are responsive to several hormones including oxytocin, atriopeptin, and parathyroid hormone. These findings suggest the potential for modulation of cerebral microvascular pressure by several humoral mechanisms, as illustrated in Figure 3.

Mechanisms by which circulating hormones affect large arteries are not clear. Responses may occur through endothelium-dependent mechanisms, or small quantities of hormones may diffuse across the endothelial blood-brain barrier in large arteries. In addition, when resistance of large arteries is calculated from measurements of aortic pressure, pial artery pressure, and cerebral blood flow, the value that is obtained includes resistance of extracranial arteries such as the carotid and vertebral arteries. These extracranial segments may also respond to bloodborne stimuli and contribute to changes in resistance of large arteries.

**Implications of Neurohumoral Effects on Microvascular Pressure**

We speculate that there may be at least two functional consequences of changes in cerebral microvascular pressure. First, changes in microvascular pressure may affect "central baroreceptors." Compensatory adjustments may be initiated by the central nervous system if sites within the brain vasculature function in an analogous manner to carotid sinus baroreceptors, which are specialized neural elements within the arterial wall, or to the juxtaglomerular apparatus of the kidney (the "renal baroreceptor"). Direct evidence for the existence of baroreceptors in the brain or its vasculature is limited. There is morphological evidence for baroreceptor-type nerve endings in the adventitia of large cerebral arteries. Specific neural pathways that transmit signals from these putative baroreceptors are not known. In addition, Nicolaids et al. have suggested, based on recordings of nerves that alter their rate of discharge in response to changes in blood pressure, that the subfornical organ may be part of a central baroreceptor mechanism. It is not known whether neurons in this region initiate neural or humoral responses to changes in pressure.

We speculate that activation of sympathetic nerves or increases in circulating angiotensin may constrict large arteries and reduce cerebral microvascular pressure. This reduction in pressure may activate neural or humoral compensatory mechanisms that produce acute increases in arterial pressure or perhaps contribute to development of chronic hypertension. Possibly related to this mechanism is the finding that small decreases in pressure within the cerebral ventricles produce sustained increases in systemic blood pressure.

Second, changes in microvascular pressure may affect capillary fluid exchange, particularly in regions of the brain where the blood-brain barrier is not present and where the microvessels are relatively permeable. Such regions include the choroid plexus and the other circumventricular organs. If the observed increases or decreases in arteriolar pressure are also associated with changes in capillary pressure, the hydrostatic pressure in capillaries of the choroid plexus may change sufficiently to affect the formation of cerebrospinal fluid. Similarly, changes in hydrostatic pressure may alter the normal rate of capillary fluid filtration in circumventricular organs and, thus, change the osmolarity of interstitial fluid. Such changes in local osmolarity may stimulate or inhibit central osmoreceptors.

**Pathophysiology**

**Chronic Hypertension**

When acute increases in systemic pressure exceed the autoregulatory capacity of cerebral vessels, cerebral blood flow increases passively. Although levels of systemic pressure that produce "breakthrough" of autoregulation in normotensive individuals are often
exceeded during chronic hypertension, cerebral blood flow usually remains at normal levels in humans with chronic hypertension and in animal models of hypertension, because cerebral vascular resistance is elevated.\textsuperscript{10,73,74} Approximately one half of this increase in total cerebral vascular resistance is due to an increase in resistance of large cerebral arteries.\textsuperscript{73}

Increases in resistance of large arteries greatly attenuates increases in cerebral microvascular pressure. For example, aortic pressure is 60–100 mm Hg higher in stroke-prone spontaneously hypertensive rats than in normotensive Wistar-Kyoto rats, but pressure in pial arterioles is only 20–50 mm Hg above normal.\textsuperscript{73,75,76} It should be noted, however, that despite increases in resistance of large arteries, pressure in cerebral arterioles and venules is elevated slightly, which indicates that capillary pressure probably is also elevated.\textsuperscript{75,76}

Several mechanisms may contribute to increases in resistance of large cerebral arteries during chronic hypertension. First, activation of sympathetic nerves increases resistance of large cerebral arteries,\textsuperscript{9} and if sympathetic innervation is increased in stroke-prone spontaneously hypertensive rats,\textsuperscript{10} neural mechanisms may contribute to increases in resistance of large arteries.

Several lines of evidence suggest that structural changes, including hypertrophy and "remodeling" of large arteries, may occur during chronic hypertension,\textsuperscript{10,74} due in part to a trophic effect of sympathetic nerves on cerebral vessels.\textsuperscript{10} Hypertrophy of the vessel wall, which consists primarily of an increase in the content of smooth muscle, encroaches on the lumen of the vessels and increases resistance of large arteries during maximal dilatation.\textsuperscript{10,73}

Humoral mechanisms also may contribute to increased resistance of large arteries during chronic hypertension. For example, circulating angiotensin II constricts large cerebral arteries\textsuperscript{4} and, thus, may contribute to cerebral vasconstriction in types of hypertension that are associated with increased plasma levels of angiotensin. In addition, recent evidence suggests that a vascular renin-angiotensin system may contribute to the resting tone of blood vessels.\textsuperscript{77} Activity of angiotensin-converting enzyme is greater in some large cerebral arteries in spontaneously hypertensive rats than in Wistar-Kyoto rats.\textsuperscript{78} These findings raise the possibility that a portion of the increase in resistance of large arteries during chronic hypertension may be due to an elevation of the tonic influence of a local vascular renin-angiotensin system.

A recent series of experiments demonstrate that treatment of chronic hypertension, with reduction of systemic pressure to normal levels, completely prevents increases in cerebral microvascular pressure.\textsuperscript{79} These studies demonstrate that both genetic spontaneously hypertensive rats and renal (two-kidney, one-clip) models of hypertension produce similar alterations in the cerebral microcirculation and that both respond effectively to antihypertensive therapy.

**Atherosclerosis**

Although intracranial arteries are relatively spared by atherosclerosis, large extracranial arteries are very susceptible to atherosclerotic lesions.\textsuperscript{80,81} Because large arteries play an important role in regulation of the cerebral circulation, atherosclerotic lesions of large arteries might be expected to affect regulation of blood flow and microvascular pressure.

Because there is marked proliferation of the intima during atherosclerosis, one might anticipate substantial encroachment on the vascular lumen, with an increase in resistance of large arteries and alterations in cerebral blood flow. Cerebral blood flow is normal under control conditions, however, and the pressure gradient from aorta to cerebral arteries is not increased in atherosclerotic monkeys.\textsuperscript{11,12,18} The explanation for these observations became apparent when it was found that atherosclerotic lesions may be displaced outward with only minimal encroachment on the vessel lumen.\textsuperscript{12}

When platelets adhere and aggregate at atherosclerotic lesions, the platelets release relatively large quantities of vasoactive products, including serotonin, ADP, and thromboxane.\textsuperscript{82,83} These vasoactive products may have important vascular effects in both the brain and the eye (Figure 4). We have suggested that release of serotonin and thromboxane may contribute to vasospasm and transient ischemic attacks. This hypothesis is based on the finding that atherosclerosis greatly potentiates constrictor responses of atherosclerotic arteries.\textsuperscript{12,85}

Intravascular infusion of serotonin or thromboxane, to simulate release from platelets during aggregation, produces at most only modest constriction of
large cerebral arteries in normal monkeys. In contrast, serotonin or thromboxane produce a marked increase in resistance of large cerebral arteries in atherosclerotic monkeys.

Intravascular infusion of serotonin and thromboxane has little effect on blood flow to the eye in normal monkeys. In atherosclerotic monkeys, however, serotonin and thromboxane produce marked decreases in blood flow to the retina and choroid of the eye. These reductions in blood flow to the eye may result from proximal spasm of large extracranial arteries, but they also may involve constriction of smaller blood vessels, such as the ophthalmic artery, which surprisingly develop atherosclerotic lesions.

The marked reductions in blood flow to the retina in atherosclerotic monkeys are associated with profound reductions in the amplitude of the electroretinogram. These findings lead us to suggest that the mechanism of transient blindness associated with transient ischemic attacks may be due in part to reductions in blood flow to the retina in response to local release of serotonin and thromboxane from aggregating platelets (Figure 4).

A mechanism that may contribute to augmented constriction responses to serotonin and thromboxane during atherosclerosis is alteration in endothelium-dependent modulation of vascular reactivity. Endothelium-dependent relaxation in response to ADP or aggregation of platelets is impaired, and platelet-induced contraction is augmented, in basilar arteries from hypercholesterolemic pigs.

When distal vessels are normal, constriction of large atherosclerotic arteries and reduction in cerebral microvascular pressure may not impair local perfusion, because downstream vessels can autoregulate effectively to maintain blood flow. However, we speculate that, in the presence of a distal stenosis or partial obstruction of a distal cerebral artery by a platelet-rich embolus, reduction in microvascular pressure by constriction of a large atherosclerotic artery may produce focal cerebral ischemia (Figure 4).

Regression of atherosclerosis in primates reduces the intimal area in the carotid arteries by 50–75% and completely abolishes augmented responses of large arteries to serotonin. These findings suggest that regression of atherosclerosis may be effective in correcting functional abnormalities of large cerebral arteries produced by atherosclerosis.

Ischemia

Occlusion of a major artery supplying the brain reduces microvascular pressure and may produce ischemia. The extent of ischemia depends in part on the effectiveness of the local collateral circulation. For example, total occlusion of one carotid artery in primates reduces pressure in ipsilateral cerebral arteries but does not reduce blood flow. Dilatation of downstream vessels and the very effective collateral network of the circle of Willis is sufficient to maintain blood flow at normal levels.

In contrast to carotid occlusion, more distal occlusion of the middle cerebral artery in the cat sharply reduces pressure in cerebral arteries and local blood flow, thus producing ischemia. Pressure in cerebral arteries in the affected region decreases from 55–60 mm Hg to approximately 8 mm Hg after 15 minutes of occlusion and then increases to approximately 16 mm Hg after 2 hours. These findings suggest that there is only modest improvement or “delayed collateralization” with time in the ischemic region. It should be noted, however, that small increases in cerebral arterial pressure are associated with significant increases in local blood flow and electrocortical function during ischemia.

The effects on microvascular pressure of gradual, rather than abrupt, occlusion of the middle cerebral artery have also been examined. In cats, it was necessary to reduce the diameter of the middle cerebral artery from approximately 700–800 μm to about 200 μm to reduce downstream pressure or local blood flow. As pressure in distal cerebral arteries fell below approximately 35 mm Hg, blood flow also began to decrease.

Occlusion of the middle cerebral artery produces cerebral infarction in stroke-prone spontaneously hypertensive rats, but not in Wistar-Kyoto rats. This finding suggests that chronic hypertension impairs the effectiveness of the collateral circulation in maintaining an adequate blood supply. Occlusion of the middle cerebral artery probably produces greater reductions in microvascular pressure in stroke-prone spontaneously hypertensive rats than in Wistar-Kyoto rats.

Summary and Future Directions

In several species, resistance of large arteries appears to be greater in the cerebral circulation than in other vascular beds. Large cerebral arteries are important determinants of local microvascular pressure and also contribute significantly to total cerebrovascular resistance.

Mechanisms that regulate the release of endothelium-derived relaxing and contracting factors and their effects on blood vessels are being investigated intensively in vitro. Lee was the first to examine endothelium-dependent responses of large cerebral arteries in vitro. Some recent studies have addressed the role of endothelium in modulating responses of pial arteries in vivo. Very little is known about the role of endothelium in regulating tone of large cerebral arteries in vivo. We have recently begun to examine the effects of endothelium-dependent agonists on the basilar artery in vivo.

The observation that microvascular pressure may be altered without any change in cerebral blood flow forms the basis for the hypothesis that cerebral microvascular pressure may be an independently regulated variable. The potential functional consequences of changes in microvascular pressure are not clear. A major hypothesis that needs to be tested is that there are central baroreceptors that sense cerebral micro-
vascular pressure and contribute to regulation of blood pressure by neurohumoral mechanisms.

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