Cerebral Circulation in Chronic Arterial Hypertension

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SUMMARY Several new concepts have emerged recently regarding the effects of chronic hypertension on cerebral blood vessels. First, hypertrophy of large cerebral arteries in chronic hypertension attenuates increases in pressure of downstream vessels and protects the cerebral microvasculature. Second, in contrast to large cerebral arteries, which become less distensible during chronic hypertension, distensibility of cerebral arterioles increases during chronic hypertension despite hypertrophy of the arteriolar wall. Third, dilatation of cerebral blood vessels with disruption of the blood-brain barrier, and not vasospasm, appears to be the critical factor in the pathogenesis of hypertensive encephalopathy. This concept is supported by the finding that cerebral edema in stroke-prone spontaneously hypertensive rats is preceded by vasodilatation and disruption of the barrier. Fourth, alterations of endothelium-mediated dilatation may impair vasodilator responses in chronic hypertension and predispose to ischemia. Finally, chronic hypertension impairs dilatation of collateral blood vessels in the cerebral circulation. The implication of this finding is that increased susceptibility to cerebral infarction in chronic hypertension may be related in part to compromised responses of the collateral circulation.

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KEY WORDS • vascular mechanics • blood-brain barrier • collateral circulation

Ten years ago, two concepts dominated thinking regarding the effects of chronic hypertension on the cerebral circulation. First, hypertrophy of cerebral blood vessels during prolonged hypertension was thought to lead to encroachment of the wall on the vascular lumen and to reduced vascular distensibility, thereby limiting dilator responses of cerebral vessels and possibly contributing to an increase in susceptibility to cerebral infarction. Second, hypertensive encephalopathy was believed to result from vasospasm of cerebral vessels in response to elevation of arterial pressure, with cerebral ischemia secondary to the vasospasm. During the past 10 years, our understanding of the cerebral circulation in chronic hypertension has undergone substantial change. It is now known, for example, that cerebrovascular hypertrophy protects against stroke. It also appears that hypertensive encephalopathy is produced by cerebral vasodilatation, with disruption of the blood-brain barrier, rather than by vasoconstriction. In addition, entirely new concepts have emerged. It is clear that endothelium-dependent relaxation, which was discovered by Furchgott, is important in the brain, as well as in other vascular beds, and is altered by chronic hypertension. Another new concept is that cerebral collateral vessels may be fundamentally abnormal in chronic hypertension and that this abnormality may increase susceptibility to ischemia and infarction.

The purpose of this review is to summarize several recent concepts concerning alterations of cerebral circulation in chronic hypertension. The discussion focuses on changes in vessel wall properties and in cerebral vascular hemodynamics. We will speculate about the relationship of these changes to the cerebrovascular pathology that is associated with chronic hypertension.

Resistance of Large Arteries

The cerebral circulation is susceptible to damage by sudden increases in arterial pressure. During episodes of acute, severe hypertension, cerebral vessels dilate passively and there is "break-
through’’ of autoregulation. Acute, severe hypertension also results in generation of oxygen radicals, impairs autoregulation, and disruption of the blood-brain barrier. During chronic hypertension, the level of arterial pressure that is observed often is sufficiently high that one might expect passive dilatation and breakthrough of autoregulation. Cerebral blood flow, however, usually is normal in patients with chronic hypertension and in experimental models of chronic hypertension. Furthermore, the blood-brain barrier is less susceptible to disruption by acute increases in pressure in the presence of chronic hypertension. Thus, there must be powerful mechanisms that protect cerebral vessels during chronic hypertension.

Large cerebral arteries play an important role in the protection of cerebral microvessels during chronic hypertension. At normal levels of systemic arterial pressure, large arteries (>200 μm in diameter) account for about 40% of total cerebral vascular resistance. Large cerebral arteries, therefore, are important resistance vessels. The contribution of large arteries to cerebral vascular resistance increases even further during chronic hypertension. For example, resistance of large cerebral arteries is much greater in stroke-prone spontaneously hypertensive rats (SHRSP) than in normotensive Wistar-Kyoto rats (WKY). Consequently, pial arteriolar pressure is only about 20 mm Hg higher in SHRSP than in WKY, even though aortic pressure is nearly 60 mm Hg higher in SHRSP. Thus, large artery resistance increases during chronic hypertension, thereby attenuating increases in cerebral microvascular pressure and protecting cerebral microvessels from the detrimental effects of systemic hypertension.

One factor that may contribute to increases in resistance of large cerebral arteries during hypertension is humoral vasoactive substances, such as angiotensin. Most vasoactive substances, however, have little effect on total cerebral vascular resistance. The lack of response has been attributed to the endothelial blood-brain barrier, which prevents humoral agents from reaching cerebral vascular muscle. Recently, we found that intravenous infusion of angiotensin in cats increases resistance of large arteries and reduces pressure in pial arteries. Total cerebral vascular resistance did not increase, because small cerebral vessels dilated. Thus, angiotensin may increase resistance of large cerebral arteries and protect microvessels downstream, without reducing cerebral blood flow.

Another factor that may contribute to increases in resistance of large cerebral arteries during hypertension is autoregulation augmented by sympathetic neural discharge. During moderate increases in arterial pressure, large cerebral arteries autoregulate and constrict. During severe increases in pressure, the autoregulatory capacity of cerebral vessels is exceeded and large cerebral arteries dilate. The detrimental effects of acute, severe hypertension, however, may be prevented by sympathetic nerves. Stimulation of sympathetic nerves during acute hypertension extends the upper limit of autoregulation and prevents dilatation of large cerebral arteries and attenuates disruption of the blood-brain barrier.

During chronic hypertension, sympathetic nerves provide a tonic stimulus to cerebral vessels and promote cerebrovascular hypertrophy. Hypertrophy of the vessel wall encroaches on the vascular lumen and attenuates increases in pressure in microvessels downstream. The finding that minimal resistance of large cerebral arteries is increased in SHRSP indicates that large arteries undergo significant hypertrophy during chronic hypertension. Vascular hypertrophy, which primarily affects smooth muscle, also may contribute to an increase in the active component of large artery resistance in chronic hypertension.

The protective nature of cerebral vascular hypertrophy becomes apparent when the stimulus for hypertrophy is reduced. Chronic sympathetic denervation attenuates hypertrophy of cerebral vessels in SHRSP. The consequences of chronic sympathetic denervation and attenuation of cerebrovascular hypertrophy are twofold. First, in SHRSP that have undergone chronic sympathetic denervation, autoregulation of cerebral blood flow is impaired during acute increases in pressure. Second, chronic sympathetic denervation increases the incidence of cerebral hemorrhages and infarction in SHRSP. These findings provide evidence that, by stimulating the development of cerebrovascular hypertrophy, sympathetic nerves may protect cerebral blood vessels during chronic hypertension.

**Figure 1.** Resistance of large cerebral arteries, systemic arterial pressure, and pial arteriolar pressure in WKY and SHRSP. Resistance of large cerebral arteries increases in SHRSP, so that the difference in systemic pressure (1 SAP) in WKY and SHRSP is greater than the difference in pial arteriolar pressure (1 PAP). The increase of large artery resistance (1 LAR) in SHRSP therefore attenuates increases in cerebral microvascular pressure and protects microvessels from the effects of chronic hypertension. Values are means ± SE.
Alterations in Vascular Mechanics

Effects of chronic hypertension on cerebral vascular mechanics have been examined in vitro by several investigators. Distensibility of basilar artery and of branches of posterior cerebral artery has been reported to be reduced in spontaneously hypertensive rats (SHR) and SHRSP compared with normotensive WKY. Thus, as one might anticipate, distensibility of large arteries in the brain is reduced by chronic hypertension.

Studies of maximal dilator capacity of cerebral vessels in vivo provide indirect evidence that distensibility of cerebral vessels is reduced. Increases in cerebral blood flow during seizure or hypercapnia are less in hypertensive than in normotensive rats. During topical application of adenosine, the diameter of pial arterioles is similar in SHR and WKY, even though pial arteriolar pressure is significantly higher in SHR. These findings have led to the conclusion, which is only partially correct, that maximal dilator capacity is reduced during chronic hypertension by a reduction of vascular distensibility.

Recently, we examined the effect of chronic hypertension on mechanical characteristics of cerebral arterioles in vivo. The stress-strain curve was shifted to the right in SHRSP (Figure 2), which indicates that distensibility of pial arterioles is greater in SHRSP than in WKY. Thus, in contrast to large cerebral vessels, which become less distensible in chronic hypertension, our findings suggest a paradoxical increase in distensibility of cerebral arterioles during chronic hypertension, despite hypertrophy of the arteriolar wall.

A likely explanation for the difference in our findings and those of previous studies is that the basilar artery and branches of posterior cerebral artery, in which distensibility is reduced by hypertension, are much larger than the vessels that we examined. Pressure is elevated more in larger arteries than in cerebral arterioles during chronic hypertension. Also, the composition of the arterial wall varies with vessel size. It is possible, therefore, that the effects of chronic hypertension on the structure of cerebral vessels, and consequently on vascular mechanics, are not the same in large arteries as in arterioles. For example, large cerebral arteries contain proportionately about fourfold more collagen than do cerebral arterioles. Furthermore, the absolute amount of collagen is greater in posterior cerebral artery of SHR than of WKY, but not in cerebral arterioles of SHRSP. Thus, chronic hypertension may have different effects on mechanical, as well as structural, characteristics of large arteries and arterioles in the brain.

An implication of our findings is that cerebral arterioles may benefit from the advantages of hypertrophy while retaining important elements of normal vascular function. Hypertrophy of cerebral arterioles does not lead to a decrease in arteriolar distensibility. Thus, cerebral arterioles may adapt to hypertension with minimal impairment of mechanical characteristics.

The advantages of hypertrophy are twofold. First, hypertrophy attenuates increases in wall stress that accompany increases in intravascular pressure. Second, hypertrophy may encroach on the lumen of cerebral vessels (Figure 3). Encroachment on the lumen contributes to the rightward shift of the autoregulatory curve, which permits cerebral vessels to autoregulate blood flow at a higher range of systemic blood pressure during chronic hypertension.

A potential disadvantage of hypertrophy is that encroachment on the lumen impairs maximal dilator capacity of cerebral vessels. Impairment of maximal dilatation would reduce the effectiveness of cerebral vascular responses to dilator stimuli, such as

![Figure 2](image-url)

**Figure 2.** The stress-strain relationship of deactivated pial arterioles in WKY and SHRSP is an indicator of arteriolar distensibility. A shift of the curve to the right in SHRSP indicates an increase in distensibility. Values are means ± SE. APAD/PAD₀ = change in diameter/original diameter.

![Figure 3](image-url)

**Figure 3.** Proposed relationship of vascular hypertrophy with effects on diameter during constriction and dilatation of cerebral arterioles and increased vascular distensibility during chronic hypertension. During constriction of cerebral arterioles, hypertrophy of the arteriolar wall allows encroachment on the lumen and reduction of wall stress. During maximal dilatation, an increase in distensibility would tend to counteract encroachment on the lumen by hypertrophy and thus facilitate vasodilator responses.
as autoregulatory dilatation during severe hypoten-
sion. We speculate, however, that the increase in
distensibility of cerebral arterioles, when they are
maximally dilated, tends to counteract encroachment
on the lumen (see Figure 3), thus minimizing impair-
ment of maximal dilatation by hypertrophy. Further-
more, because distensibility of blood vessels is altered
by activation of smooth muscle, the protective
effect of encroachment on the lumen during vasocon-
striction probably is preserved in the hypertrophied
vessel despite the increase in distensibility.

We have emphasized the beneficial effects of
increased arteriolar distensibility in cerebral arte-
rioles of SHRSP. One must consider the possibility,
however, that an increase in arteriolar distensibility
has detrimental effects. For example, as distensibil-
ity is increased, the tensile strength of the arteriolar
wall may be reduced. Thus, an increase in arteriolar
distensibility by chronic hypertension may increase
the susceptibility of cerebral arterioles to rupture
when the vessels dilate passively during acute,
severe increases in systemic arterial pressure.

Blood-Brain Barrier

Hyperosmolar solutions produce disruption of the
blood-brain barrier.\textsuperscript{54} Disruption of the blood-brain
barrier to albumin after hypertonic arabinose is greater
in SHRSP than in WKY, even when systemic pres-
sure is reduced acutely in hypertensive rats to nor-
motensive levels before disruption of the barrier.\textsuperscript{55}
Osmotic disruption of the barrier produces fatal
cerebral edema in SHRSP, but not in WKY. These
findings suggest that there is an inherent defect of the
blood-brain barrier to osmotic disruption in chronic
hypertension.

Disruption of the blood-brain barrier also occurs
during acute hypertension.\textsuperscript{17, 22, 24} A recent finding
is that the primary site of disruption of the barrier
is cerebral veins.\textsuperscript{56} During acute hypertension,
increases in pial venular pressure are smaller and
disruption of the blood-brain barrier is less in SHRSP
than in WKY.\textsuperscript{57} In chronic hypertension, therefore,
cerebral vascular hypertrophy may protect the blood-
brain barrier\textsuperscript{29-31} by attenuating increases in micro-
vascular pressure.\textsuperscript{26, 48}

Disruption of the blood-brain barrier may play a
critical role in the development of hypertensive encephalopathy. Two alternative hypotheses have
been proposed with respect to the pathogenesis of
hypertensive encephalopathy. One view is that a
rapid rise in arterial pressure produces prolonged
vasospasm and ischemia.\textsuperscript{3, 58, 59} More recently, how-
ever, another hypothesis has emerged. Hyperten-
sive encephalopathy may result from passive dilata-
tion of cerebral vessels and disruption of the
blood-brain barrier.\textsuperscript{16, 60}

In a recent study, we examined cerebral blood
flow and permeability of the blood-brain barrier in
SHRSP when the rats exhibited signs of encepha-
lopathy.\textsuperscript{3} Our goals were to determine whether there
are focal changes in blood flow in areas of the
cerebrum with disruption of the barrier and whether
these changes precede or follow development of
edema. Two patterns were observed in the relation-
ship of regional cerebral blood flow to disruption of
the blood-brain barrier and cerebral edema: 1) regions
with disruption of the barrier, in which there was
minimal or no edema and normal or increased cere-
bral blood flow, and 2) regions with disruption of the
barrier, in which there was severe edema and marked
decreases in cerebral blood flow.

These findings provide evidence against the hypoth-
esis that vasospasm is the initiating event in the de-
velopment of hypertensive encephalopathy. If vaso-
spasm were the primary event and disruption of the
blood-brain barrier was secondary, one would antic-
ipated that disruption of the barrier would have been
observed only after reduction of blood flow. The
finding that blood flow was normal or increased in
regions with disruption of the blood-brain barrier and
minimal edema, however, suggests that disruption of
the barrier is not preceded by vasospasm, and instead
results from passive dilatation of cerebral blood
vessels. We speculated\textsuperscript{3} that ischemia results from
reductions in blood flow secondary to disruption of
the blood-brain barrier, from vascular compression
by edema, from vasoconstrictor hormones that gain
access to vascular muscle after disruption of the
barrier, or from neuronal dysfunction and damage
after disruption of the barrier (Figure 4). Our finding
that regional cerebral blood flow is not reduced until
there is marked focal edema is compatible with this
hypothesis.

Endothelium-Mediated Vasodilatation

Chronic hypertension impairs the response of
cerebral blood vessels to several vasodilator stim-
uli. Cerebral blood vessels dilate less in hyperten-
sive than in normotensive animals during
hypercapnia,\textsuperscript{61} hypotension,\textsuperscript{27} and seizure.\textsuperscript{4} Hyper-

\begin{figure}[h]
\centering
\includegraphics[width=\linewidth]{figure4.png}
\caption{Proposed role of passive dilatation and dis-
ruption of the blood-brain barrier (BBB) in the pathogen-
esis of hypertensive encephalopathy. Severe hyperten-
sion exceeds the autoregulatory capacity and produces
passive dilatation rather than vasospasm, of cerebral
vessels. Passive dilatation leads to disruption of the
blood-brain barrier, cerebral edema, and vascular stasis.}
\end{figure}
trophy of large arteries, with encroachment on the vessel lumen, presumably accounts for the increase in minimal cerebral vascular resistance.

Recently, it has become apparent that another mechanism also contributes to impairment of dilator responses in chronic hypertension. Endothelium-dependent vasodilatation, as originally described by Furchgott,6 is profoundly impaired in several models of hypertension. Impairment of endothelium-dependent dilatation in aorta has been found in SHR52 and in rats with renal and deoxycorticosterone acetate–salt hypertension.10 However, the effect of chronic hypertension on endothelium-dependent dilatation in cerebral vessels is not clear. Soltis and Bohr63 examined rats with deoxycorticosterone acetate–salt hypertension and found that endothelium-mediated dilatation produced by acetylcholine in the basilar artery was unaltered. In the same study,63 they found an increase in the sensitivity of the basilar artery to constriction by serotonin.

Recently, we examined the effects of chronic hypertension on endothelium-dependent responses of cerebral arterioles in vivo.11 In contrast to the finding in the basilar artery,63 endothelium-dependent dilatation of cerebral arterioles was markedly impaired in SHRSP.11 Acetylcholine failed to dilate pial arterioles in SHRSP, even though dilatation of pial arterioles produced by adenosine (which is not endothelium-dependent) was comparable in SHRSP and WKY.

We also found that the response of cerebral arterioles to serotonin is reversed in SHRSP.11 Serotonin produces dilatation of pial arterioles in WKY and constriction in SHRSP, probably as the result of impairment of endothelium-dependent dilatation. This finding suggests that platelet aggregation, with the release of serotonin, may have constrictor rather than dilator effects on cerebral blood vessels in the presence of chronic hypertension.

In summary, in addition to the contributions of altered distensibility and cerebrovascular hypertrophy, impairment of endothelium-dependent vasodilatation may play a role in reducing dilator responses of cerebral vessels in chronic hypertension. We speculate that impaired endothelium-dependent dilator responses of cerebral arterioles contribute to the increase in susceptibility to cerebral ischemia and infarction that is associated with chronic hypertension.2

### Collateral Circulation

Coyle and Jokelainen12, 13 have demonstrated that chronic hypertension predisposes to the development of cerebral infarction following occlusion of the middle cerebral artery. Occlusion of the middle cerebral artery results in cerebral infarction in SHRSP but not in WKY.12 The primary mechanism responsible for the variable response to occlusion of the middle cerebral artery probably is related to variations in collateral circulation. Distal branches of the three major cerebral arteries anastomose and form an extensive collateral network.64–66 The diameter of collateral vessels increases during occlusion of the middle cerebral artery.67 Following occlusion of the middle cerebral artery, increases in collateral blood flow are less in SHRSP than in WKY, and the magnitude of reduction in blood flow is significantly greater in SHRSP.68 These findings suggest that chronic hypertension reduces dilator capacity of collateral blood vessels in cerebrum. We speculate that impairment of collateral blood flow during chronic hypertension increases susceptibility to cerebral infarction during vascular occlusion by reducing blood flow below the level that is required for survival of tissue.

### Conclusion

We have summarized several new concepts that have emerged recently in relation to the effects of chronic hypertension on the cerebral circulation. These concepts are based primarily on studies of experimental models of hypertension. The concepts relate to factors that protect the cerebral circulation from chronic hypertension and those that contribute to the development of encephalopathy and stroke in chronic hypertension (Figure 5).

Of the factors that protect cerebral blood vessels, we have emphasized the role of vascular hypertrophy. Hypertrophy counteracts increases in stress in the vessel wall that accompany increases in arterial pressure. Vascular hypertrophy also encroaches on the lumen, increases cerebral vascular resistance, and thereby attenuates increases in cerebral microvascular pressure. It was formerly thought that the benefits of hypertrophy came at the expense of a reduction in vascular distensibility. This concept appears to be true only for large cerebral arteries.43–46 As the distensibility of cerebral arteries is increased in SHRSP despite marked hypertrophy.49

Concerning the pathophysiology of encephalopathy, dilatation of cerebral blood vessels and disruption of the blood-brain barrier, rather than vaso-

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**FIGURE 5.** Balance of protective mechanisms and factors that predispose to encephalopathy and stroke in chronic hypertension. BBB = blood-brain barrier; EDRF = endothelium-derived relaxing factor.
spasm, appear to be critical in the pathogenesis of hypertensive encephalopathy. To test this hypothesis, it will be necessary to demonstrate a causal relationship between passive dilatation of cerebral vessels, with disruption of the blood-brain barrier, and the eventual development of ischemic damage of brain tissue.

Concerning the pathophysiology of ischemic infarction, chronic hypertension appears to impair both endothelium-dependent relaxation of cerebral arterioles and responses of collateral blood vessels. It may become apparent that both of these factors play a major role in ischemic infarction. It is possible, for example, that when platelet emboli occur and release serotonin, which dilates cerebral arterioles in normotensive persons, vasoconstriction and reduction of cerebral blood flow occur in chronic hypertension. In this setting, the limited collateral circulation in chronic hypertension may compromise compensatory increases in cerebral blood flow. Thus, impaired endothelium-dependent relaxation and inadequate collateral circulation in chronic hypertension may convert a small, innocuous insult into focal ischemia and cerebral infarction.

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