Hypertension (HTN) is a major risk factor for all stroke subtypes, infarction as well as hemorrhage. Evidence from clinical trials shows that control of blood pressure (BP) leads to a substantially lower risk of stroke. HTN exerts detrimental actions on the cerebral circulation that play a critical role in its ability to promote cerebrovascular diseases. Angiotensin II (Ang II) is a key mediator by which HTN exerts its deleterious vascular effects. Recent findings raise the possibility that some of the detrimental actions of Ang II are independent of the associated elevation in BP. Here we will discuss the effect of HTN on stroke in light of recent advances indicating that the renin angiotensin system (RAS) may play a role greater than previously believed in the deleterious cerebrovascular actions of HTN and, as such, is a promising target for stroke prevention.

**Hypertension Is a Major Risk Factor for Stroke**

HTN is the most prevalent and powerful modifiable risk factor for stroke, irrespective of geographic region and ethnic group. Persons with HTN are about 3 or 4 times more likely to have a stroke. Whereas diastolic BP was once thought to be the most important predictor of stroke, the relationship between stroke and HTN may be stronger for systolic than for diastolic BP. The association between BP and stroke risk seems to occur on a continuum rather than as a threshold effect. The majority of strokes have been reported among persons with only “borderline” or “mild” HTN, and both persons classified as “hypertensive” as well as “normotensive” may benefit from BP lowering. Therefore, although the highest BP levels predict the highest relative risk of stroke, the conceptual pendulum has swung in the direction of the continuum of absolute BP levels and somewhat away from the construct of “hypertension” per se. Furthermore, as discussed below, recent evidence points to the fact that mediators of HTN, such as Ang II, may influence stroke risk independently of BP elevation.

**Hypertension Has Profound Effects on the Cerebral Circulation**

Why is HTN such a strong predictor of stroke risk? HTN exerts powerful effects on the cerebral circulation. In cerebral blood vessels, HTN produces hypertrophy and remodeling, defined as a reduction in the external diameter of the vessels. These proliferative changes increase vascular compliance and promote atherosclerosis. In addition, HTN alters the ability of endothelial cells to release vasoactive factors and increases the constrictor tone of systemic and cerebral arteries. HTN also alters cerebrovascular autoregulation, a property of cerebral arterioles that maintains cerebral blood flow (CBF) relatively constant despite variations in perfusion pressure within a certain range, usually 70 to 150 mm Hg. Chronic HTN shifts the autoregulated range toward higher pressures, rendering the brain more vulnerable to reductions in perfusion pressure. These structural and functional alterations increase the susceptibility of the brain to ischemic injury. For example, due to the shift in autoregulation and increased vascular compliance, the drop in perfusion pressure occurring distal to an occluded artery is likely to produce a greater reduction in CBF. Furthermore, the failure of endothelium-dependent relaxation impairs the ability of cerebral arterioles to dilate and supply collateral flow to the ischemic area.

**Ang II Is a Major Causative Factor in the Cerebrovascular Effects of Hypertension**

Ang II is a key mediator in the mechanisms of HTN. Ang II exerts its effects through specific G-protein–coupled receptors, 2 of which, AT1 and AT2, have been well characterized. AT1 receptors mediate vasoconstriction, vascular proliferation, and inflammation, while AT2 receptors mediate vasodilation, promote apoptosis, and inhibit proliferation. Thus, AT1 receptors are thought to mediate the deleterious vascular effects of Ang II, while the AT2 receptors are potentially protective. Ang II mimics some of the effect of HTN on cerebral blood vessels. Structurally, Ang II induces both cerebrovascular hypertrophy and remodeling. Functionally, Ang II alters autoregulation, inhibits endothelium-dependent relaxation, and disrupts the blood-brain barrier. Ang II also impairs the increase in CBF produced by neural activity. This phenomenon, termed *functional hyperemia*, is a critical adaptive mechanism by which the brain matches increased energy demands with increased delivery of substrates and removal of metabolic waste. The Ang II–induced impairment of functional hyperemia renders the brain more vulnerable to reductions in blood supply and more susceptible to cerebral ischemia. Some of the cerebrovascular effects of Ang II are independent of the elevation in BP. For example, remodeling of cerebral arteries occurs in hypertensive mice overexpressing human renin and angiotensinogen but not in BHP-2 mice, in which HTN is independent of RAS, while...
vascular hypertrophy is observed in both strains. 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Conclusions

These basic and clinical findings indicate that BP, due to its profound effects on the cerebral circulation, is the most critical determinant of the risk of stroke. Therefore, it is unquestionable that reduction in BP should be the centerpiece of any strategy for stroke prevention. Any of the commonly used antihypertensive agents (ACE-Is, AT1RBs, calcium channel blockers, beta-blockers, diuretics) reduce the risk of stroke, with larger reductions in BP resulting in larger reduction in risk.[26] On the other hand, there is highly suggestive evidence from clinical trials that pharmacological strategies to inhibit the RAS reduce the risk of stroke beyond the degree expected from the reduction in BP. These clinical findings are supported by experimental evidence indicating that Ang II has powerful cerebrovascular effects unrelated to its ability to elevate BP. Therefore ACE-Is and AT1RBs may possess unique properties that influence reduction of stroke risk beyond BP lowering. More focused therapies targeting the mechanisms by which the RAS may increase the risk for stroke, such as inhibition of vascular NADPH oxidase, could more selectively counter the deleterious effects of Ang II, sparing the purported beneficial actions of AT2 receptor activation. However, in the clinical arena, the evidence for BP-related and unrelated stroke risk is not sufficiently strong to justify favoring the exclusive use of agents targeting the RAS system or its signaling pathways. Nevertheless, these new findings expand our views by emphasizing that agents involved in the mechanisms of cardiovascular diseases may exert their detrimental actions independently of their ability to elevate BP. This line of thinking may lead to new and more powerful treatments to limit the devastating cerebrovascular effects of HTN and its mediators.

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