Cerebral Autoregulation and Blood Pressure Lowering

Sean Ruland, Venkatesh Aiyagari

Despite its comparatively small size, the brain receives a disproportionate amount of blood flow compared with most other organ systems. Cerebral blood flow is closely coupled to brain metabolism and can be affected by respiratory-induced CO2 changes and arterial blood pressure. Autoregulation is the intrinsic capacity of resistance vessels in end organs, such as heart, kidney, and brain, to dilate and constrict in response to dynamic perfusion pressure changes, maintaining blood flow relatively constant (Figure). This rapid vascular response occurs within seconds of arterial pressure fluctuations. The exact mediators of cerebral autoregulation are not completely understood. However, neurogenic stimuli; metabolic factors, such as adenosine accumulation during low perfusion; and direct intravascular pressure effects on smooth muscle or mediated via endothelial-derived relaxation factor (ie, NO) and constriction factor (ie, endothelin-1) have been implicated.

The cerebral resistance vessels in normotensive individuals are known to autoregulate across a broad range of mean arterial pressures. Perfusion pressures below the lower limit result in initially increased oxygen extraction from hemoglobin and, subsequently, global ischemia. Pressures above the upper bound may result in breakthrough edema, hemorrhage, seizures, and posterior leukoencephalopathy (ie, hypertensive encephalopathy). The normal autoregulatory curve may be right shifted in chronically hypertensive patients, although the magnitude and duration over which this occurs cannot be determined on an individual basis. Hypertensive animal models have shown impaired endothelium-dependent relaxation in the basilar artery, middle cerebral arteries, and cerebral arterioles compared with controls. Studies have also suggested that this impairment is reversible with blood pressure-lowering therapy. However, the potential for acute hypoperfusion is a concern when initiating blood pressure-lowering treatment, considering the unknown lower limit of an individual hypertensive patient’s autoregulation. Impaired autoregulation and the adverse effects of acute blood pressure lowering have been clearly shown for those with malignant hypertension, although other groups, such as the elderly, those with deep white matter ischemic disease, and those with cognitive impairment, are thought to be at higher risk because of similar, albeit less profound, vascular impairment.

In this issue of Hypertension, Zhang et al3 elaborately investigate the hemodynamic response to blood pressure lowering in those with mild and moderate hypertension. At 2 weeks and 3 months after initiation of therapy, there was no detectable difference in cerebral blood flow and autoregulatory response to orthostatic challenge as assessed with continuous transcranial Doppler ultrasonography of the middle cerebral artery compared with normotensive control subjects. Of note, the hypertensive patients achieved mean 24-hour blood pressure control similar to normotensive patients within the first 2 weeks of therapy. These findings are reassuring given the recommendations for increasingly aggressive therapeutic strategies and treatment goals.

These data should be interpreted with caution considering the relatively small sample, young age, and unknown duration of pre-existing hypertension. Although the statistical differences between groups were not significant, individual subject data were not reported. Furthermore, a standardized method for dynamically assessing autoregulation has not been established, limiting direct comparison and interpretation of existing studies. The transcranial Doppler ultrasonography assessment technique allows convenient continuous noninvasive monitoring of flow velocities concomitant with blood pressure monitoring and orthostatic maneuvers. However, using transcranial Doppler ultrasonography mean velocity changes as a surrogate for flow assumes static caliber of the vessel, and current vascular imaging modalities may be insensitive to detection of these small-caliber changes.

Despite these limitations, this study complements and is consistent with previous studies regarding the cerebral hemodynamic affects of blood pressure lowering. Serrador et al5 using similar techniques, demonstrated preserved autoregulation with orthostatic challenge (mean arterial pressure decrease: 21 to 25 mm Hg) in elderly subjects age 72±4 years with normotension (mean systolic blood pressure [SBP]: 125 mm Hg), controlled hypertension (SBP: <140 mm Hg at screening; mean SBP: 135 mm Hg), and uncontrolled hypertension (SBP: >160 mm Hg at screening; mean SBP: 162 mm Hg). In addition, improved cerebral blood flow in elderly uncontrolled hypertensive subjects after 6 months of aggressive blood pressure control has been observed. Another study of patients with and those without clinically silent white matter ischemic lesions demonstrated similar vasomotor responses to acetazolamide challenge despite higher baseline pulsatility in those with white matter lesions, suggesting more resistant vessels.

Lastly, consideration must be given to the variable effects on cerebral blood flow of different antihypertensive agents. The cerebral circulation has angiotensin receptors that may account for the improved cerebral blood flow and favorable
Autoregulatory responses in studies of hypertensive subjects treated with angiotensin-converting enzyme inhibitors and angiotensin receptor blockers. α-Adrenergic innervation of cerebral resistance vessels may result in similar effects from α-antagonists. Calcium channel blockers have variable specificity for cerebral vessels, and studies of β-blockers have shown either no effect on cerebral blood flow or a slight decrease.8,9

Clearly, long-term blood pressure control is effective for vascular disease prevention, and normal blood pressure should be the treatment goal for most patients.4 Rapid blood pressure normalization is generally well tolerated for most patients with mild and moderate hypertension. The report of Zhang et al3 and other studies enhance our understanding of the physiological impact of blood pressure lowering in these groups. Hopefully, ongoing and future studies will clarify treatment strategies for special populations, such as those with cerebrovascular disease, severe hypertension, and cognitive impairment.

Disclosures

S.R. has received a speaker honoraria from VasSol, Inc, Genentech, and Boehringer Ingelheim; is a consultant at Novartis; and has received compensation for expert witness testimony for various legal firms. V.A. reports no conflicts.

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