May not the elevation of systemic blood pressure be a natural response to guarantee a more normal circulation to the heart, brain and kidneys? These words, taken from a renowned textbook of medicine, clearly illustrate that in the 1940s the teaching doctrine was to consider elevated blood pressure a compensatory mechanism serving to force blood through sclerotic arteries to the ischemic target organs. Hypertension was regarded as “essential” and therefore “should not be tampered with, even were it certain that we could control it.” We have since learned that hypertension is a powerful risk factor for stroke, heart attacks, and renal failure and that lowering blood pressure dramatically reduces the risk of these events. The only clinical situation in which blood pressure elevation often still is considered protective is in the sequence of an acute ischemic stroke. Indeed, authoritative voices such as that of Adams and Victor have warned and continue to warn against lowering blood pressure in this setting with statements such as, “We agree with Britton and colleagues that it is prudent not to be tampered with, even were it certain that we could control it.” We have since learned that hypertension is a powerful risk factor for stroke, heart attacks, and renal failure and that lowering blood pressure dramatically reduces the risk of these events. The only clinical situation in which blood pressure elevation often still is considered protective is in the sequence of an acute ischemic stroke. Indeed, authoritative voices such as that of Adams and Victor have warned and continue to warn against lowering blood pressure in this setting with statements such as, “We agree with Britton and colleagues that it is prudent not to be tampered with, even were it certain that we could control it.”

This statement can be found in the 1989 edition of this venerable neurology textbook and is repeated verbatim in every single subsequent edition until 2005. It thus has taught numerous neurologists that elevated blood pressure in the sequence of an ischemic stroke was a “noli me tangere” and that lowering blood pressure should be avoided. Because Adams and Victor obviously considered the referenced study to be definitive enough to be taught for many years, I took the liberty to look at it carefully. In their article, Britton et al reported on a series of 6 patients presenting with acute onset of neurological symptoms and extremely high blood pressure who had either a hypertensive crisis or a stroke. Five of 6 patients were comatose before admission, and in 4 of the 6 patients, a hemorrhagic (not an ischemic) stroke was documented. With prompt institution of antihypertensive therapy, systolic pressure was lowered precipitously to <100 mm Hg. Not unexpectedly, of the 6, only 1 patient survived. On the basis of their few cases, the authors concluded that convincing evidence of a beneficial effect of blood pressure reduction in the setting of an acute stroke was lacking but also considered that “the deterioration might have been the natural terminal cause in these patients with severe brain lesions.” Clearly, from this meager study, no conclusion can be drawn on the management of blood pressure in patients with ischemic stroke.

The article by Turan et al in the present issue of *Circulation* throws some light on this contested issue. The authors reported that in patients with intracranial stenosis, the risk of ischemic stroke was increased rather than decreased with higher blood pressure and that this also was true in the territory of the stenotic vessel. Whether stenosis was moderate (<70%) or more severe, increased blood pressure, diastolic more than systolic, increased the risk of stroke in the territory of the stenotic vessel. Although the risk of a subsequent stroke was driven mainly by systolic blood pressure elevations >160 mm Hg, no evidence existed that maintaining systolic pressure in the stage I hypertensive range (between 140 and 159 mm Hg) was cerebroprotective. Of note, this study is a post hoc analysis based on average follow-up blood pressures and therefore does not allow any conclusions on the relationship between ischemic stroke and blood pressure at the time of the acute event. However, the findings argue strongly against the common clinical wisdom of leaving high blood pressure untreated in patients with intracranial stenosis. Lowering blood pressure was not associated with an increased stroke risk after 4 months. Moreover, the cerebrovascular benefits of a decrease in blood pressure continued to grow for several years. Both the Perindopril Protection Against Recurrent Stroke Study (PROGRESS) and the Individual Analysis of Antihypertensive Intervention Trials (INDANA) database have clearly shown that in patients with cerebrovascular disease, blood pressure remains the most important risk factor for a recurrent event.

Recent experimental data fully support the view of Turan et al. Neurovascular protection was conferred by lowering blood pressure with antihypertensive therapy 3 hours after middle cerebral artery occlusion during reperfusion after experimental cerebral ischemia in rats. Although enalapril or dihydralazine caused a decrease in infarct size without influencing neurological outcome, the angiotensin receptor blocker (ARB) candesartan caused a similar decrease in blood pressure and infarct size but also resulted in improved neurological outcome. We have previously suggested that antihypertensive medications that increase angiotensin II levels such as thiazide diuretics, calcium antagonists, and ARBs could be more cerebroprotective than agents that lower angiotensin II levels such as β-blockers and angiotensin-converting enzyme inhibitors. This hypothesis was based on experimental findings but also was supported by a recent meta-analysis of 206,632 patients in 26 prospective randomized clinical trials. Angiotensin II--decreasing drugs proved to be less stroke protective than antihypertensive drugs.
that increased angiotensin II levels. Thus, ARBs may well have stroke protective effects beyond blood pressure lowering. In the recent Morbidity and Mortality After Stroke, Eprosartan Compared With Nitrendipine for Secondary Prevention (MOSES) trial, eprosartan, for a similar blood pressure reduction, reduced cerebrovascular events better than nitrendipine in hypertensive stroke patients.14 Whether these stroke protective effects occur in the arterial tree of the brain or in the brain tissue itself is unknown. However, if indeed the brain tissue is involved, the effect may depend on the ability of the ARB to cross the blood-brain barrier. Conceivably, not all ARBs are created equal in this regard.15

Most patients with an acute ischemic stroke experience a transient increase in blood pressure regardless of whether they were hypertensive or normotensive before the event. The pathogenesis of stroke-associated hypertension is likely to be multifactorial, possibly related to stress and anxiety, intracerebral pressure, reactive bradycardia, increased activity of the sympathetic nervous system, etc. The penumbra is an under-perfused but viable zone surrounding the infarcted area in the cerebrum. Current dogma teaches that survival of the penumbra depends on an increase in blood pressure and that any fall in blood pressure could possibly threaten survival of the penumbra and increase the infarcted area.16 Indeed, in patients with ischemic stroke, injections of epinephrine have been recommended as a means of raising the systemic blood pressure above the usual levels to guarantee adequate perfusion of the penumbra.3 Not surprisingly, no outcome data are available to support the clinical use of this heroic procedure. Conversely, we should consider that elevated blood pressure in the sequence of an ischemic stroke may not only increase the risk of cerebral hemorrhage into the infarcted area but also give rise to ischemic edema. Thus, at the present, no consensus exists on how to best treat patients with elevated blood pressure after ischemic stroke. Even a thorough Cochrane review was unable to produce conclusions, finding the data “wholly inadequate” to guide clinical practice.17 Fortunately, 2 trials—Continue or Stop Post-Stroke Antihypertensives Collaborative Study (COS-SACS)18 and Controlling Hypertension and Hypotension Immediately Post-Stroke (CHIPPS)19—are underway that may throw some light on the risks and benefits of blood pressure lowering in patients with acute stroke.

Where does this leave the consulting physician who has to deal with an acute blood pressure elevation in a poststroke patient? The blood pressure in such patients may be exquisitely sensitive to antihypertensive therapy, and a gingerly approach is advisable. A precipitous fall in systolic blood pressure to <100 mm Hg, such as in the case series of Britton et al.,4 certainly should be avoided. Abrupt, uncontrolled drops in blood pressure such as occur with sublingual nifedipine are known to actually cause cerebrovascular events.20 Even a less rapid blood pressure reduction to <140/90 mm Hg is probably unwise unless mandated by other target organ disease. However, after 24 to 48 hours, elevated blood pressure should be lowered gradually, and as indicated by experimental and clinical data, an ARB should be part of the regimen. Most important, in the weeks, months, and years after an ischemic stroke, good blood pressure control remains the single most important measure to prevent a recurrence of this devastating event.

Disclosures
Dr Messerli reports having served as an ad hoc consultant/speaker for the following organizations: Abbott, GlaxoSmithKline, Novartis, Pfizer, AstraZeneca, Bayer, Boehringer Ingelheim, Merck, Bristol-Meyers Squibb, Forest, Sankyo, and Sanofi.

References

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