Clinical Conference

Pathophysiology and Management of Hypertension in Acute Ischemic Stroke

Principal Discussant
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Hypertension, defined in different ways by various investigators over a period of many years, has been shown to be a major risk factor for stroke. In fact, the strength of the evidence suggests that hypertension causes stroke. But by what mechanisms? The value of treating chronic hypertension to prevent stroke is well established, but what should be done about blood pressure elevations in the setting of acute stroke?

Stroke is a generic term for a clinical syndrome that includes focal cerebral infarction (ischemic stroke), focal hemorrhage in the brain, and subarachnoid hemorrhage. Hypertension is an important precursor of cerebral infarction and intracerebral hemorrhage. Whether hypertension predisposes to subarachnoid hemorrhage is less certain because of conflicting evidence from epidemiologic, clinical, and laboratory investigations.

This article will focus on the pathophysiologic mechanisms of acute ischemic stroke. A review of the subject seems timely given the frequency of the problem, the paucity of clinically relevant scientific data, and contemporary interest in salvaging ischemic brain before infarction occurs.

How Does Hypertension Cause Cerebral Infarction?

Attempts to answer this question have tended to focus on the pathoanatomic effects of chronic hypertension, mainly because they are more amenable to study than the pathophysiologic mechanisms of hypertension and cerebral ischemia during the acute phase of stroke. Clearly, one would expect both types of mechanisms to be involved, but unfortunately, the picture is incomplete and our knowledge fragmentary. Insights into pathoanatomic mechanisms come from epidemiologic investigations, autopsy studies, and clinical trials. Study of the pathophysiologic mechanisms of acute focal cerebral ischemia has been enhanced by the development of new techniques such as positron emission tomography and diffusion-weighted magnetic resonance imaging. Animal models of stroke permit rigorous scientific study of the mechanisms of cerebral infarction, but the relevance of such laboratory findings to human stroke is not always clear.

Chronic hypertension aggravates atherosclerosis and induces complex pathological changes in the mediae arteries and arterioles. These structural changes increase vascular resistance and protect the cerebral microcirculation from the deleterious effects of systemic hypertension. Paradoxically, however, the structural changes may predispose to cerebral ischemia by impairing vasodilator responsiveness.

The small-diameter penetrating end arteries in the brain have been considered particularly vulnerable to the deleterious effects of elevated blood pressure because they arise directly from main arterial trunks. The hypertension-associated morphologic changes that occur in these vessels include microaneurysm formation, lipoxyalinosis, and microatheroma. Apparently as a consequence of these changes but by mechanisms not fully understood, either rupture or occlusion of the diseased vessel may occur, producing intracerebral hemorrhage or infarction. The small infarcts that occur deep in the cerebral hemispheres or brain stem as a consequence of occlusion of these diseased vessels have been postulated to represent a specific complication of hypertension (lacunar infarction), recognizable clinically as lacunar syndromes.

More recent clinical and epidemiologic data, however, suggest that hypertension is no more important in the pathogenesis of lacunar infarction (small-vessel territory stroke) than in the development of large-vessel territory stroke caused by presumed atherothromboembolic mechanisms (Table). Cerebral small-vessel disease also occurs in aged normotensive subjects. Collectively, the data suggest that hypertension has an aggravating and accelerating but nonspecific influence on degenerative cerebrovascular disease, and the existence of a unique cerebrovascular lesion attributable to hypertension remains in question.

An overview analysis of 14 randomized trials of antihypertensive drug therapy showed that coronary heart disease events were reduced by only 14% (95% confidence interval, 4% to 22%). A reduction of 20% to 25% would have been expected on the basis of evidence from observational epidemiologic studies. In contrast, stroke was reduced by 42% (95% confidence interval, 33% to 50%). The disparate effect of antihypertensive...
treatment on apparently similar pathological processes has generated considerable debate and has not been fully explained. Because myocardial infarction (the major contributor to the end point "coronary heart disease" in clinical trials) is almost invariably a complication of coronary artery atherosclerosis, whereas cerebral infarction has several causes, the data suggest that the effect of antihypertensive therapy on stroke incidence was not mediated solely through an effect on atherothrombembolic mechanisms.

The results of the antihypertensive treatment trials indicate that both fatal and nonfatal strokes are prevented within just a few years of blood pressure lowering, even among chronically hypertensive elderly subjects who would be expected to have advanced irreversible structural arterial disease. This suggests that differences in the physiological regulatory mechanisms of the cerebral and myocardial circulations and their dynamic adaptation to changes in perfusion pressure may be important determinants of the effects of antihypertensive treatment.

Functional brain imaging studies using positron emission tomography have helped reveal the pathophysiological consequences of acute cerebral arterial occlusion. Some compensatory responses to reduced cerebral perfusion pressure are shown in Fig 1. The influence of blood pressure on these responses is not well understood. In a recent study of 16 patients who had hypertension and an acute middle cerebral artery territory infarct, blood flow in the ischemic region (as estimated by single-photon emission computed tomography) increased as blood pressure fell in patients treated with captorpril (n = 3) or clonidine hydrochloride (n = 2). In the patients who were given placebo (n = 6) or nicardipine hydrochloride (n = 5), the fall in blood pressure was not associated with a significant change in cerebral blood flow. The nicardipine-treated patients had the greatest fall in blood pressure from baseline. These data are difficult to interpret because of the small number of patients studied.

The time interval between arterial occlusion and irreversible brain injury may be as long as 6 to 9 hours. Conceptualized as the ischemic penumbra, this period is viewed as a "window of opportunity" for therapeutic intervention to restore regional cerebral blood flow. The window would be expected to be widest in zones of cortical ischemia where the potential for collateral flow is greatest, and narrowest in the territory of small-diameter penetrating end arteries, occlusion of which results in small, deep (lacunar) cerebral infarcts. The influence of blood pressure on this window is, clearly, worthy of further study.

Acute increases in blood pressure superimposed on a chronic hypertensive state ("acute-on-chronic hypertension") is common in acute ischemic stroke; about half of all patients have a history of preexisting hypertension, and on average these individuals have higher blood pressures than those who were previously normotensive. After 3 or 4 days in the hospital, blood pressure falls spontaneously (Fig 2). The reasons for acute hypertension in the setting of acute stroke are poorly understood. Because it occurs in patients with transient ischemic attacks as well as stroke patients, Cushing's phenomenon (increased blood pressure secondary to elevated intracranial pressure) cannot be responsible, except in cases of massive cerebral infarction. There seems to be no definite correlation with lesion site or location. Therefore, it is difficult to incriminate ischemic damage to the insular cortex, nucleus tractus solitarius, or other structures involved in the physiological regulation of blood pressure. Most explanations are based on the premise that the hypertension is secondary to the stroke, e.g., a response to increased plasma catecholamines, or the stress of hospital admission.

How Should Elevated Blood Pressure Be Managed in the Setting of Acute Ischemic Stroke?

The answer to this question is "rarely and cautiously" according to the recent report of the Emergency Care Committee and Subcommittees of the American Heart Association. This statement stems mainly

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**Comparison of Frequency of Prestroke Hypertension Among Patients With First-Ever Ischemic Stroke in the Rochester Epidemiology Project**

<table>
<thead>
<tr>
<th></th>
<th>Rochester*</th>
<th>Oxfordshire†</th>
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<tbody>
<tr>
<td>Lacunar infarction, %</td>
<td>80</td>
<td>44</td>
</tr>
<tr>
<td>Nonlacunar infarction, %</td>
<td>70</td>
<td>47</td>
</tr>
</tbody>
</table>

Prestroke hypertension was defined by two blood pressure readings >160/90 mm Hg in the Rochester project and two blood pressure readings >160/90 in the Oxfordshire project.

Difference between proportions within studies: *P = .05 (P = .11 if patients with a cardiac source of emboli are excluded); †P = .6.

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![Figure 1](http://hyper.ahajournals.org/)

1. Plot shows compensatory responses to reduced cerebral perfusion pressure. As cerebral perfusion pressure falls, cerebral blood flow (CBF) is initially maintained by dilation of precapillary resistance vessels. When vasodilation can no longer compensate, cerebral autoregulation fails, and blood flow begins to fall (vertical line at 60 mm Hg). If perfusion pressure continues to fall, an increase in the oxygen extraction fraction (OEF) maintains cerebral oxygen metabolism (CMRO2). Once this mechanism becomes maximal (vertical line at 30 mm Hg), further decline in blood flow leads to substrate depletion, energy failure, disruption of cellular homeostasis, and ultimately, ischemic necrosis (ie, infarction). Dashed lines indicate conditions for which data are inadequate to draw firm conclusions. (Used with permission from Powers.)

2. The answer to this question is "rarely and cautiously" according to the recent report of the Emergency Care Committee and Subcommittees of the American Heart Association. This statement stems mainly

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from the fact that there had been no randomized trials of antihypertensive treatment in acute ischemic stroke. The single trial reported since these recommendations of antihypertensive treatment in acute ischemic stroke. Although cerebrovascular catastrophes and trends stimulated by the development and use of new drugs, and the experience and recommendations of experts. Not surprisingly, then, considerable controversy surrounds this issue.

Although severe hypertension during acute ischemic stroke is an indicator of poor prognosis, there is no convincing evidence that rapid lowering of elevated blood pressure is beneficial in this situation. On the contrary, there are several published reports of patients in whom neurological deterioration was associated with precipitous falls in blood pressure induced by emergency antihypertensive treatment. Although cerebral blood flow was not measured in these patients, it is generally assumed that neurological deterioration occurred because blood pressure dropped below the lower limit of cerebral blood flow autoregulation and caused more widespread cerebral hypoperfusion. The frequency of this occurrence in clinical practice has not been established. It has been suggested that such complications are more common than reported in the literature. The risk of causing harm, together with the lack of evidence of benefit, and knowledge that elevated blood pressure settles spontaneously in a few days suggest that rapid lowering of blood pressure is best avoided during the acute phase of an uncomplicated ischemic stroke.

However, given the quality of the evidence, the absence of proof of benefit does not mean that antihypertensive therapy is of no value. Some clinical investigators have argued persuasively in favor of aggressive blood pressure management (particularly if the diastolic pressure is in excess of 120 mm Hg) to attenuate edema formation and reduce the risk of hemorrhage into ischemic brain. In addition, comorbid conditions may be present, such as aortic dissection or acute myocardial ischemia, that would require antihypertensive treatment in their own right.

The clinician who elects to treat a hypertensive stroke patient has to decide next which drug to use and how far to lower the blood pressure. Two recent reviews of the management of hypertensive urgencies and emergencies recommended sodium nitroprusside as the drug of first choice for patients with acute ischemic stroke. Others have objected to the use of sodium nitroprusside in this setting because cerebral vasodilatation caused by the drug may compromise cerebral perfusion pressure by increasing intracranial pressure. This risk is probably more theoretical than real, except in patients who have poor intracranial compliance caused by a massive stroke. Therefore, intracranial pressure should be monitored if it is decided to lower elevated blood pressure in a patient who has had a massive stroke.

Alternatives to sodium nitroprusside include labetalol, diazoxide, and nifedipine. The effect of intravenously administered labetalol on cerebral blood flow in humans has not been well studied. Chronic oral therapy with labetalol has been shown not to reduce cerebral blood flow in hypertensive patients. Diazoxide does not cross the blood-brain barrier and so does not cause direct cerebral vasodilatation. Nifedipine is frequently used to treat hypertensive urgencies and emergencies and has been shown to lower blood pressure without causing a reduction in cerebral blood flow but may not be an option for acute stroke patients who cannot swallow because it has to be administered orally.

Intravenous phentolamine or sodium nitroprusside is recommended for rapid control of severe hypertension associated with the purposeful or accidental ingestion or injection of sympathomimetic agents such as cocaine. Drug use or abuse is becoming increasingly recognized as an important cause of stroke in young adults.

Hydralazine is contraindicated in patients with acute ischemic stroke because it causes cerebral vasodilatation and impaired autoregulation. Clonidine and methyldopa are relatively contraindicated because of their tendency to depress higher cerebral functions.

How far should blood pressure be lowered? Most authorities agree that mean arterial blood pressure (calculated as diastolic pressure plus one third of the pulse pressure) should be reduced by about 20% to 25% over 24 hours. This recommendation is largely based on the results of a study of global cerebral blood flow in 22 hypertensive patients and 10 normotensive control subjects which showed that mean arterial blood pressure could be reduced by about 25% before the lower limit of autoregulation was reached and by about 50% before symptoms of cerebral hypoperfusion occurred. The 24-hour time frame is somewhat arbitrary; positron emission tomography has shown that cerebral blood flow is unstable for a few days after stroke onset.

Closing Comments

We do not know exactly how hypertension causes stroke, and we do not understand the pathophysiologi-
by studying large numbers of patients in randomized trials.

Dr William Lawton (University of Iowa, Iowa City): Are there different effects of various calcium blockers in terms of efficacy; eg, does nimodipine or nicardipine have special properties to commend their use over other dihydropyridines?

Dr Phillips: Not as far as we know. Nimodipine is of proven value for the prevention of secondary cerebral ischemic damage in patients with acute subarachnoid hemorrhage but has not been shown to be of definite value in patients with acute ischemic stroke. The benefit of nimodipine therapy in subarachnoid hemorrhage patients is probably due to a cytoprotective effect rather than a blood pressure–lowering effect. In two randomized placebo-controlled trials of nimodipine in patients with acute ischemic stroke, there were no significant differences in blood pressure between the nimodipine- and placebo-treated groups. Different calcium channel blockers have not been compared in clinical stroke trials.

Dr William Lawton (University of Iowa, Iowa City): Do calcium channel blockers or other vasodilators produce a “steal syndrome” in acute stroke and worsen ischemic areas?

Dr Phillips: Possibly. Vorstrup et al measured regional cerebral blood flow using the xenon-133 inhalation method before and after the intravenous administration of PY 108-068 (a dihydropyridine calcium antagonist developed by Sandoz Ltd) in 11 patients who had a cerebral infarct confirmed by computed tomography in the preceding 1 to 9 days. Cerebral blood flow in the ischemic areas did not improve. In 3 patients, cerebral blood flow decreased even further in the ischemic area. In 1 other patient, cerebral blood flow increased in part of the peri-infarct area. These changes in cerebral blood flow were not accompanied by any change in the patients’ clinical status. The results are difficult to interpret because the experiment was uncontrolled, a small number of patients were studied, and the cerebral blood flow measurements were made at different times after each stroke. The investigators did not clearly demonstrate an increase in blood flow in one area of the brain and a concomitant decrease in another (ie, a “steal” phenomenon).

References


Key Words • antihypertensive agents • cerebral ischemia • cerebral infarction • hypertension, chronic • hypertension, acute

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