Effect of Reducing Elevated Blood Pressure on Cerebral Circulation

RAY W. GIFFORD, JR., M.D.

SUMMARY Circulation to the brain is protected not only by autoregulation, which maintains cerebral blood flow (CBF) in spite of a decrease in mean arterial pressure, but also by baroreflexes that tend to prevent or minimize hypotension. Hypertensive patients have impaired cerebral autoregulation and depressed baroreflex sensitivity, suggesting that the brain might be vulnerable to a reduction in blood pressure. Nevertheless, in clinical experience, studies of cerebral blood flow during drug-induced reduction of elevated blood pressure have shown that control of hypertension can usually be achieved without jeopardizing cerebral blood flow or inducing signs and symptoms of cerebral ischemia, even in patients with cerebrovascular disease. Indeed, control of hypertension reduces both the risk of stroke and the recurrence rate for second strokes.

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KEY WORDS • cerebral autoregulation • stroke prevention • hypertension • antihypertensive therapy • cerebral blood flow

SINCE potent antihypertensive agents first became available over 30 years ago, there has been concern about the possible adverse effects of reducing blood pressure on perfusion of vital organs, especially the brain. Indeed, one of the earliest recognized adverse effects of some of the adrenergic inhibiting agents was orthostatic faintness or syncope. Theoretically, it would seem that hypertensive patients with atherosclerotic cerebrovascular disease might be especially vulnerable to reduction of blood pressure.

The purpose of this paper is to examine the mechanisms that control cerebral blood flow (CBF), and how they are affected by hypertension and antihypertensive therapy, in an effort to answer the question: Is it safe to reduce blood pressure for patients who have clinical evidence of cerebrovascular disease and, if so, how low?

Results of the Hypertension Detection and Follow-up (HDFP) study suggest that one of the reasons the mortality rate was 16.9% lower in the Stepped Care (SC) group than in the Referred Care (RC) group was because a goal diastolic blood pressure was ardently pursued in the SC group. This goal diastolic blood pressure was 90 mm Hg or less for patients whose initial diastolic blood pressure was 100 mm Hg or more, or at least a 10 mm Hg decrement for patients whose initial diastolic blood pressure was 90 to 99 mm Hg. Indeed, at the end of the 5-year study, the average diastolic blood pressure for patients in SC was 84 mm Hg, compared to 89 mm Hg in RC. The 5-year incidence of stroke was 34% lower in SC than RC (1.9/100 persons in SC vs 2.9 in RC). This would strongly suggest that treatment of hypertension is beneficial, not detrimental, to the cerebral circulation. Other controlled treatment trials have also demonstrated that antihypertensive therapy reduces the risk of stroke. However, only 2.5% of the participants in the HDFP study had a history of stroke at the time of enrollment and the effect of antihypertensive therapy on cerebrovascular complications in this key subgroup was not specifically reported.

Cerebral Autoregulation

Cerebral blood flow (CBF) is maintained within narrow limits over a wide range of blood pressure levels, a phenomenon known as autoregulation. When blood pressure falls, cerebral vasodilatation occurs, and when blood pressure rises, cerebral vasoconstriction occurs, so that, in normal individuals, the CBF remains constant during fluctuations in mean arterial pressures (MAP) from 60 or 70 mm Hg to well over 150 mm Hg. When MAP drops below the lower limit of autoregulation, the brain extracts more oxygen from the blood to compensate for the reduced CBF. Consequently, clinical manifestations of cerebral ischemia do not occur until this mechanism fails, at which
TABLE 1. Cerebral Hemodynamics During Induced Hypotension

<table>
<thead>
<tr>
<th>Group</th>
<th>MAP (mm Hg)</th>
<th>CBF (cc/min/100 g)</th>
<th>CVR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>C</td>
<td>E</td>
<td>C</td>
</tr>
<tr>
<td>Normotensive</td>
<td>30-46 yr (n = 7)</td>
<td>84</td>
<td>35*</td>
</tr>
<tr>
<td></td>
<td>59-93 yr (n = 10)</td>
<td>79</td>
<td>29*</td>
</tr>
<tr>
<td>Hypertensive</td>
<td>53-72 yr (n = 8)</td>
<td>113</td>
<td>47*</td>
</tr>
<tr>
<td>Malignant hyper-</td>
<td>33-47 yr (n = 7)</td>
<td>179</td>
<td>89*</td>
</tr>
</tbody>
</table>

MAP = mean arterial pressure (mm Hg); CBF = cerebral blood flow (cc/min/100 g brain); CVR = cerebral vascular resistance (mm Hg/cc blood/min/100 g brain); C = control; E = during induced hypotension at time of symptomatic cerebral ischemia. *p < 0.01. Adapted from: Finnerty et al. J Clin Invest 1959; 33:1227, with permission.

The subject develops symptoms of global cerebral ischemia (faintness, yawning, hyperventilation, nausea, blurred vision, clamminess). The MAP at which symptoms of cerebral hypoperfusion supervene is known as the lowest tolerated blood pressure, which in normal individuals is usually between 40 and 50 mm Hg.

Finnerty and colleagues' reduced blood pressure acutely by infusing hexamethonium intravenously into volunteers during 30° to 40° headup tilt until signs of cerebral ischemia developed. Table 1 summarizes the results. Normotensive subjects developed symptoms when the MAP fell to the range of 30 to 35 mm Hg on average, and the CBF was in the range of 30 cc/min/100 g of brain. It is interesting that normotensive subjects older than 50 years of age tolerated hypotension as well as normotensive subjects younger than 50 years (table 1). Since cerebral autoregulation appears to be largely independent of the sympathetic nervous system, the observed decrease in cerebral vascular resistance was almost certainly the result of autoregulation and not a drug effect from hexamethonium, which is an inhibitor of the adrenergic nervous system.

Cerebrovascular autoregulation is probably due to a myogenic mechanism initiated by stretch receptors in the smooth muscle of cerebral arterioles, although Kontos's suggested that metabolic changes in response to hypoxia may play a role.

Chronic hypertension impairs cerebral autoregulation, shifting the curve to the right so that reduction of CBF is observed at a higher MAP in hypertensive than in normotensive subjects (table 2). Strandgaard found that the lower limit of autoregulation occurred at an average MAP of 113 mm Hg in 13 untreated hypertensive patients compared to 73 mm Hg in 10 normotensive patients. The average lowest tolerated MAP was 65 mm Hg in the hypertensive group compared to 43 mm Hg in the normotensive group (table 2). Hypertensive patients on treatment had values that were midway between the normotensive group and the untreated hypertensives, suggesting that hypotensive therapy tends to restore autoregulation towards normal.

It is interesting that the percentage of resting MAP at which CBF begins to decline remains remarkably constant when comparing normotensives to hypotensives or to controlled hypertensives (table 2). The same was true for the lowest tolerated MAP. Thus, it is possible to predict that the CBF will start to decrease when MAP is reduced to approximately 75% of the resting control, and symptoms of cerebral ischemia will appear when MAP is reduced to approximately 45% of resting MAP (table 2).

Finnerty and colleagues' found that hypertensive patients developed symptoms of cerebral ischemia at a higher MAP than did normotensive subjects, even though CBF was not greatly different between the two groups at the time symptoms appeared. This represents a failure of cerebrovascular resistance to decrease appropriately when blood pressure is reduced acutely in hypertensive patients (table 1).

Studies in rats have shown that autoregulation of CBF is impaired in spontaneously hypertensive rats (SHR) compared to Wistar-Kyoto (WKY) controls. Old SHR have a greater reduction in CBF when blood pressure is reduced acutely than do younger SHR, demonstrating that both age and hypertension impair cerebral autoregulation. Antihypertensive therapy improved cerebral autoregulation in aged SHR.

**Baroreflexes**

Circulation to the brain is protected not only by autoregulation, which maintains CBF in spite of a de-
dopa is an inhibitor of the sympathetic nervous system, the tone of cerebral arteries and arterioles. and CBF was significantly increased. Since methyl-
discontinued when symptoms of cerebral ischemia su-
tients. The infusion and upright tilt were promptly
when blood pressure is reduced by adrenergic inhibit-
drug effect. Furthermore the improvement is noted
in medial hypertrophy, but too slowly to be a direct
mechanism for this has not been elucidated. It seems to
improve cerebral autoregulation, 6 although the
mechanism for this has not been elucidated. It seems to
occur too rapidly to be explained by a structural change
in medial hypertrophy, but too slowly to be a direct
drug effect. Furthermore the improvement is noted
when blood pressure is reduced by adrenergic inhibiting
drugs which are not thought to have any effect on
the tone of cerebral arteries and arterioles.

Meyer et al. 17 used methyldopa to treat 13 hyperten-
sive patients with cerebral vascular disease (cerebral
infarction and/or transient ischemic attacks). Average
CBF for the group was low initially (table 3). At the
end of the 2-week treatment period, MAP and cerebro-
vascular resistance were both significantly reduced
by effective antihypertensive therapy. 2 although the
mechanism for this has not been elucidated. It seems to
occur too rapidly to be explained by a structural change
in medial hypertrophy, but too slowly to be a direct
drug effect. Furthermore the improvement is noted
when blood pressure is reduced by adrenergic inhibiting
drugs which are not thought to have any effect on
the tone of cerebral arteries and arterioles.

Clinical Implications

Even though hypertensive patients have impaired
cerebral autoregulation and depressed baroreflex sen-
itivity, conditions that should place the brain in jeop-
ardy when blood pressure is reduced, clinical experi-
en has shown that antihypertensive therapy rarely
leads to irreversible ischemic events in the brain. In-
deed, most controlled therapeutic trials have demon-
strated that the incidence of stroke is sharply reduced
by effective antihypertensive therapy. 6

Perhaps this is because treating hypertension seems
to improve cerebral autoregulation, 6 although the
mechanism for this has not been elucidated. It seems to
occur too rapidly to be explained by a structural change
in medial hypertrophy, but too slowly to be a direct
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Harmsen et al. 18 produced symptoms of cerebral ischemia by reducing MAP acutely with intravenous
infusions of pentolinium during upright tilt in 47 pa-
tients. The infusion and upright tilt were promptly
discontinued when symptoms of cerebral ischemia su-
pervened. Although MAP was reduced by an average
of 55%, no patient developed focal neurologic symp-
toms or signs and there were no changes in the EEG.
All patients were hypertensive, and 40 had evidence of
previous cerebrovascular infarction or transient ischemic
tacks.

Evidence of focal neurologic deficits was not elicited
when MAP was reduced to the point of producing
global symptoms of cerebral ischemia in the studies by
Strandgaard 6 and by Finnerty et al. 7

Antihypertensive therapy for patients who have had
one stroke has been reported to reduce the incidence of
second strokes, fatal or nonfatal. 19–21 Beevers and asso-
ciates 21 have shown that the better the control of the
hypertension, the less the chance of a second stroke
(table 4).

The U.S. Hypertension-Stroke Cooperative Group 22
failed to show any significant reduction in the occurrence
of second strokes by treating hypertension compared
to a placebo in a double-blind study. On the other hand, antihypertensive treatment was not associ-
ated with more recurrent strokes than in the untreated
group.

Finally, Whisnant et al. 23 have found that diastolic
blood pressure is the most significant variable in deter-
miming the risk of subsequent strokes for patients who
have had one or more transient ischemic attacks. The
5-year probability of stroke after the first transient at-
tack was nearly 50% for 32 patients who had diastolic
blood pressures > 105 mm Hg, whereas it was less
than 25% for patients who had diastolic blood pressure< 105 mm Hg or who were receiving antihyper-
tensive therapy.

The crucial role of autoregulation in maintaining
CBF during antihypertensive therapy is not fully ap-
preciated until one realizes that hypotensive drugs can
only reduce blood pressure in one of two ways — by

### Table 3. Effect of Antihypertensive Therapy on Cerebral Hemodynamics in 13 Patients with Cerebrovascular Disease

<table>
<thead>
<tr>
<th>MAP</th>
<th>C</th>
<th>Rx</th>
<th>C</th>
<th>Rx</th>
<th>C</th>
<th>Rx</th>
</tr>
</thead>
<tbody>
<tr>
<td>125.2±16.6</td>
<td>105.9±14.6</td>
<td>44.5±11.0</td>
<td>48.9±10.6</td>
<td>2.97±0.76</td>
<td>2.27±0.58</td>
<td></td>
</tr>
<tr>
<td>p &lt; 0.01</td>
<td>p &lt; 0.05</td>
<td>p &lt; 0.001</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

MAP = mean arterial pressure (mm Hg); CBF = cerebral blood flow (ml/100 g brain/min); CVR = cerebral vascular resistance (mm Hg/ml/100 g brain/min); C = before treatment; Rx = at end of 2 weeks treatment with methyldopa. From Meyer et al. Neurology 1968;18:772, with permission.
reducing cardiac output or total peripheral resistance. A reduction in cardiac output would have a detrimental effect on CBF without an autoregulatory decrease in cerebrovascular resistance.

A decrease in total peripheral resistance, not shared by the cerebral circulation or compensated for by an increase in cardiac output, would lead to a diversion of blood away from the brain if it weren't for autoregulation of the cerebral circulation. Some of the adrenergic blocking agents, such as guanethidine, bethanidine, and hexamethonium, reduce both cardiac output (especially in the upright position) and total peripheral resistance without having any dilating effect on the cerebrovascularature. This could obviously be devastating to the CBF if it weren't for the autoregulatory mechanism. Indeed, it is these drugs which are most often responsible for orthostatic faintness and syncope when inappropriate doses are administered. Fortunately, irreversible ischemic events rarely ensue even in patients who have cerebrovascular disease.

Hemodynamically, the ideal antihypertensive drugs for patients with cerebrovascular disease would maintain cardiac output and reduce total peripheral resistance, including cerebrovascular resistance. A direct vasodilator, such as hydralazine, minoxidil, or one of the calcium channel entry blockers would fit this description, although the effect of these drugs on cerebrovascular resistance hasn’t been extensively studied.

It is important to note that the measurement of total CBF can be misleading and mask perfusion deficits in localized areas of the brain. Future studies of the effect of antihypertensive agents on CBF should include measurements of regional CBF in an effort to identify areas that might actually be deprived of adequate flow by a steal mechanism.

Conclusions

In spite of the fact that hypertensive patients have impaired cerebral autoregulation and baroreflex function, clinical studies have clearly shown benefit from antihypertensive therapy in the primary and secondary prevention of stroke.

Cerebral autoregulation tends to improve as elevated blood pressure is reduced. The goal blood pressure for hypertensive patients with evidence of cerebrovascular disease should be the same as it is for hypertensive patients without evidence of cerebrovascular disease: \( \leq 90 \) mm Hg if the initial diastolic blood pressure is \( \geq 100 \) mm Hg and at least a 10 mm Hg decrement when the initial diastolic blood pressure is 90-99 mm Hg.

For patients who have had an acute atherothrombotic stroke, it has been my practice not to initiate antihypertensive therapy until the neurologic deficit has been stable for 2 to 3 weeks and the patient has begun to ambulate, unless the diastolic blood pressure is \( \geq 110 \) mm Hg. During this initial period following cerebral infarction a decrease in blood pressure might endanger the ischemic zone surrounding the infarcted area because of deficient autoregulation and/or impaired or absent baroreflexes. Thereafter, blood pressure should be reduced gradually over a period of several weeks, avoiding, if possible, agents that might cause abrupt orthostatic hypotension (guanethidine, bethanidine, ganglion blocking agents, and prazosin).

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