Effect of Perindopril on Cerebral Vasomotor Reactivity in Patients With Lacunar Infarction

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Background and Purpose—There is growing evidence that pharmacologic interference with the renin-angiotensin system may reduce risk of stroke, although the mechanism is unclear. Impaired reactivity of cerebral vessels has recently been recognized as a risk factor for stroke. We examined the effect of the angiotensin-converting enzyme (ACE) inhibitor perindopril on cerebral vasomotor reactivity to acetazolamide in patients with lacunar cerebral infarction.

Methods—We studied a cohort of male patients between 3 and 12 months after lacunar infarction confirmed on computed tomography. Each patient received perindopril 4 mg daily or matching placebo for 2 weeks in a randomized, double-blind, placebo-controlled crossover fashion. A 1-week washout period was observed between dosing periods. Cerebral vasomotor reactivity (increase in middle cerebral artery mean flow velocity in response to intravenous injection of 15 mg/kg acetazolamide) was measured before and after each dosing period using standard Doppler ultrasound techniques.

Results—Twelve patients (mean age 63.2±2.3 years) completed the protocol. There was no treatment order effect. Cerebral vasomotor reactivity was significantly greater after perindopril treatment (percent change from baseline +18.8±10.1% after perindopril, −4.6±4.1% after placebo; \( P=0.032 \)). Dosing with perindopril did not affect resting cerebral blood flow velocity (percent change from baseline +3.1±9.5% after perindopril, −0.6±5.4% after placebo), nor was there a change in resting blood pressure (1.8 mm Hg±3.1 after perindopril, +1.4 mm Hg±2.5 after placebo).

Conclusions—This study provides evidence of a significant improvement in cerebral vasomotor reactivity induced by perindopril, beyond any effect on blood pressure. The results suggest a possible mechanism for the beneficial effect of ACE inhibition on stroke risk observed in recent clinical trials, and suggest a role for the renin-angiotensin axis in the pathophysiology of subcortical small vessel disease. (Stroke. 2004;35:1899-1902.)

Key Words: hemodynamics ■ ultrasonography, Doppler, transcranial ■ white matter

Pharmacological interference with the renin-angiotensin system (RAS) either alone or in combination with diuretic may confer protection against stroke.1-3 This effect has been observed independent of2 or associated with very modest reduction in blood pressure.3 It is possible that such protection may arise as a consequence of improvement in cerebrovascular endothelial function, a phenomenon previously reported in other vascular beds after administration of angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers. This observation is supported by evidence of beneficial effects of ACE inhibition and angiotensin receptor blockade on cerebral blood flow in hypertensive subjects4 and patients with acute stroke5 and carotid disease.6

Cerebral vasomotor reactivity (CVR) is the compensatory dilatatory capacity of cerebral resistance vessels in response to increased arterial carbon dioxide concentration, and this phenomenon can be harnessed to provide a functional assessment of the cerebral vasculature.5 CVR can be assessed using a variety of methods, including ultrasound, single photon emission tomography (SPET), and magnetic resonance imaging (MRI) techniques. Of these, transcranial Doppler ultrasound (TCD)8 has been most widely adopted; its validity is supported by angiographic studies9 that demonstrate that the stimulus does not alter the diameter of the middle cerebral artery, hence changes in flow velocity are representative of changes in blood flow. TCD is also relatively inexpensive and more readily available than alternative techniques. Impaired CVR has been observed in association with hypertension,10,11 long-standing insulin-dependent diabetes mellitus,12 and cerebrovascular disease.7 Reduced CVR correlates with severity of leukoencephalopathy seen on MRI,13,14 and confers an increased risk of ischemic stroke, possibly caused by increased rigidity in the arteriolar wall and to failure of the cerebral vasculature to compensate for fluctuations in perfusion pressure.15

Some improvement of impaired CVR has been reported after control of hypertension in a small number of young subjects.10 The potential reversibility of impaired cerebral vasomotor reactivity has not yet been explored in stroke patients.
We sought to investigate the effect of the ACE inhibitor perindopril on CVR in a group of patients with recent subcortical cerebral infarction.

Subjects and Methods
We performed a prospective, randomized, double-blind, placebo-controlled crossover study to investigate the effect of ACE inhibition on CVR in patients with lacunar stroke.

Male patients with MRI- or CT-confirmed first-ever lacunar infarction were studied. Lacunar infarction was defined as a classic clinical lacunar syndrome supported by CT or MR evidence of an ischemic lesion of <15 mm³ in lenticulostriate, thalamoperforate, or pontine arterial territory. Because acute cerebral ischemia may lead to transient disruption of cerebral autoregulation, only patients with index stroke between 2 and 6 months before randomization were included. Full inclusion and exclusion criteria are given in Table 1.

Once informed consent had been obtained, patients underwent baseline assessment of CVR as described later. They then received a supply of perindopril 4 mg tablets or matching placebo, 1 tablet to be taken each morning for 2 weeks. They returned on day 7 for safety bloods, and again on day 15 for repeat assessment of CVR. A 1-week “washout” period of no medication followed, then the protocol was repeated with the alternate agent (either active drug or placebo). Study design is summarized in Figure 1.

Hemodynamic Profile
Because diurnal variation in CVR may occur, all examinations were performed at 11:00 AM. Patients underwent TCD examination lying supine in a quiet room. An Acuson TCD machine with 2-MHz transducer was used for all studies. Simultaneous bilateral MCA insonation was performed for a period of 2 minutes and the mean flow velocity (MFV) was recorded. Each subject then received an intravenous infusion of 15 mg/kg acetazolamide over 3 minutes. Fifteen minutes after cessation of acetazolamide infusion, the TCD recordings were repeated for a further 2 minutes, and the postacetazolamide MFV was recorded. Preacetazolamide and postacetazolamide MFV was calculated as the average MFV of all waveforms recorded in each 2-minute interval.

Power Calculation
We calculated that a study of the proposed size would detect a 10% difference in CVR between treated and control periods with 90% power.

Results
We studied 12 patients (mean age 63.2±2.3 years) between 3 and 12 months after lacunar infarction. Demographics are shown in Table 2.

Cerebrovascular Reactivity
There was no treatment order effect. CVR was significantly greater after perindopril treatment (percent change from baseline +18.8±10.1% after perindopril, −4.6±4.1% after
placebo; P = 0.032). CVR before and after treatment with perindopril and placebo are shown in Figure 2.

Resting Cerebral Blood Flow
Dosing with perindopril did not affect resting cerebral blood flow velocity (percent change from baseline +3.1 ± 9.5% after perindopril, −0.6 ± 5.4% after placebo).

Blood Pressure
ACE inhibition did not affect blood pressure (+1.8 mm Hg ± 3.1 after perindopril, +1.4 mm Hg ± 2.5 after placebo) (Figure 3).

Discussion
The effects of ACE inhibition on cerebral vasculature are complex. In experimental animals, the RAS plays an important role in modulation of cerebral blood flow. In both hypertensive16 and normotensive17 rats, captopril administration reduces blood pressure without adversely affecting cerebral perfusion. ACE inhibitors shift the cerebral autoregulatory curve of both hypertensive and normotensive animals to the left, leading to higher levels of cerebral perfusion at relatively lower perfusion pressures. This effect has been attributed to blockade of luminal vascular wall ACE in large cerebral vessels.18 The vascular tone maintained by angiotensin II is therefore diminished, resulting in dilatation of larger cerebral arteries. Further studies in rats have confirmed that angiotensin II receptors within large cerebral arteries are involved in cerebral autoregulation after an increase in blood pressure, and inhibition of ACE resets cerebral autoregulation at a lower level.19 Studies of the effect of ACE inhibition in healthy volunteers have shown reductions in blood pressure with increased cerebral blood flow.20 These findings are supported by the recognized pressor effects of angiotensin II in the cerebral vasculature of experimental animals21 and suggest that ACE inhibitors exert a more marked vasodilatory effect in the cerebral circulation compared with other vascular beds.

This is the first study to demonstrate the effect of ACE inhibition on cerebral vasomotor reactivity in patients with cerebrovascular disease. Previous studies have demonstrated improvement in vascular function after similar pharmacological intervention in other areas;22–26 however, because the mechanisms that regulate cerebral blood flow are more sophisticated than those governing myocardial and forearm blood flow, there are dangers in extrapolating results between vascular beds. The acetazolamide stimulus used in this study promotes vasodilatation through endothelial- and nonendothelial-dependent means, hence the mechanistic basis of our observation is unclear. Given the short dosing interval, it is unlikely that major changes in arterial geometry are responsible for the amelioration in vascular responsiveness and an improvement in endothelial function is the most likely explanation. Similarly, ACE inhibitors may improve vascular responsiveness by a number of processes. Blood pressure reduction per se is unlikely to have played a major role in the differences observed, and the relatively modest reductions in blood pressure observed in much larger clinical studies of ACE inhibition also suggest that a blood pressure independent mechanism may contribute to the observed benefit of treatment. Neurohumeral modulation, either attenuation of angiotensin II activity or potentiation of bradykinin-mediated vasodilatation, would be a biologically plausible explanation, and further studies to clarify this area are justified.

Conclusions
This study provides evidence of a significant improvement in CVR induced by perindopril. The results suggest a possible mechanism for the beneficial effect of ACE inhibition on stroke risk observed in recent clinical trials and suggest a role
for the RAS in the pathophysiology of subcortical small vessel disease.

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References


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