Long-Term Angiotensin-Converting Enzyme Inhibitor Perindopril Therapy Improves Cerebral Perfusion Reserve in Patients With Previous Minor Stroke

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Background and Purpose—Angiotensin-converting enzyme (ACE) inhibitor–based therapy reduces the recurrence of stroke. The present study assessed the effects of long-term ACE inhibitor therapy on cerebral circulation in patients with previous minor stroke.

Methods—After a run-in period, 19 patients were randomized to ACE inhibitor therapy (n=9; 4 mg of perindopril daily; mean age, 64±8 years; mean systolic/diastolic blood pressure [BP]±SD, 133±12/77±9 mm Hg) or placebo therapy (n=10; mean age, 66±9 years; mean BP, 139±10/78±8 mm Hg). Cerebral blood flow (CBF) was measured during hypercapnia, normocapnia, and hypocapnia using a positron emission tomography with H$_2^{15}$O at entry into the study and after 3 to 12 months. Cerebral perfusion reserve (CPR) was defined as percent CBF response to a 1 mm Hg change in arterial partial pressure of CO$_2$ between hypercapnia and hypocapnia.

Results—Systolic/diastolic BP and CBF during normocapnia showed no significant changes between entry and completion of the trial in the perindopril and placebo groups. Mean value of CPR showed a significant increase in the perindopril group (from 3.7±1.7%/mm Hg to 4.8±1.7%/mm Hg; P<0.05) but not in the placebo group (from 4.1±0.8%/mm Hg to 4.2±0.6%/mm Hg; NS). Statistical parametric mapping analysis also showed global and significant increase (P<0.01, uncorrected) in CPR in the perindopril group alone.

Conclusions—Long-term ACE inhibitor–based therapy had a beneficial effect on the cerebral circulation by improving CPR in patients with previous minor stroke. (Stroke. 2004;35:2117-2122.)

Key Words: angiotensin-converting enzyme inhibitors • cerebral blood flow • hypertension • perfusion • tomography, emission-computed

The Perindopril Protection Against Recurrent Stroke Study (PROGRESS) has shown that angiotensin-converting enzyme (ACE) inhibitor therapy combined with diuretics can decrease recurrence of stroke by 44% in hypertensive patients and by 42% in nonhypertensive patients. Chronic ACE inhibitor therapy reduced the systemic blood pressure (BP) and improved the capacity of cerebral vessels to dilate in response to a lower cerebral perfusion pressure in hypertensive and normotensive rats. In clinical studies, ACE inhibitors have been shown to lower systemic BP without decreasing cerebral blood flow (CBF) in hypertensive patients, recent ischemic stroke patients, and stroke patients with carotid stenosis or occlusion. In another study, CBF was unchanged despite a reduction of cerebral perfusion pressure after ACE inhibitor administration. Although the acute and short-term effects of ACE inhibitors have been investigated in this manner, few clinical studies have addressed the long-term effects of ACE inhibitors on cerebral perfusion.

In the present study, we investigated the long-term effects of ACE inhibitor therapy on cerebral perfusion in patients with previous minor stroke who fulfilled the criteria of PROGRESS. We compared basal CBF and CBF response to changes in arterial partial pressure of CO$_2$ (Paco$_2$) before and during ACE inhibitor therapy lasting ≥3 months by a single-blind, placebo-controlled randomized trial.

Patients and Methods

Patients

Patients who had a history of minor ischemic stroke within the previous 5 years were eligible. As in the PROGRESS trial, participants had no definite indications for ACE inhibitor therapy.
Concomitant diseases

Resting CBF, cerebral blood volume (CBV), cerebral oxygen extraction fraction (OEF), and cerebral metabolic rate of oxygen (CMRO2), were measured in all 24 patients using positron emission tomography (PET) at entry into the study to measure cerebral perfusion reserve (CPR). CPR was induced by hyperventilation from 1 minute before scanning until the end of scanning, whereas hypocapnia was induced by hyperventilation from 1 minute before scanning until the end of scanning. Two arterial blood samples were taken, 1 at the beginning and 1 at the end of scanning, for measurement of PaCO2. The cerebral perfusion reserve (CPR) was defined as the percent CBF response to hypercapnia and hypocapnia, which was calculated as follows:11–14

$$\text{CPR (}\%\text{CBF/mmHg}) = \frac{100 \times (\text{CBF}_{\text{hyper}} - \text{CBF}_{\text{hypo}})}{\text{CBF}_{\text{rest}}} \times \left(\frac{\text{PaCO2}_{\text{hypo}}}{\text{PaCO2}_{\text{hypo}}} - 1\right)$$

where “hypo,” “hypo,” and “rest” denote measurement during hypercapnia, hypocapnia, and under resting conditions.

**Region of Interest Analysis**

To obtain quantitative data, regions of interest (ROIs) were drawn on the resting CBF image obtained at the level of the basal ganglia (20 mm above and parallel to the AC-PC line) by manually outlining the right and left cerebral hemispheres. The scans analyzed were blind to knowledge of treatment allocation. Next, the same ROIs were superimposed on the CBV, OEF, and CMRO2 images, as well as on the CBF images obtained during hypercapnia and hypocapnia. The mean value of both hemispheres was calculated as the global cerebral blood flow (CBF), cerebral blood volume (CBV), CMRO2, OEF, and CPR. Parametric maps were compared using 2-way repeated-measures ANOVA for treatment effect and time effect to examine between-group differences. Within-group differences were examined in the perindopril group and placebo group by the paired t test to compare values between entry and completion of the trial.

**Statistical Parametric Mapping Analysis**

The data were analyzed with statistical parametric mapping (SPM99; Wellcome Department of Cognitive Neurology) software implemented in MATLAB (version 5.3; Mathworks).15 All images of each subject were realigned to the image scanned during resting condition and were transformed into a standard stereotaxic space. Each image was smoothed using a Gaussian filter of 12 mm (full-width half maximum) in the x, y, and z axes to improve the signal-to-noise ratio. After standardization, brain images of all subjects had the same anatomical format. From the standardized CBF images, a CPR image was created for each patient according to the equation described above. Treatment duration was included in the analysis as a nuisance variable. Corrections for the global values were not performed. The descriptive 3D t-maps (paired t test) of CPR at the end of treatment minus CPR at entry into the trial were created for the perindopril group and the placebo group. Areas on the t-maps showing a difference of $P<0.01$ (uncorrected) on a pixel-by-pixel basis were considered to indicate statistically significant difference.

**TABLE 1. Clinical Profile of Each Group**

<table>
<thead>
<tr>
<th></th>
<th>Placebo Group</th>
<th>Perindopril Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. (male/female)</td>
<td>10 (6/4)</td>
<td>9 (7/2)</td>
</tr>
<tr>
<td>Age (y)</td>
<td>64±9</td>
<td>64±8</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>64±11</td>
<td>64±7</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>156±11</td>
<td>160±8</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>72±6</td>
<td>73±2</td>
</tr>
<tr>
<td>Treatment duration (y)</td>
<td>0.93±0.23</td>
<td>1.02±0.04</td>
</tr>
<tr>
<td>BP (mm Hg)</td>
<td>139±10/78±8</td>
<td>133±12/77±9</td>
</tr>
<tr>
<td>Average during the study</td>
<td>140±7/79±3</td>
<td>134±6/75±5</td>
</tr>
<tr>
<td>Compliance (%)</td>
<td>94±7</td>
<td>93±7</td>
</tr>
<tr>
<td>Coadministered drugs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcium antagonist</td>
<td>7/10</td>
<td>3/9</td>
</tr>
<tr>
<td>β-blocker</td>
<td>1/10</td>
<td>4/9</td>
</tr>
<tr>
<td>Diuretics</td>
<td>1/10</td>
<td>0/9</td>
</tr>
<tr>
<td>Antiplatelet agents</td>
<td>10/10</td>
<td>9/9</td>
</tr>
<tr>
<td>Concomitant diseases</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>10/10</td>
<td>7/9</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>6/10</td>
<td>4/9</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>5/10</td>
<td>3/9</td>
</tr>
<tr>
<td>Detection of new lacunae</td>
<td>5/10</td>
<td>3/9</td>
</tr>
</tbody>
</table>

bpm indicates beats per minute.

and no definite contraindications to use of ACE inhibitors. Patients with a systolic/diastolic BP <160/95 mm Hg were enrolled. They were normotensive (BP <140/90 mm Hg) or had hypertension that was controlled with antihypertensive agents other than ACE inhibitors. They also had to be stable for ≥1 month after the most recent symptomatic stroke. MRI of the brain (T1- and T2-weighted) and magnetic resonance angiography of the carotid and cranial arteries were performed. No participant had stenosis or occlusion of any of the major arteries. MRI was repeated at the end of trial, and development of new arterial or brain lesions during the study was evaluated. Lacunar infarction was defined as high- and low-intensity spots on T2- and T1-weighted MRIs, respectively, in the central gray matter or deep white matter.

After positron emission tomography (PET) was performed, 27 participants entered a 4-week run-in period during which they received open-label treatment with perindopril (2 mg daily for 2 weeks, followed by 4 mg daily for 2 weeks). Three of the participants withdrew during this period because of dizziness or cough, and the remaining 24 were randomized on a single-blind basis to an active treatment group (perindopril at 4 mg per day) or a placebo group. The patients were monitored every 2 weeks to assess symptoms, BP, and compliance with treatment. The clinical profiles of the perindopril group and placebo group are shown in Table 1. Average value of the BP measured every 2 weeks during the trial was estimated in each patient. The mean average BP in the perindopril group and placebo group were also shown as average BP in Table 1. The ethics committee of our institution approved the present study, and written informed consent was obtained from all the patients.

PET Measurements

In all 24 patients, PET was done at entry into the study to measure resting CBF, cerebral blood volume (CBV), cerebral oxygen extraction fraction (OEF), and cerebral metabolic rate of oxygen (CMRO2), and CBF was also assessed during hypercapnia and hypocapnia. PET study was repeated at the end of trial.

The HEADTOME-V PET system (Shimadzu) was used to obtain 47 slices with a center-to-center distance of 3.125 mm. The intrinsic spatial resolution was 4.0 mm in plane and 4.3 mm at full-width half maximum axially. Data were acquired in the 2D mode, with axial planes being scanned parallel to the anterior commissure–posterior commissure (AC–PC) line. PET was performed with intravenous injection of H215O and with inhalation of C18O and O18O in each patient. The arterial input function was obtained by continuous β-probe measurement of the radioactivity in blood flowing through the radial artery. Two blood samples were collected (1 at the beginning and 1 at the end of scanning) for measurement of the PaCO2 and PaO2 and the pH. During scanning, arterial BP was measured with an ordinary mercury sphygmomanometer placed on the opposite upper arm to that used for blood sampling. A head fixation system with an individual mold for each subject was used to minimize head movement during PET. Details of the PET procedure and the methods used for calculation of quantitative parameters have been described previously.10

Cerebral Perfusion Reserve

H215O PET studies were performed at rest as well as during hypercapnia and hypocapnia with the eyes closed.11 Hypercapnia was induced by inhalation of 7% CO2 gas from 1 minute before scanning until the end of scanning, whereas hypocapnia was induced by hyperventilation from 1 minute before scanning until the end of scanning. Two arterial blood samples were taken, 1 at the beginning and 1 at the end of scanning, for measurement of PaCO2. The cerebral perfusion reserve (CPR) was defined as the percent CBF response to hypercapnia and hypocapnia, which was calculated as follows:11–14

$$\text{CPR (}\%\text{CBF/mmHg}) = \frac{100 \times (\text{CBF}_{\text{hypo}} - \text{CBF}_{\text{hypo}})}{\text{CBF}_{\text{rest}}} \times \left(\frac{\text{PaCO2}_{\text{hypo}}}{\text{PaCO2}_{\text{hypo}}} - 1\right)$$

where “hypo,” “hypo,” and “rest” denote measurement during hypercapnia, hypocapnia, and under resting conditions.

Statistical Parametric Mapping Analysis

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Results

One patient in the placebo group experienced intracerebral hemorrhage 6 months after starting the trial. Two patients violated the protocol because of treatment with vasoactive agents. In 2 other patients, the second PET study was not performed properly (failure of CO₂ inhalation and arterial blood sampling). Therefore, these 5 patients were withdrawn from the study, leaving 9 patients receiving active treatment and 10 patients receiving placebo to complete the trial.

Average values of PaCO₂, arterial partial pressure of O₂ (PaO₂), and pH during each PET scanning procedure are shown for the perindopril group and the placebo group in Table 2. Mean values of PaCO₂, PaO₂, and pH were significantly different among normocapnia, hypercapnia, and hypocapnia. No significant differences of BP, PaCO₂, PaO₂, and pH were found between the perindopril group and the placebo group for all conditions at the start or finish of the trial.

In the ROI analysis, there was a significant interaction between a treatment effect and a time effect (P<0.05; 2-way repeated measures ANOVA). The mean CPR at the end of perindopril treatment (4.8±1.7%/mm Hg) was significantly higher than at entry (3.7±1.7%/mm Hg; P<0.05; paired t test). In the placebo group, the final mean CPR (4.2±0.6%/mm Hg) was not significantly different from the initial value (4.1±0.8%/mm Hg). Under normocapnic conditions, values of CBF, CBV, OEF, and CMRO₂ showed no significant differences between active and placebo treatment in the initial and final PET studies (Table 3).

Figure 1 shows average CPR images at entry into the trial and at the end of treatment for perindopril group and placebo group. Figure 2 demonstrates the t-maps of CPR (at end minus entry) for perindopril group and placebo group. Significant CPR increase was identified for global brain in the perindopril group (P<0.01), but significant difference was not found in the placebo group.

Discussion

This is the first study to demonstrate a long-term pharmacological effect of ACE inhibitor therapy on the cerebral circulation in patients with previous minor ischemic stroke. CPR (represented by the CBF response to a change of PaCO₂) was significantly improved in the perindopril group but not in the placebo group.

Hypercapnia produces cerebral vasodilation and increases CBF, whereas hypocapnia causes cerebral vasoconstriction and decreases CBF.15–17 Therefore, the CBF response to changes of PaCO₂ in the brain has been used as an alternative estimate of autoregulatory CPR in patients with occlusive
cerebrovascular diseases. Nishimura et al found that CBF did not decrease during trimethaphan-induced hypotension (mean systemic arterial BP reduction 15 mm Hg) when CPR was ≈5%, whereas CBF was reduced by 0% to 5% and 5% to 10% when CPR was ≈4% and 3%, respectively. Although vasoreactivity to PaCO₂ may not fully reflect the autoregulatory perfusion reserve in response to changes of perfusion pressure, the improved CPR from 3.7% to 4.8%/mm Hg during chronic ACE inhibitor therapy seems to represent the recovery of autoregulatory protection against hypotension, as observed in experimental and clinical studies.

Mean CPR was predominantly increased in cerebellum and basal ganglia, but the SDs were large. Regional ROI analysis indicated that among the deep brain structures, thalamus showed significant improvement of CPR in the perindopril group, but basal ganglia and white matter did not. It remains unproven whether specific structures of the brain or types of vessels are affected by perindopril treatment.

ACE inhibitors prevent the breakdown of bradykinin, which stimulates prostacyclin synthesis and NO release by endothelial cells. Improvement of cerebral autoregulation by chronic ACE inhibitor therapy may be partly attributable to enhancement of the bradykinin-induced release of cerebral vasodilators. Another effect of chronic ACE inhibitor therapy is normalization of the structure of resistance vessels. Resistance vessels of hypertensive patients are characterized by a smaller lumen and an increased media-lumen ratio, and angiotensin II is known to cause vascular hypertrophy. Thybo et al reported that perindopril treatment for 12 months resulted in a more prominent increase of small artery diameter and a greater reduction of the media-lumen ratio than treatment with the β-blocker atenolol in patients with previously untreated essential hypertension. Because atenolol reduced BP more extensively than perindopril, the structural improvement achieved by perindopril was not attributable to a BP-lowering effect. These effects of ACE inhibitors, mediated by another mechanism than their antihypertensive activity, may be responsible for CPR improvement.

What is the clinical implication of this study? Most of the patients had been treated with various antihypertensive drugs before enrollment in this trial and had a BP < 160/95 mm Hg at entry. As reported previously, the subsequent decrease of BP was not significant in the perindopril group. However, this 3- to 12-month ACE inhibitor–based therapy improved CPR, which may indicate an additional benefit of ACE inhibitors beyond BP reduction in patients with previous minor stroke who are already controlled by other antihypertensive drugs.

Figure 1. Average CPR images (percent CBF change/mm Hg) at entry (A) and at end (B) for placebo group and at entry (C) and at end (D) for perindopril group. Image maximum and minimum values are 10% and 0%, respectively.
There were several limitations of the present study. First, normotensive or controlled-hypertensive patients were enrolled because the aim of the study was to evaluate the effect of ACE inhibitor therapy on cerebral hemodynamics rather than revisiting the BP-lowering effect that was demonstrated in the PROGRESS trial. Second, the number of participants was small, and 5 patients (≈20%) withdrew from the trial. Third, there were notable differences in baseline characteristics between the perindopril group and the placebo group. Baseline BP was higher in the placebo group (139/78 mm Hg) than in the perindopril group (133/77 mm Hg). Because BP is a major factor determining CPR, recovery of the CPR may be induced by the increase in BP alone. However, average BP during the trial and BP at the PET studies were stable in the placebo and perindopril groups. There were differences in antihypertensive medications during the trial, although the differences were not statistically significant by Fisher exact test. Fourth, there was a selection bias toward patients with small-vessel cerebrovascular disease rather than patients with large-artery atherosclerosis or cardioembolic infarction. MRI revealed new lacunar infarctions in 8 of 19 patients. The high incidence of new lacunar formation would partly be the result of this selection bias. Finally, we decided to perform a single-blind trial instead of double-blind to avoid any clinical disadvantage to the participants.

In conclusion, long-term ACE inhibitor perindopril therapy improved CPR in patients with previous minor stroke, which may help to ameliorate a decrease of cerebral perfusion pressure by boosting the vasodilatory response of cerebral autoregulation.

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References


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