Pravastatin Improves Cerebral Vasomotor Reactivity in Patients With Subcortical Small-Vessel Disease

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Background and Purpose—Recent investigations have suggested an important role of statins in the prevention of stroke and dementia independent of their lipid-lowering properties. Using transcranial Doppler sonography (TCD), we examined acetazolamide reactivity as a marker of cerebral vasoreactivity in patients with subcortical small-vessel disease before and after pravastatin treatment.

Methods—In 16 patients (mean age 68 ± 10 years) with subcortical small-vessel disease, cerebral vasomotor reactivity was tested using TCD insonating the middle cerebral artery. Cerebral blood flow velocity (CBFV) increase after bolus injection of 1 g acetazolamide was determined before and after 2-month treatment with pravastatin sodium 20 mg daily.

Results—Relative CBFV increase was significantly greater after pravastatin treatment (41.9 ± 23.7% versus 55.7 ± 18.3%, \( P = 0.004 \)). Comparison of CBFV at rest before and after treatment with pravastatin did not show significant differences. There was a strong negative correlation between the pravastatin-induced enhancement of vasomotor reactivity and the pretreatment CBFV increase (\( \beta = -0.64, \ P = 0.019 \)). No associations were found between the effect of pravastatin on vasomotor reactivity and pretreatment levels or changes of LDL cholesterol.

Conclusions—This pilot study provides the first evidence for a significant improvement of cerebral vasomotor reactivity by statin therapy in patients with cerebral small-vessel disease. The results may help to elucidate the preventive effect of statins and provide insights into the pathophysiology of cerebral small-vessel disease. (Stroke. 2001;32:2817-2820.)

Key Words: endothelium ■ HMG-CoA reductase inhibitors ■ small-vessel disease ■ ultrasonography ■ vasomotor reactivity

Subjects and Methods

We prospectively studied 16 patients (9 men, 7 women; mean age 68 ± 10 years) with subcortical small-vessel disease, defined by periventricular or subcortical white matter lesions on fluid-attenuated inversion recovery (FLAIR)-weighted MRI in addition to one or more of the following criteria: ≥1 ischemic events consistent with transient ischemic attack or lacunar infarction, history of cognitive decline, gait instability, and symptomatic epileptic seizure with no evident cause other than cerebral small-vessel disease. Exclusion criteria were previous statin treatment, severely impaired cognitive function (Mini-Mental State Examination <20 points), internal carotid or middle cerebral artery (MCA) stenosis of >40% luminal narrowing as evidenced by duplex sonography, and territorial infarction on MRI. All patients gave written informed consent for the study. Prevalences of vascular risk factors were as follows: smokers (2/16), arterial hypertension (11/16), diabetes mellitus (4/16), and fasting LDL cholesterol > 3.9 mmol/L (150 mg/dL) (10/16).

Cerebral vasomotor reactivity was tested using TCD (2-MHz pulsed-wave, TC 4040, EME, Pioneer) insonating the MCA unilaterally (50- to 60-mm depth) with the patient in a supine position. The mean cerebral blood flow velocity (CBFV\(_{\text{mean}}\)) was calculated from the envelope curve of the velocity spectrum during rest and 5 minutes after bolus injection of 1 g acetazolamide over an averaging period of 5 minutes each. Relative CBFV\(_{\text{mean}}\) changes were calcu-
pravastatin effect on vasomotor reactivity ($\beta = -0.033$, $P = 0.911$).

LDL cholesterol was decreased by pravastatin treatment from $4.40 \pm 1.31$ mmol/L ($169.3 \pm 50.5$ mg/dL) to $3.30 \pm 1.24$ mmol/L ($126 \pm 47.8$ mg/dL), a reduction of 25% ($P = 0.001$). No significant associations were found between pravastatin-induced vasomotor reactivity changes and pretreatment LDL cholesterol ($\beta = -0.096$, $P = 0.745$) or LDL cholesterol changes ($\beta = 0.193$, $P = 0.497$). Pretreatment vasomotor reactivity tended to be positively correlated with LDL cholesterol levels ($\beta = 0.498$, $P = 0.050$).

**Discussion**

This pilot study provides the first evidence of a significant improvement of vasomotor reactivity by statin therapy in patients with cerebral small-vessel disease. The effect was more pronounced in patients with a more severe impairment of vasomotor reactivity. Because the baseline CBFV$_{\text{mean}}$ remained unchanged, the findings indicate a specific effect of pravastatin on the reactivity of the cerebral microvasculature. Despite a considerable interindividual variability in CBFV$_{\text{mean}}$ and vasomotor reactivity, this effect was present even when absolute increases before and after pravastatin treatment were compared. Pretreatment vasomotor reactivity and the effect of pravastatin were independent of baseline CBFV$_{\text{mean}}$, excluding that the results were confounded by different levels of baseline values. It should be mentioned that pravastatin considerably enhanced vasomotor reactivity even though we applied a relatively low dosage (20 mg daily) as compared with previous studies.1

From a pathophysiological point of view, it is tempting to speculate that the observed increase in vasomotor reactivity was the result of an improvement of endothelial function. Statin treatment has been shown to improve NO-dependent coronary vasomotor regulation and endothelial function in the forearm vasculature in patients with

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**Figure 1.** Vasomotor reactivity, defined as the percent change in cerebral blood flow velocity (CBFV$_{\text{mean}}$) after injection of 1 g acetazolamide, was significantly greater ($P = 0.004$, Wilcoxon test) after a 2-month treatment with pravastatin. Box plots show median values, 25th and 75th percentiles, and total ranges.

**Figure 2.** The effect of pravastatin, expressed as the difference of cerebral blood flow velocity (CBFV$_{\text{mean}}$) change after and before treatment, was negatively correlated with vasomotor reactivity (CBFV$_{\text{mean}}$ change) prior to treatment ($\beta = -0.64$, $P = 0.019$).
hypercholesterolemia. Since these effects could be blocked by simultaneous administration of an inhibitor of NO synthesis, the statin-induced improvement of endothelial function was suggested to be mediated by an increased bioavailability of NO. Endothelial function has been shown to be impaired in hypercholesterolemia, suggesting that the statin-induced improvement of vasoregulation is mediated by its cholesterol-lowering properties. In accordance with this hypothesis, a recent study demonstrated an increased cerebral CO₂ reactivity after lowering LDL cholesterol by heparin-mediated extracorporal LDL precipitation. In our study, the statin-induced improvement of vasomotor reactivity did not correlate with the decrease in serum cholesterol. It could be argued that the relatively small sample size might be responsible for this lack of correlation. However, pretreatment vasomotor reactivity even tended to be positively correlated with higher LDL cholesterol levels, which makes the effect of pravastatin treatment unlikely to be solely the result of its cholesterol-lowering properties. Of note, in other studies also it has been difficult to establish correlations between LDL cholesterol levels or the extent of its reduction and the statin-induced improvement of vasoregulation in extracranial vessels. A likely explanation for the effect of statins on vasoregulation in previous studies seems to be the well-documented enhancement of eNOS activity by statins. In fact, recent animal studies have shown an improvement of cerebral blood flow by statin treatment that was not only independent of changes in cholesterol levels but also absent in eNOS-deficient animals. It has to be mentioned that the vasomotor reactivity test used in the present study has not been proven to be endotheli-um-dependent. Acetazolamide acts as a competitive inhibitor of carbonic anhydrase. Its effects on cerebral blood flow and MCA flow velocity are most probably the result of a decrease in perivascular pH, very similar to CO₂ reactivity. The exact mechanism by which pH decreases induce vascular smooth muscle cell relaxation in arterioles is not completely understood, and whether NO is involved in this effect remains controversial. However, in the light of the potential of statins (1) to upregulate eNOS activity and (2) to favorably modify NO-dependent vasoregulation, it seems likely that these mechanisms at least participate in the effect of pravastatin on vasomotor reactivity observed in the present study.

Of course, the small sample size and short follow-up do not allow the correlation of changes of vasomotor reactivity with the clinical course (i.e., cognitive decline, stroke) or the progression of MRI abnormalities under statin treatment. It also has to be emphasized that this was an exploratory pilot study that aimed to demonstrate an effect in a specific group of patients. For that reason, no control group without small-vessel disease was included at this stage. We therefore cannot exclude that increases in vasomotor reactivity might also occur in normal individuals treated with statins. However, the interindividual variability of vasomotor reactivity in the present sample of patients was high and the statin-induced changes were greater in those patients with more severe initial reductions, suggesting a specific effect of pravastatin on a disturbed microvasculature. Also, even though the observed effect was profound and highly significant and therefore unlikely to be just the result of a lack of reliability of vasomotor reactivity testing, future investigations should also include a placebo group to study the intraindividual reliability of the acetazolamide test.

In conclusion, our study suggests that cerebral vasomotor reactivity can be improved by short-term administration of pravastatin in patients with cerebral small-vessel disease. This may stimulate further clinical studies to better understand the preventive effects of statins and may help to elucidate the pathophysiology of cerebral small-vessel disease.

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References

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