Effect of Systemic Administration of Simvastatin on Retinal Circulation

Taiji Nagaoka, MD, PhD; Atsushi Takahashi, MD; Eiichi Sato, MD, PhD; Naohiro Izumi, MD; Travis W. Hein, PhD; Lih Kuo, PhD; Akitoshi Yoshida, MD, PhD

Objective: To investigate the effect of systemic administration of simvastatin on the retinal circulation.

Methods: The effects of systemic administration of simvastatin on the retinal circulation after 90 minutes and after 7 days were studied in a placebo-controlled, double-masked, clinical trial among 12 healthy men. We used laser Doppler velocimetry to measure vessel diameter and blood velocity and calculated the blood flow in retinal arteries and veins. We also measured the intraocular pressure and the plasma nitrite/nitrate levels, the stable end products of nitric oxide metabolism.

Results: There were no significant changes in any retinal circulatory parameters at 90 minutes after administration of simvastatin. Daily administration of simvastatin for 7 days significantly increased blood velocity and blood flow in retinal arteries and veins but did not significantly change vessel diameter. The intraocular pressure significantly decreased at 90 minutes and at 7 days after administration of simvastatin. Simvastatin also significantly increased the plasma nitrite/nitrate levels.

Conclusion: Simvastatin induced an increase in blood velocity and blood flow in retinal arteries and veins, increased the plasma nitrite/nitrate levels, and decreased the intraocular pressure, probably through the increase in nitric oxide.


INDINGS FROM RECENT STUDIES suggest that, in addition to inhibiting cholesterol syn-

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The results of 2 recent studies suggest that simvastatin may exert a neuroprotective effect by inhibiting leukocyte-endothelium interaction through the release of NO from the endothelium during ischemic reperfusion injury and in the retinas of rats with streptozotocin-induced diabetes. In addition, clinical studies show that long-term statin use may contribute to reductions of the risk of age-related macular degeneration, diabetic retinopathy, and glaucoma. Because such ocular disorders are thought to be associated with impaired ocular circulation, it is important to study the effect of systemic administration of statins on the ocular circulation. In this study, we investigated the effect of systemic administration of simvastatin on the retinal circulation using a laser Doppler velocimetry system in healthy young men. The changes in systemic blood pressure, serum cholesterol level, and intraocular pressure (IOP) associated with simvastatin administration were investigated. In addition, to determine whether NO is involved in the effect of simvastatin on the retinal circulation, using the Griess method, we measured the plasma nitrite/nitrate levels, which are stable NO end products in biologic fluid.

METHODS

SUBJECTS

This randomized, placebo-controlled, double-masked, 2-way crossover study examined the effect of short-term (single dose) and long-term (7 days after daily dosing) administration of simvastatin on the retinal circulation and the IOP. The present study adhered to the tenets of the Declaration of Helsinki and the Good Clinical Prac-
The baseline values of all variables among the subjects are given in Table 1. There were no significant differences in hemodynamic variables or IOP between the simvastatin and placebo groups at baseline.

### MEASUREMENT OF RETINAL BLOOD FLOW

To estimate the blood flow in retinal arteries and veins (RBF), we used a laser Doppler velocimetry system (Canon Laser Blood Flowmeter, CLBF model 100; Canon, Tokyo, Japan), which has been described in detail elsewhere. In brief, this fundus camera–based machine facilitates noninvasive measurement of absolute values of the red blood cells flowing in the centerline of a retinal vessel, based on bidirectional laser Doppler velocimetry. The device includes a vessel diameter measurement system and a vessel tracking system. The RBF was calculated according to the following formula: 

\[ \text{RBF} = \frac{V}{(C/2)} \]

where \( V \) is the mean of the centerline blood velocity during the cardiac cycle, and \( C \) is the area of the centerline vessel. The RBF measurements were performed in the superotemporal artery and vein in the right eye. The measurement sites were generally between the disc margin and the first bifurcation and were recorded in monochromatic photographs to confirm the measurement position at every measurement phase. Ocular perfusion pressure (OPP) was determined according to the following formula: OPP = \( \frac{\text{MAPF} - \text{IOP}}{2} \), where MAPF indicates the mean arterial blood pressure.

### RESULTS

The study medication was distributed to the subjects according to a randomized list. After an overnight fasting of 12 hours, the study began at 8 AM. Baseline, 5 measurements of each variable were obtained every minute at a single site along a major temporal artery; the mean of the values was defined as the baseline value. We then measured the serum total cholesterol, triglyceride, high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol levels using an autoanalyzer.

### STATISTICAL ANALYSIS

All values are expressed as mean ± SE. Repeated-measures analysis of variance was performed, followed by post hoc comparison using Dunnett procedure in each group. The changes in the RBF measurements at 90 minutes and at 7 days after administration of study medication were compared between the simvastatin and placebo groups using a nonparametric Wilcoxon signed rank test. \( P < .05 \) was considered statistically significant.

### CHANGES IN SERUM CHOLESTEROL LEVELS AND SYSTEMIC VARIABLES

In the placebo group, all systemic and retinal variables remained unchanged following short-term and long-term administration of the drug (Table 2). In the simvastatin group, compared with the baseline values, the serum total cholesterol and low-density lipoprotein cholesterol levels decreased by 9.2\% \((P < .05)\) and by 14.8\% \((P < .05)\), respectively, after 7 days of treatment with simvastatin. High-density lipoprotein cholesterol and triglyceride serum levels remained unchanged by simvastatin. Short-term or long-term administration of simvastatin had no effect on systemic blood pressure or pulse rate.

### Table 1. Retinal and Choroidal Circulation at Baseline in the Simvastatin and Placebo Groups*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Simvastatin Group</th>
<th>Placebo Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retinal artery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diameter, µm</td>
<td>111.6 ± 6.0</td>
<td>113.1 ± 5.4</td>
</tr>
<tr>
<td>Velocity, mm/s</td>
<td>33.4 ± 2.9</td>
<td>34.5 ± 1.6</td>
</tr>
<tr>
<td>RBF, µL/min</td>
<td>10.4 ± 1.7</td>
<td>10.9 ± 1.4</td>
</tr>
<tr>
<td>Retinal vein</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diameter, µm</td>
<td>134.2 ± 2.7</td>
<td>137.2 ± 4.0</td>
</tr>
<tr>
<td>Velocity, mm/s</td>
<td>23.7 ± 1.6</td>
<td>23.1 ± 1.7</td>
</tr>
<tr>
<td>RBF, µL/min</td>
<td>10.2 ± 0.9</td>
<td>10.2 ± 0.8</td>
</tr>
<tr>
<td>Intracocular pressure, mm Hg</td>
<td>14.3 ± 0.4</td>
<td>15.1 ± 0.7</td>
</tr>
</tbody>
</table>

Abbreviation: RBF, retinal blood flow.

*Data are given as mean ± SE.
Chang es in Retinal Circulation

Ninety minutes after administration of simvastatin, the diameter, velocity, and RBF had not changed significantly compared with the baseline values in retinal arteries and veins (Figure 1). Seven days after administration of simvastatin, the changes in the diameter of retinal arteries and veins were not significant (1.2%±1.6% in the arteries and 0.3%±1.2% in the veins) (P>.05). In contrast, the blood velocity and RBF were increased significantly by 20%±6% (P<.05) and 21%±7% (P<.01) in the retinal arteries (Figure 1A) and by 21.6%±9.8% (P<.05) and 23.0%±10.8% (P<.05) in the retinal veins, respectively (Figure 1B). The group-averaged percentage changes in the blood velocity and RBF after 7 days of treatment were significantly higher with simvastatin than with placebo (P<.05).

Changes in IOP

The IOP decreased significantly from 14.3±0.4 mm Hg at baseline to 12.6±0.5 mm Hg at 90 minutes (P<.05) and to 12.4±0.6 mm Hg at 7 days (P<.01) after administration of simvastatin (Figure 2A). However, the OPP did not change significantly after administration of simvastatin in either phase of the study (Figure 2B).

Changes in Plasma Nitrite/Nitrate Levels

The plasma nitrite/nitrate levels did not change significantly in the placebo group. In the simvastatin group, the plasma nitrite/nitrate levels increased significantly (P<.05) from 18±2 µmol/mL at baseline to 28±5 µmol/mL at 7 days after administration of simvastatin (ie, a 60% increase from baseline) (Figure 3).

Comment

In the present study, we observed for the first time (to our knowledge) that systemic administration of simvastatin induced an increase in the RBF and the plasma nitrite/nitrate levels in healthy men. These results suggest that simvastatin increases retinal blood flow, probably via the increase in NO.

Vasodilation by simvastatin has been reported in previous studies in other vascular beds. Simvastatin produced vasodilation of the aorta and mesenteric artery in rats. In addition, Mital et al report that simvastatin up-regulates endothelial NO production and increases coronary blood flow and the plasma nitrite/nitrate levels in conscious dogs. Despite the differences in vascular tissue and species, these in vivo findings appear to support our finding that simvastatin increases the RBF.

The increased RBF was primarily the result of the increased blood velocity, because the vessel diameter did not change significantly in retinal arteries or veins (Figure 1). The increase in blood velocity without a change in vessel diameter indicates vasodilation of the small arteriole and capillary vessels that are located downstream from the measured point (first branch retinal artery). Furthermore, NO in the retinal circulation modulates the tone of the capillary pericytes and affects the RBF in the capillaries. In accord, our findings of the increase in the plasma nitrite/nitrate levels in the simvastatin group (Figure 3) suggest that the increase in the RBF may be exerted mainly on the more downstream vessels, especially the capillaries. Therefore, we speculate that simvastatin may cause vasodilation of the resistance vessels, which are smaller than the measured large artery (first branch), in the downstream in the retinal microvascular network.

Previous studies examined the effect of statins on the human ocular circulation. Pravastatin sodium enhanced the inhibition of constitutive NO formation by N-monomethyl-L-arginine, an NO synthase inhibitor, in the choroid microvasculature in patients with hypercholesterolemia. These results suggest the increased production or action of NO in the ocular microcirculation by statins and support our findings on the beneficial effect of simvastatin in the retinal circulation. In contrast, another clinical study demonstrated that retrobulbar blood
velocity did not change after 3 months of cholesterol-lowering therapy with simvastatin in patients with hypercholesterolemia. This may be due to differences in the duration of follow-up (3 months vs 7 days) or in patient conditions. Further clinical study is needed to examine whether simvastatin can increase the RBF in patients with hypercholesterolemia.

Our observation of the increased RBF after administration of simvastatin can be interpreted in several possible ways. First, simvastatin caused an increase in the plasma nitrite/nitrate levels (Figure 3) and a decrease in the total cholesterol and low-density lipoprotein cholesterol levels (Table 2). Because low-density lipoprotein cholesterol can impair NO release by the endothelial cells through down-regulation of endothelial NO synthase messenger RNA and protein, the increased RBF may be a consequence of improving NO release. In addition, the enhanced NO effect is associated with a decrease in total
cholesterol levels in patients with hyperlipidemia. Therefore, it is possible that not only the increase in NO level but also the decrease in cholesterol level induced by simvastatin are associated with the increased RBF that we observed. Because this was a pilot study with a small number of subjects, we could not perform multivariate analysis to detect variables that may be important in the increased RBF. Further clinical study among a large number of subjects is needed to determine the exact mechanism of the simvastatin-driven increase in the RBF.

In the present study, we examined the short-term and long-term effects of simvastatin on the retinal circulation. One dose of simvastatin had no effect on the retinal circulation, but 7-day administration induced a significant change in the RBF (Figure 1). Investigators of previous clinical studies in other vascular beds report that improvement in endothelial function by statins was detected between 3 days and 2 weeks after administration in humans. Therefore, this may explain our results that the positive effect of simvastatin was observed in association with 7-day administration. In contrast, Bayerle-Eder et al report that an enhanced NO effect on pulsatile choroidal blood flow with pravastatin was not observed after 7 days of treatment but was observed after 28 days of treatment. This may be due to their measurement of choroidal endothelial function in patients with hyperlipidemia vs our observations on increased retinal blood flow in healthy subjects.

The effect of statin therapy on diabetic retinopathy was examined in a small previous study. Treatment with statins was associated with an improvement in hard exudates and microaneurysms in this study of 6 patients. In addition, findings from an animal study suggest that simvastatin may prevent diabetic retinopathy by attenuating leukocyte–endothelial cell interactions and the subsequent blood-retina barrier breakdown. Although the data concerning hemodynamic change in the retinal arteries of patients with diabetes are controversial, it was recently reported that the RBF was decreased in patients with type 2 diabetes mellitus without clinical manifestations of retinopathy or early-stage retinopathy. Therefore, we believe that the impaired retinal circulation may contribute to the development of retinopathy in these patients. Although the findings in the present study are obtained from healthy men whose physiological response to simvastatin may be different from that of patients with diabetes, the increased RBF associated with treatment with simvastatin may be a potential therapy for diabetic retinopathy.

McGwin et al recently reported that statin use may be associated with a reduced risk of glaucoma, but the authors did not provide data on the effect of statins on the IOP in that study. In the present study, we document for the first time (to our knowledge) that the IOP was slightly but significantly decreased by simvastatin (Figure 2A). Many statins inhibit the activity of Rho kinase, which leads to an enhanced aqueous outflow and thereby a presumably lower IOP. These previous findings may support the simvastatin-mediated IOP-lowering effect that we observed. Alternatively, simvastatin may decrease the IOP via an increase in the plasma NO. Although the role of NO in the regulation of the IOP is controversial, some researchers report that NO could modulate not only the ocular circulation but also the IOP in humans and rabbits. However, the present results suggest that simvastatin reduces the IOP independent of the release of NO, because the IOP was decreased at 90 minutes after administration of simvastatin without a change in the plasma nitrite/nitrate levels. Although the precise underlying mechanisms causing the simvastatin-induced IOP-lowering effect are incompletely understood, our data provide important information that statins might be useful as IOP-lowering therapy and as glaucoma treatment agents. Moreover, this action may be a newly observed pleiotropic effect of statins.

It is possible that the decrease in the IOP per se may lead to an increase in the RBF, because the OPP was determined by the systemic blood pressure and the IOP. However, the decrease in the IOP was small (approximate mean, 2 mm Hg) and the calculated OPP did not change after short-term or long-term administration of simvastatin (Figure 2B). Moreover, if the decrease in the IOP by simvastatin can increase the RBF, the RBF should be increased at 90 minutes after simvastatin administration, which was not observed in the present study. Therefore, we believe that the decrease in the IOP had little contribution to the increased RBF caused by simvastatin.

Our study had some limitations. First, this was a pilot study among a small number of healthy young men. Further study among more subjects is needed to examine the effects of age, sex, and systemic disorder, such as hyperlipidemia, hypertension, and diabetes mellitus, on the retinal circulation that are associated with systemic administration of simvastatin. Second, the increased plasma nitrite/nitrate levels may not be a direct indication of the increase in NO in the retina. The relation between the nitrite/nitrate levels in the plasma and the vitreous should be investigated.

The present data indicate that simvastatin increases the RBF in healthy subjects and that this increase may be as-

![Figure 3. Changes in plasma nitrite/nitrate levels. Asterisk indicates P<.05 compared with baseline values by repeated-measures analysis of variance followed by Dunnett procedure.](image-url)
associated with an elevation in plasma NO. Further clinical study is needed to elucidate the usefulness of statins in treating retinal ischemic diseases.

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REFERENCES