Influence of Atorvastatin Treatment on L-Arginine Cerebrovascular Reactivity and Flow-Mediated Dilatation in Patients With Lacunar Infarctions

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Background and Purpose—In our study we hypothesized that statins improve endothelial function in patients with lacunar infarctions (LI). Cerebral and systemic endothelial function was determined before and after 3-months treatment with atorvastatin.

Methods—Cerebral endothelial function was determined by L-arginine reactivity and systemic endothelial function by flow-mediated dilatation (FMD) in patients with LI (18 patients, aged 61.1±7.6 years), 20 age- and gender-matched patients with similar risk factors (SR) and 19 age- and gender-matched healthy controls. The mean arterial velocity (vm) in both middle cerebral arteries was measured by transcranial Doppler sonography before, during and after a 30-minute intravenous infusion of L-arginine. FMD of the brachial artery after hyperaemia was determined. The measurements were repeated after 3-months treatment with 40 mg of atorvastatin per day.

Results—L-arginine reactivity was decreased in LI patients (13.1±8.4%) and in patients with SR compared with healthy controls (P<0.01). FMD was more impaired in patients with LI (0.06±4.9%) compared with patients with SR and healthy controls (P≤0.01). After atorvastatin treatment, L-arginine reactivity and FMD improved in both patients with LI (17.1±7.6%; 7.0±5.7%) and patients with SR (P≤0.01). Previously mildly increased cholesterol values normalized.

Conclusion—The decreased L-arginine reactivity and FMD improve after atorvastatin treatment in both patients with LI and patients with SR. (Stroke. 2006;37:2540-2545.)

Key Words: endothelium ■ lacunar infarction ■ risk factors ■ statins ■ transcranial Doppler sonography

The role of statin therapy in the prevention of stroke is currently being determined.1 The lower incidence of cerebrovascular events after statin therapy in patients with different cerebrovascular risk factors and normal cholesterol levels suggests that statins have many properties besides their lipid-lowering effect.1,2,3 However, most studies are based on the incidence of cerebrovascular events and provide only indirect information about the mechanism of statin treatment.3,4 Animal studies have shown that the mechanism by which statins protect against stroke is likely to be multifactorial, including improving endothelial homeostasis by increasing the bioavailability of nitric oxide.5,6 However, there are no experimental human studies that would support the beneficial effect of statins on the cerebral endothelium.

Patients with lacunar infarctions (LI) are thought to have a primary endothelial impairment.7 However, it is not known whether statins improve cerebral endothelial function in these patients. On the other hand, it is not easy to evaluate cerebral endothelial function. Cerebrovascular reactivity to L-arginine, measured by transcranial Doppler sonography (TCD), is thought to reflect cerebral endothelial function.8,9,10,11 It seems that L-arginine induces vasodilatation through enhanced production of nitric oxide in the cerebral endotheliun.12 Several authors have described increased velocity through cerebral arteries, which could be a consequence of cerebral vasodilatation, after intravenous application of L-arginine.8,9,11 Furthermore, decreased cerebrovascular reactivity to L-arginine has been found in patients with LI.13 To our knowledge L-arginine cerebrovascular reactivity has not been used previously to determine the effect of statin treatment. In addition, flow-mediated dilatation (FMD), a widely used method for evaluation of endothelial function, has not been used previously to determine the effect of statin treatment in patients with LI.

The aim of our study was to investigate whether treatment with atorvastatin, a widely used statin in cerebrovascular diseases,14 improves L-arginine reactivity and FMD in patients with LI. Furthermore, we compared the effect of atorvastatin treatment on L-arginine cerebrovascular reactivity and FMD in patients with LI, subjects with similar cardiovascular risk factors (SR) and healthy controls. The patients with LI had clinically expressed disease in addi-
tion to cardiovascular risk factors\textsuperscript{15} that are themselves known to be associated with endothelial dysfunction.\textsuperscript{16}

**Materials and Methods**

Eighteen patients, aged 61.1±7.6 years, with multiple LI >4 weeks after a minor stroke or transient ischemic attack (Group A), participated in our study. The control groups consisted of 20 age-matched (62.7±5.3 years) patients with similar risk factors (Group B) and 19 age-matched (59.2±7.1 years) healthy controls (Group C). Group A comprised 10 men and 8 women; Group B, 11 men and 9 women and Group C, 11 men and 8 women. The study was approved by the National Medical Ethics Committee of the Republic of Slovenia.

Patients from Group A were recruited from the neurology outpatient clinic and hospital ward and Group B patients, with long-standing treated arterial hypertension and previously untreated hypercholesterolemia, from several general practices. CT head scans of Group A and B patients were performed within 4 weeks before study entry. Group A patients were selected on the basis of multiple lacunar infarcts using the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification system. The CT lesions had a diameter of <1.5 cm and were located subcortically or within brain stem. At least one of the lesions explained the clinical picture of the patient’s previous LI. CT head scans from all Group B patients were reported to be normal. Healthy controls, recruited from among friends and family, had been found to be healthy on regular systematic general practice risk factor assessments and did not receive any therapy.

Cardiovascular risk factors were evaluated based on patient history, clinical examination, body mass index determination, laboratory tests and electrocardiography. Laboratory tests included total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL) and blood glucose. Healthy volunteers had normal values and normal blood pressure. The patients in Groups A and B had similar risk factors for stroke (Table 1) and all had long-standing arterial hypertension. At the time of the study, patients from both groups had normal blood glucose concentrations (≤6.1 mmol/L), based on regular general practice blood glucose measurements, were included. In Group A, 13 patients were treated with an angiotensin-converting enzyme inhibitor, 4 with a calcium antagonist, 5 with a β-blocker, 2 with an α-blocker, 6 with a diuretic and 4 with a sartane. Five patients received 1 antihypertensive drug, 10 patients were on a combination of 2 drugs and the rest received >2 drugs. In Group B, 15 patients were treated with an angiotensin-converting enzyme inhibitor, 4 with a calcium antagonist, 6 with a β-blocker, 3 with an α-blocker, 5 with a diuretic and 5 with a sartane. Six patients received 1 antihypertensive drug, 9 patients were on a combination of 2 drugs and the rest received >2 drugs. None of the patients had received statin therapy before the study although cholesterol concentrations were checked regularly by the general practitioner. All patients in Group A and 10 patients in Group B received antiaggregatory therapy. With exception of atorvastatin intervention the therapy remained unchanged in all patients until the study was completed. Patients with a known source of cardiogenic embolism were excluded from the study. Color-coded duplex sonography and power Doppler sonography of the carotid arteries were performed in all patients. Patients with unstable plaques\textsuperscript{17} or significant carotid artery stenosis (≥50%) according to ultrasonographic criteria were excluded from the study.

All subjects gave informed consent to their participation in the study. The trial was performed in a quiet room under constant room conditions. In the test preparation, each subject rested for 10 to 15 minutes. The experiment consisted of a 15-minute baseline period, a 30-minute intravenous infusion of 100 mL 30% l-arginine and a 15-minute interval after l-arginine application.

The mean arterial velocity ($v_m$) was recorded bilaterally in the trunks of both middle cerebral arteries through the temporal acoustic windows. Throughout the procedure the mean arterial blood pressure (MAP) and heart rate were measured continuously using noninvasive plethysmography (Colin, CBM 7000). EtCO$_2$ was measured with an infrared capnograph (Dräger, Capnodig).

TCD software (TCD-8) was used to determine $v_m$ during the 10-minute rest interval and the 10-minute interval after l-arginine infusion. $v_m$ was calculated according to the formula:

\[ v_m = \frac{4}{d} \sqrt{\frac{2P}{d}} \]

where $d$ is the diameter of the middle cerebral artery and $P$ is the pulse pressure.

|TABLE 1. Comparison of Cerebrovascular Risk Factors for the 3 Groups: Values of Cholesterol, LDL and HDL at Study Onset and After 3 Months; Serum Glucose, Diabetes, Previously Treated Hyperlipidemia, BMI, Duration of Hypertension, No. of AH Drugs, Smoking, Excessive Alcohol Use, History of Migraine and CAD or PAD—Presence of Other Atherosclerotic Disease at Study Entry |
|---|---|---|---|---|---|---|
| | Group A Stroke Patients | Group B Patients With Risk Factors | Group C Healthy Volunteers |
| Cholesterol | 5.5±0.8 mmol/l | 5.9±0.8 mmol/l | 5.8±0.8 mmol/l |
| Cholesterol, after 3 months | 4.1±0.9 mmol/l* | 3.8±0.8 mmol/l* | 5.8±0.9 mmol/l |
| LDL | 3.6±0.6 mmol/l | 4.0±0.8 mmol/l | 3.8±0.7 mmol/l |
| LDL, after 3 months | 2.3±0.7 mmol/l* | 2.0±0.5 mmol/l* | 3.9±0.8 mmol/l |
| HDL | 1.4±0.4 mmol/l | 1.4±0.4 mmol/l | 1.4±0.3 mmol/l |
| HDL, after 3 months | 1.3±0.3 mmol/l | 1.3±0.3 mmol/l | 1.3±0.3 mmol/l |
| Serum glucose | 5.0±1.0 mmol/l | 5.3±0.7 mmol/l | 4.8±0.7 mmol/l |
| Diabetes | 0% | 0% | 0% |
| Previously treated hyperlipidemia | 0% | 0% | 0% |
| BMI | 27.5±4.0 Kg/m² | 28.1±3.7 Kg/m² | 24.8±3.2 Kg/m² |
| Duration of hypertension | 5.8±7.2 years | 9.7±7.1 year | 0±0 years |
| No. of AH drugs | 1.6±0.9 | 2.0±1.1 | 0±0 |
| Smoking | 17% | 20% | 0% |
| Excessive alcohol use | 3% | 0% | 0% |
| History of migraine | 11% | 15% | 8% |
| CAD or PAD | 28% | 25% | 0% |

*Significance of t test Between Groups

\begin{tabular}{|c|c|c|c|c|c|}
\hline
 & Group A & Group B & Group C & A–B & A–C & B–C \\
\hline
Cholesterol & 5.5±0.8 mmol/l & 5.9±0.8 mmol/l & 5.8±0.8 mmol/l & \ldots & \ldots & \ldots \\
Cholesterol, after 3 months & 4.1±0.9 mmol/l* & 3.8±0.8 mmol/l* & 5.8±0.9 mmol/l & \ldots & * & * \\
LDL & 3.6±0.6 mmol/l & 4.0±0.8 mmol/l & 3.8±0.7 mmol/l & * & \ldots & \ldots \\
LDL, after 3 months & 2.3±0.7 mmol/l* & 2.0±0.5 mmol/l* & 3.9±0.8 mmol/l & \ldots & * & * \\
HDL & 1.4±0.4 mmol/l & 1.4±0.4 mmol/l & 1.4±0.3 mmol/l & \ldots & \ldots & \ldots \\
HDL, after 3 months & 1.3±0.3 mmol/l & 1.3±0.3 mmol/l & 1.3±0.3 mmol/l & \ldots & \ldots & \ldots \\
Serum glucose & 5.0±1.0 mmol/l & 5.3±0.7 mmol/l & 4.8±0.7 mmol/l & \ldots & * & \ldots \\
Diabetes & 0% & 0% & 0% & \ldots & \ldots & \ldots \\
Previously treated hyperlipidemia & 0% & 0% & 0% & \ldots & \ldots & \ldots \\
BMI & 27.5±4.0 Kg/m² & 28.1±3.7 Kg/m² & 24.8±3.2 Kg/m² & \ldots & * & * \\
Duration of hypertension & 5.8±7.2 years & 9.7±7.1 year & 0±0 years & * & * & \ldots \\
No. of AH drugs & 1.6±0.9 & 2.0±1.1 & 0±0 & \ldots & * & * \\
Smoking & 17% & 20% & 0% & \ldots & * & * \\
Excessive alcohol use & 3% & 0% & 0% & \ldots & \ldots & \ldots \\
History of migraine & 11% & 15% & 8% & \ldots & \ldots & \ldots \\
CAD or PAD & 28% & 25% & 0% & \ldots & * & * \\
\hline
\end{tabular}

BMI indicates body mass index; AH, antihypertensive; CAD, coronary artery disease; PAD, peripheral arterial disease.

\textsuperscript{*}P<0.05; \ldots P>0.05.
MAP, heart rate, CO₂ and Et-CO₂ were calculated for the same intervals as \( v_m \) using TCD software.

The second part of the trial was performed in another ultrasound laboratory under constant conditions. The researcher (M. Sebestjen) who performed FMD was blinded as to which group the patient belonged to. FMD (endothelium-dependent) and glyceryl trinitrate (GTN)–induced dilation (endothelium-independent) of the brachial artery were studied using a high-resolution B-mode Diasonics VST ultrasound system with a 10-MHz linear array transducer. The right brachial artery was scanned in the longitudinal section and the end-diastolic mean arterial diameter was measured. The flow velocity was measured and the baseline blood flow estimated. A hyperemic flow increase was induced by inflation of a blood pressure cuff placed around the forearm to a pressure of 300 mm Hg for 4.5 minutes. Hyperemic flow was recorded and diameter measurements were taken 1 minute after cuff deflation. After vessel recovery a sublingual tablet of 0.5 mg GTN was administered and the final scan performed 5 minutes later. The endothelium-dependent and -independent dilation were expressed as the percentage change in the artery diameter.

After the patients had received treatment with 40 mg of atorvastatin per day for a period of at least 3 months the tests were repeated and blood was again collected for cholesterol measurements. Both the researcher who performed the transcranial Doppler with l-arginine reactivity (J.P.-O.) and the researcher who performed the FMD (M. Sebestjen) were blinded to the results of the previous recording. Each patient received a letter for his personal physician detailing his involvement in our study and requesting that the patient’s therapy would not be changed during the study.

The following variables were statistically analyzed by the statistic software SPSS 13.0.1: \( v_m \), MAP, heart rate, CO₂ and Et-CO₂. The paired \( t \) test was used to compare \( v_m \), MAP, heart rate, CO₂ and Et-CO₂ before and after intravenous infusion of l-arginine for each group separately before and after atorvastatin treatment. Before using 1-way ANOVA a clearly normal distribution of l-arginine reactivity and FMD was found in all 3 groups. One-way ANOVA with Bonferroni correction was used to compare the relative responses of \( v_m \) to the intravenous infusion of l-arginine in the 3 groups before and after atorvastatin treatment. The same test was used to compare FMD between the 3 groups before and after 3-months treatment. A multivariate linear model was used to control the influence of several risk factors (cholesterol, LDL, HDL, glucose, body mass index, duration of hypertension, number of antihypertensive drugs, smoking, alcohol, migraine and other atherosclerotic disease) on the initial \( v_m \) reactivity to l-arginine and FMD.

The paired \( t \) test was used to compare \( v_m \) reactivity to l-arginine and FMD before and after atorvastatin treatment in each group separately.

**Results**

During rest \( v_m \), CO₂ and Et-CO₂ did not differ between the 3 groups (Table 2). MAP and heart rate were higher in Group A (\( P<0.01 \)) compared with Groups B and C (Table 2). After 3 months the rest values of \( v_m \), CO₂ and Et-CO₂ did not differ between the 3 groups (Table 2). The heart rate was higher in Group A (\( P<0.01 \)) compared with Groups B and C (Table 2). However, MAP values were not significantly different in the 3 groups (Table 2).

**TABLE 2. Absolute Values of Parameters Before and After L-Arginine Infusion (\( v_m \), MAP, heart rate, CO₂, Et-CO₂)**

<table>
<thead>
<tr>
<th></th>
<th>Group A Stroke Patients</th>
<th>Group B Patients With Risk Factors</th>
<th>Group C Healthy Volunteers</th>
</tr>
</thead>
<tbody>
<tr>
<td>( v_m ) at rest</td>
<td>52.0±15.4 cm/s</td>
<td>50.1±13.5 cm/s</td>
<td>52.0±15.7 cm/s</td>
</tr>
<tr>
<td>( v_m ) L-A</td>
<td>59.6±19.7 cm/s</td>
<td>56.7±15.7 cm/s</td>
<td>62.4±19.8 cm/s</td>
</tr>
<tr>
<td>( v_m ) at rest, after 3 m</td>
<td>53.7±15.6 cm/s</td>
<td>52.7±16.7 cm/s</td>
<td>52.8±14.4 cm/s</td>
</tr>
<tr>
<td>( v_m ) L-A, after 3 m</td>
<td>62.3±18.4 cm/s</td>
<td>60.8±17.5 cm/s</td>
<td>63.7±18.3 cm/s</td>
</tr>
<tr>
<td>MAP at rest</td>
<td>105.1±14.4 mm Hg**</td>
<td>99.2±6.5 mm Hg</td>
<td>98.2±5.1 mm Hg</td>
</tr>
<tr>
<td>MAP L-A</td>
<td>102.2±14.9 mm Hg*</td>
<td>98.1±7.4 mm Hg</td>
<td>97.4±7.4 mm Hg</td>
</tr>
<tr>
<td>MAP at rest, after 3 m</td>
<td>97.1±7.6 mm Hg</td>
<td>99.9±6.4 mm Hg</td>
<td>99.5±6.0 mm Hg</td>
</tr>
<tr>
<td>MAP L-A, after 3 m</td>
<td>93.4±9.9 mm Hg*</td>
<td>96.3±5.6 mm Hg</td>
<td>96.3±5.6 mm Hg*</td>
</tr>
<tr>
<td>Heart rate at rest</td>
<td>67.7±9.8 bts/min**</td>
<td>61.1±10.8 bts/min</td>
<td>62.0±4.8 bts/min</td>
</tr>
<tr>
<td>Heart rate L-A</td>
<td>70.1±10.6 bts/min</td>
<td>63.1±11.0 bts/min</td>
<td>64.9±6.7 bts/min*</td>
</tr>
<tr>
<td>Heart rate at rest, after 3 m</td>
<td>64.7±8.3 bts/min**</td>
<td>61.0±11.2 bts/min</td>
<td>60.9±7.6 bts/min</td>
</tr>
<tr>
<td>Heart rate L-A, after 3 m</td>
<td>66.6±9.8 bts/min*</td>
<td>63.1±10.1 bts/min</td>
<td>64.0±7.3 bts/min*</td>
</tr>
<tr>
<td>CO₂ at rest</td>
<td>17.9±5.0 mm Hg</td>
<td>15.8±2.5 mm Hg</td>
<td>16.7±3.0 mm Hg</td>
</tr>
<tr>
<td>CO₂ L-A</td>
<td>17.6±5.5 mm Hg</td>
<td>16.4±2.4 mm Hg</td>
<td>16.6±2.7 mm Hg</td>
</tr>
<tr>
<td>CO₂ at rest, after 3 m</td>
<td>16.7±3.3 mm Hg</td>
<td>16.4±2.6 mm Hg</td>
<td>16.3±2.6 mm Hg</td>
</tr>
<tr>
<td>CO₂ L-A, after 3 m</td>
<td>16.3±3.7 mm Hg</td>
<td>16.2±2.2 mm Hg</td>
<td>16.5±2.3 mm Hg</td>
</tr>
<tr>
<td>Et-CO₂ at rest</td>
<td>28.3±5.4 mm Hg</td>
<td>29.5±2.7 mm Hg</td>
<td>30.0±3.4 mm Hg</td>
</tr>
<tr>
<td>Et-CO₂ L-A</td>
<td>27.4±5.5 mm Hg*</td>
<td>30.1±3.1 mm Hg</td>
<td>30.0±2.8 mm Hg</td>
</tr>
<tr>
<td>Et-CO₂ at rest, after 3 m</td>
<td>29.7±2.8 mm Hg</td>
<td>30.1±3.0 mm Hg</td>
<td>30.0±2.8 mm Hg</td>
</tr>
<tr>
<td>Et-CO₂ L-A, after 3 m</td>
<td>29.9±3.4 mm Hg</td>
<td>29.6±3.5 mm Hg</td>
<td>30.2±2.3 mm Hg</td>
</tr>
</tbody>
</table>

\( L-A \) indicates l-arginine. Repeated measurements, obtained after 3 months’ treatment with atorvastatin in Group A and B patients, are shown above.

*Comparison between values before and after l-arginine infusion (\( P<0.01 \)); **Comparison between values of Group A, B and C patients (\( P<0.01 \)).
During L-arginine infusion $v_m$ significantly increased in both hemispheres in the 3 groups ($P<0.01$; Table 2). The $v_m$ responses in the left and right MCA were similar in all 3 groups ($P>0.05$). A significantly higher response to L-arginine was found in females (28.4±13.1%) compared with males (18.3±8.5%; $P<0.01$) in all 3 groups of subjects collectively, as well as in Groups B and C separately. The heart rate increased in Groups B and C, but not in Group A. MAP decreased and Et-CO$_2$ increased only in Group A ($P<0.01$), whereas CO$_2$ did not change significantly during L-arginine infusion in any of the 3 groups (Table 2). After 3 months $v_m$ significantly increased, MAP decreased and heart rate increased during L-arginine infusion in all 3 groups (Table 2).

One-way ANOVA with Bonferroni correction showed that the relative $v_m$ increase after L-arginine (dv$_m$) was lower in Groups A and B compared with Group C ($P<0.01$; Table 3). The L-arginine response did not differ between Groups A and B (Table 3).

FMD was more impaired in both Group A and B patients compared with Group C ($P<0.01$; Table 3). Although the difference was not significant, FMD was more impaired in Group A patients compared with those in Group B ($P=0.08$; Table 3).

A multivariate linear model showed a significant influence of cholesterol and LDL on the initial $v_m$ reactivity to L-arginine ($P<0.05$) and a significant influence of smoking and duration of hypertension on the initial FMD ($P<0.05$) for Groups A and B ($r^2=0.501$).

Total cholesterol and LDL were significantly lower after atorvastatin treatment in Groups A and B, but remained unchanged after 3 months in Group C (Table 1). Atorvastatin treatment improved L-arginine reactivity significantly in both Groups A and B (Table 3), whereas L-arginine reactivity remained unchanged in the nontreated Group C patients. L-arginine reactivity after 3 months did not differ between the 3 groups.

FMD improved after atorvastatin treatment in Group A patients ($P<0.01$; Table 3). We also found improvement in FMD in Group B, but the change was less pronounced ($P=0.06$; Table 3). FMD remained unchanged after 3 months in Group C. After 3 months we found no difference between FMD in Groups A and C, but a significant difference remained between Groups B and C ($P<0.05$; Table 3).

**Discussion**

The main finding of our study was that atorvastatin significantly improved the decreased cerebrovascular response to L-arginine in both patients with LI and patients with SR. Similarly, FMD improved after atorvastatin treatment in both patients with LI and those with SR, with the improvement in FMD being more pronounced in the patients with LI compared with those with SR.

In our study cerebrovascular reactivity to L-arginine, which is thought to reflect cerebral endothelial function, was used to evaluate the effectiveness of treatment with atorvastatin. Previous studies have shown that intravenous infusion of L-arginine significantly increases blood flow velocity in the middle cerebral artery$^{8,9,10,11}$ and it is thought that this physiological effect is caused by increased production of nitric oxide (NO) induced by L-arginine in the endothelium of resistant cerebral vessels. Most studies have reported decreased cerebrovascular reactivity to L-arginine in patients after stroke$^{8,11}$; however, some authors have reported increased reactivity.$^{10}$ Recently, our group described decreased cerebrovascular reactivity to L-arginine in both patients with LI and those with SR.$^{13}$

The improvement in cerebrovascular reactivity to L-arginine after statin treatment in both patients with LI and those with SR has not previously been described. This improvement can probably be explained by the beneficial effects of statins on endothelial function. Statins are known to activate endothelial nitric oxide synthase (eNOS) and thereby propagate NO-dependent vasodilatation. L-arginine is a substrate for eNOS, which produces NO.$^{18}$ The eNOS conformation changes and NO production decreases under the influence of almost all cerebrovascular risk factors.$^{16}$ However, animal studies have shown that adaptation to cerebral ischemia leads to eNOS upregulation$^{19}$ and an increase in NO production.$^{20,21}$ Another aspect of this problem is the presence of definite necrotic areas of the brain and therefore a quantitative endothelial loss, which also means loss of eNOS. L-arginine cerebrovascular reactivity probably reflects all these, and possibly other effects. Because some factors down- and others upregulate the cerebral NO production in patients with LI, it is not entirely surprising that the L-arginine cerebrovascular reactivity in patients with SR is equally decreased. Nevertheless, the most important finding is that at least some of these mechanisms influencing eNOS can be reversed by atorvastatin therapy, not only in asymptomatic patients with SR, but also in patients with LI. It should be noted that the cholesterol values of our patients with LI and asymptomatic patients with SR were only mildly elevated.

**Table 3. Comparison of Cerebrovascular Reactivity to L-Arginine and FMD at Study Onset and After 3 Months, During Which Group A and Group B Patients Received Treatment With Atorvastatin**

<table>
<thead>
<tr>
<th></th>
<th>Group A Stroke Patients</th>
<th>Group B Patients With Similar Risk Factors</th>
<th>Group C Healthy Volunteers</th>
</tr>
</thead>
<tbody>
<tr>
<td>L-arginine reactivity</td>
<td>13.1±8.4%</td>
<td>13.5±8.3%</td>
<td>21.3±10.9%**</td>
</tr>
<tr>
<td>L-arginine reactivity after 3 months</td>
<td>17.1±7.6%*</td>
<td>18.2±11.0%*</td>
<td>20.2±10.2%</td>
</tr>
<tr>
<td>FMD</td>
<td>0.06±4.9%</td>
<td>3.1±4.8%</td>
<td>8.1±6.0%**</td>
</tr>
<tr>
<td>FMD after 3 months</td>
<td>7.0±5.7%*</td>
<td>5.3±3.6%***</td>
<td>8.7±4.7%**</td>
</tr>
</tbody>
</table>

*Comparison between values before and after atorvastatin treatment (Groups A and B; $P<0.01$); **Comparison between values of Groups A, B and C ($P<0.05$).
before atorvastatin therapy and normalized afterward. Our results are in agreement with previous studies, in which the improvement in endothelial function after statin therapy was attributed not only to the normalization of the cholesterol values but also to other protective mechanisms.1,2,3 We are aware of the potential bias that could exist because of the novelty of our method. However, the different responses were compared within a group and not between different groups. In addition, measurements of fixed 10-minute intervals were used instead of single values (Figure), and, therefore, even if bias was present it did not influence relative values but only absolute values, which were not used to draw the conclusion. The same predefined protocol was followed for each patient.

Cerebrovascular reactivity to L-arginine and to FMD were compared for 2 reasons: firstly, in order to evaluate a relatively new method for determination of cerebral endothelial function; and secondly, to compare cerebral and systemic endothelial function. Decreased FMD is well described in patients with cardiovascular risk factors.16 Because all our patients with LI had at least 1 risk factor, endothelial impairment could be expected because of this alone. However, only a few FMD studies on stroke patients have been undertaken. A decreased FMD response was found when symptomatic patients with carotid artery stenosis were compared with asymptomatic cases.22 A decreased FMD response was also associated with a higher incidence of stroke in some prospective studies.23 Nevertheless, before our study there was no data about the role of the FMD response in patients with LI. In addition, FMD in patients with LI and those with SR has not previously been compared. A decreased FMD response, which confirmed systemic endothelial involvement, was found in patients with LI. In addition, the FMD response in patients with LI was more impaired than that in patients with SR. Therefore, it is possible that patients with LI have a systemic predilection for endothelial damage.

The small sample size and the fact that our study was not double-blinded and randomized mean that our conclusions must be treated with caution. However, the researchers were blinded to the previous results of the studied patient and the researcher who performed FMD was blinded as to which group the patient belonged to. Although the study was not case-controlled the control groups were well balanced. Nevertheless, a large, randomized, double-blinded study would be needed in order to draw stronger conclusions.

Summary
Cerebrovascular reactivity to L-arginine was equally impaired and equally improved after atorvastatin treatment in both patients with LI and those with SR. However, FMD was more decreased and improved more after atorvastatin treatment in patients with LI compared with those with SR.

Disclosures
None.
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14. Pretnar-Oblak et al Statins and Endothelial Function in Lacunar Stroke 2545


Influence of Atorvastatin Treatment on L-Arginine Cerebrovascular Reactivity and Flow-Mediated Dilatation in Patients With Lacunar Infarctions
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