Chapter 5

Pravastatin Decreases Wall Shear Stress and Blood Velocity in the Internal Carotid Artery Without Affecting Flow Volume; Results from the PROSPER MRI Study

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Abstract

Background and Purpose Despite speculations, it is unknown whether statins affect Wall Shear Stress (WSS). Therefore, the effect of pravastatin on WSS was investigated.

Methods In 355 elderly individuals participating in the PROSPER study (FU after 3 years) the effect of pravastatin 40 mg on WSS was assessed in the internal carotid artery (ICA) using MRI.

Results WSS and blood velocity decreased both in the pravastatin group and in the placebo group but decreased faster in the pravastatin group ($p<0.04$, $p<0.02$). Blood volume flow did not differ between the groups.

Conclusion In elderly subjects the WSS and blood velocity of the ICA declines significantly over time and this decline is more pronounced in subjects treated with pravastatin 40 mg compared to the placebo group.
5.1 Introduction

Arterial vessel areas with low or oscillating Wall Shear Stress (WSS) are most prone to develop atherosclerotic plaques.¹ Statins have been shown to be important clinical pharmacological tools to prevent atherosclerosis and have other favorable effects, e.g. increasing NO availability and reducing blood viscosity.²⁻⁴ To date the possible effects of statins on WSS is unknown. An increase in WSS will decrease atherosclerotic plaques and increase NO availability, whereas a decrease in blood viscosity will reduce WSS.¹,⁵ We examined the effect of pravastatin 40 mg/day on WSS in the internal carotid artery (ICA) in subjects participating in the nested MRI study of the PROspective Study of Pravastatin in the Elderly at Risk (PROSPER).⁶

5.2 Methods

The PROSPER is a double-blind, randomized, placebo-controlled trial, aimed at assessing the effect of therapy with pravastatin 40 mg on vascular events in 5804 men and women, aged 70 to 82 years, with vascular disease or at risk for vascular disease.⁶ 355 Dutch participants of the PROSPER study had two successive MRI of the ICA, allowing the assessment of WSS. The first MRI was acquired during the lead-in period and the second MRI after an average follow-up of 33 (SD 1.4) months.

Flow measurements were performed on a 1.5 T MR-system (Philips Medical Systems) in a plane perpendicular to the ICA 4 cm distal to the bifurcation. We used a gradient echo phase-contrast technique with retrospective gating with PPU; TR/ TE 16 / 9 ms; flip angle 7.5°; slice thickness 5 mm, scan matrix 256x154, FOV 250x188 mm, VENC 100 cm/s and 1 NSA.

For a parabolic velocity profile the flow volume (Flow), the maximum velocity in the vessel cross section (Vmax), the diameter (Diam) and WSS have the following relations:⁵,⁷

\[
\text{Diam} = \sqrt{\frac{8 \text{Flow}}{\pi \text{Vmax}}} \quad (1)
\]

and

\[
\text{WSS} = 4\mu \text{Vmax}/\text{Diam} \quad (2)
\]

The viscosity (\(\mu\)) was taken as 3.39 mPa.s at baseline and 3.32 mPa.s at follow-up.⁴ The cardiac cycle was divided into 16 time phases. Parameters during systole and diastole were assessed by averaging the three consecutive phases with highest and lowest Flow respectively. For calculation of the p-values we used the linear mixed model corrected for smoking behaviour.
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Placebo (n=178)</th>
<th>Pravastatin (n=177)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y, mean ± SEM</td>
<td>75.0 ± 3.23</td>
<td>74.9 ± 3.07</td>
<td>n.s.</td>
</tr>
<tr>
<td>Male sex (%)</td>
<td>110 (61.8)</td>
<td>95 (53.7)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg, mean ± SEM</td>
<td>156 ± 20.4</td>
<td>157 ± 21.7</td>
<td>n.s.</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg, mean ± SEM</td>
<td>86 ± 10.7</td>
<td>85 ± 11.3</td>
<td>n.s.</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L, mean ± SEM</td>
<td>5.7 ± 0.91</td>
<td>5.8 ± 0.85</td>
<td>n.s.</td>
</tr>
<tr>
<td>LDL cholesterol mmol/L, mean ± SEM</td>
<td>3.9 ± 0.77</td>
<td>3.9 ± 0.75</td>
<td>n.s.</td>
</tr>
<tr>
<td>HDL cholesterol, mmol/L, mean ± SEM</td>
<td>1.3 ± 0.32</td>
<td>1.2 ± 0.34</td>
<td>n.s.</td>
</tr>
<tr>
<td>Current smoker, n (%)</td>
<td>51 (28.7)</td>
<td>28 (15.8)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>History of diabetes, n (%)</td>
<td>30 (16.9)</td>
<td>24 (13.6)</td>
<td>n.s.</td>
</tr>
<tr>
<td>History of hypertension, n (%)</td>
<td>102 (57.3)</td>
<td>119 (67.2)</td>
<td>n.s.</td>
</tr>
<tr>
<td>History of myocardial infarction, n (%)</td>
<td>26 (14.6)</td>
<td>21 (11.9)</td>
<td>n.s.</td>
</tr>
<tr>
<td>History of stroke or transient ischemic attack, n (%)</td>
<td>37 (20.8)</td>
<td>24 (13.6)</td>
<td>n.s.</td>
</tr>
<tr>
<td>History of any vascular disease, n (%)</td>
<td>83 (46.6)</td>
<td>78 (44.1)</td>
<td>n.s.</td>
</tr>
</tbody>
</table>

Table 1. Baseline Characteristics
5.3 Results

Baseline characteristics for the 355 participants are presented in Table 1. In the pravastatin group LDL decreased from 3.9 ± 0.8 mmol/L to 2.5 ± 0.5 mmol/L and HDL increased from 1.2 ± 0.3 mmol/L to 1.3 ± 0.4 mmol/L at follow-up, cholesterol in the placebo group remained unaltered. This was similar to the entire PROSPER study group. We found no significant differences in blood pressure between the two groups. Errors in data conversion and positioning of the scan plane left 328 vessels in the pravastatin group and 334 vessels in the placebo group for analysis. WSS, Flow, Vmax and Diam data are presented in Table 2. At baseline there were no significant differences in these parameters between the groups. At follow-up, WSS and Vmax-M showed a significant decrease in both groups. However, in the pravastatin group the decrease in WSS and Vmax and the increase in Diam was larger than in the control group (p < 0.05).

5.4 Discussion

Our study indicates that WSS, decreases faster over time in elderly individuals treated with pravastatin than in those treated with placebo. This finding is surprising since it can be
Table 2. WSS and related parameters
The results are: Flow in mL/min, Vmax in mm/s, Diam in mm and WSS in Pa with ± the SD. M, S and D refer to mean values over the cardiac cycle, systole and end-diastole, respectively. There was no significant difference at the baseline between the groups for all parameters. The difference at follow-up is given in the column ‘Diff pravastatin-placebo’. p < 0.05 is indicated with *.
expected that because of its reducing effect on atherosclerosis, pravastatin would lead to less decrease of WSS over time.

We confirmed WSS decline with age measured by Gnasso et al., in both groups.\textsuperscript{5} A decrease in Flow or Vmax, in the paraboloid model, gives a WSS decrease and a diameter increase gives a WSS decrease. The faster WSS decrease in the paravastatin group is probably caused by the fast decrease in Vmax. Since blood velocity increases in the presence of a stenosis,\textsuperscript{8} a relative decrease in Vmax might reflect a decrease of stenoses. Due to the limited resolution of our MRI protocol, the diameter could not be measured directly. An increase in diameter for the pravastatin group is in agreement with Stroes et al.\textsuperscript{9} However, a faster decay of Vmax compared to Flow would give a wrong impression of diameter increase (eq 1).

5.5 Summary

In elderly subjects the WSS and Vmax of the ICA declines significantly over time and this decline is more pronounced in subjects treated with pravastatin 40 mg compared to the placebo group.

Appendix


Endpoint Committee:

References


