Effect of Statin Therapy on Arterial Stiffness in Patients with Hyperlipidemia: Shiga Pravastatin Atherosclerosis Study (SHIPAS) Group

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KEY WORDS: arterial stiffness, hypertension, pravastatin

ABSTRACT
A man is as old as his arteries and the vascular remodeling is a common problem in the elderly. Aortic pulse wave velocity (PWV) provides noninvasive measurement of the mechanical properties of arteries. Objective: We measured the effects of HMA-CoA inhibitor (pravastatin) on arterial stiffness, ankle brachial index, PWV, and blood pressure (BP) in patients with hyperlipidemia.

Design and Methods: The present study involved 15 patients (mean age 65 ± 2.7 years) with hyperlipidemia who were not on any medication. Aortic pulse wave velocity was evaluated at baseline and following 3 months of drug intake (pravastatin 10 mg/day). Twenty healthy volunteers constituted a control group.

Results: Following 6 months of conventional treatments of hyperlipidemia, brachial systolic BP and diastolic BP did not change significantly with pravastatin from baseline (Not significant; NS). The PWV decreased significantly after treatment with pravastatin (1912 ± 90.3 vs 1755 ± 96.9 cm/sec, P < 0.001). There was no significant difference in control subjects (1677 ± 71.5 vs 1796 ± 56 cm/sec. NS). The decrease in PWV with pravastatin was independent of blood pressure (P < 0.05).

Conclusions: The study shows that HMA-CoA inhibitor might improve arterial wall stiffness in patients with hyperlipidemia.

INTRODUCTION
Statins have been found to significantly reduce myocardial infarctions or cardiac deaths and also to reduce the total mor-
tality based on the results of clinical mega-trials.\textsuperscript{1,2}

Recent epidemiologic studies have shown that, independently of confounding factors as age, blood pressure, and cardiac mass, aortic pulse wave velocity (PWV) is a predictor of cardiovascular mortality in populations of hypertensive subjects,\textsuperscript{3} whether they have or not end-stage renal disease.\textsuperscript{4} Because aortic PWV is predominantly influenced by age, this finding might be of major importance for the evaluation of cardiovascular risk in geriatric populations. Aortic pulse wave velocity (PWV), a classic index of aortic stiffness, can be measured easily in humans using noninvasive ultrasound methods of high reproducibility.\textsuperscript{5} Therefore, we examined the PWV before and after treatment with pravastatin in patients with hyperlipidemia.

**METHODS**

The study subjects included consecutive patients who attended clinics of Shiga Pravastatin Arteriosclerosis Study Group (SHIPASS), between September 2002 and December 2003 and who had a diagnosis of arterial stiffness with brachial-ankle pulse wave velocity (baPWV). In 15 patients, age 32 to 70 years, with hyperlipidemia, or subjects without hyperlipidemia, the ability of pravastatin to modify aortic stiffness after a 24-week treatment was evaluated. Demographic data with details of cardiovascular risk factors were collected on the day when PWV was measured. Diabetes and hypertension were indicated by a previous diagnosis or by the use of an oral hypoglycemic agent or an anti-hypertensive drug. Smoking status was defined as current or past versus never.

**Measurement of Pulse Wave Velocity**

Brachial-ankle pulse wave velocity was measured using a volume-plethysmographic apparatus (form PWV/ABI; Colin, Co., Ltd., Komaki, Aichi, Japan). This instrument records PWV, blood pressure, electrocardiogram, and heart sounds simultaneously.\textsuperscript{6} Electrocardiographic electrodes were placed on both wrist, and cuffs were wrapped around both brachia and ankles. Pulse volume waveforms at the brachium and ankle were recorded using a semiconductor pressure sensor. The brachial-ankle PWV was measured after the subject had rested for at least 5 minutes.\textsuperscript{5}

**Laboratory Measurement**

Plasma total cholesterol, high density lipoprotein cholesterol, and blood sugar were measured enzymatically. All blood samples were obtained in the morning after an overnight fast.

**Statistics** Data are expressed as means \( \pm \) standard deviation of the mean (SD). Wilcoxon’s \( t \) test was used for comparison of the 2 groups. A \( P \) value of \( < 0.05 \) was considered statistically significant.

**RESULTS**

Clinical characteristics in all subjects are listed in Table 1. There was no significant difference in baseline values between the hyperlipidemia group and the non-hyperlipidemia group.

**Changes in lipid status after treatment with pravastatin**

In 15 patients with hypercholesterolemia, the average total cholesterol level at baseline was 256 \( \pm \) 8.5 mg/dL, and pravastatin decreased the total cholesterol level to 219 \( \pm \) 3.4 mg/dL. Pravastatin also significantly decreased LDL cholesterol level (145 \( \pm \) 2.5 mg/dL to 120 \( \pm \) 2.7 mg/dL). The level of triglyceride decreased significantly from 252 \( \pm \) 14 to 188 \( \pm \) 12 with pravastatin.

**Blood Pressure and Pulse Wave Velocity**

Brachial systolic blood pressure and
diastolic blood pressure did not decrease significantly with from baseline pravastatin ($P < 0.01$).
At baseline, PWV was significantly correlated to systolic blood pressure ($r = 0.75$, $P < 0.01$) and diastolic blood pressure ($r = 0.6$, $P < 0.01$).

Figure 1 depicts baPWV in patients with hyperlipidemia. The PWV decreased significantly after the 6-month treatment with pravastatin (1912 ± 90.3 vs 1755 ± 96.9 cm/sec, $P < 0.001$), in part, there was no significant difference in control subjects (1677 ± 71.5 vs 1796 ± 56 cm/sec, no significance) (Figure 2). The decrease in PWV with pravastatin was independent of blood pressure ($P < 0.05$).

**DISCUSSION**

This study prospectively showed that pravastatin, a 3-hydroxy-3-methylglutaryl coenzyme A (HMGCo-A) reductase inhibitor, was effective in reducing arterial stiffness in patients with hyperlipidemia.

Arterial wall stiffness can be noninvasively assessed by either direct or indirect methods.$^{6,7}$ Direct techniques involve the measurement of relative change in arterial diameter and pressure during the cardiac cycle. Indirect measurements are also used, including pulse wave velocity (PWV) and augmentation of the central arterial pressure due to early pulse wave reflection.$^{7}$ The PWV is widely used as an indirect index of arterial distensibility. Patients with hyperlipidemia are known to have stiffer arteries and abnormal PWV. Recent study showed that statin decreases cardiovascular events even in normocholesterolemic hypertensive patients.$^{8}$ It is reported generally that increased arterial PWV is associated with increased cardiovascular risk factors and events.$^{1}$

Aging and diabetic status are known to be associated with decreased elasticity of large arteries. In an observational study on 127 hypertensive patients with hypercholesterolemia, the use of pravastatin or simvastatin in combination with antihypertensive drugs was related with a greater reduction in both systolic and diastolic pressure compared with hypertensive medication alone.$^{9}$

Pathogenesis of atherosclerosis involves multiple factors: hypertension as a physical factor, hyperlipidemia, hyperhomocysteinemia and parathyroid hormone as a metabolic factors, and C-reactive protein and reactive oxygen species as inflammatory factors. Recent reports have demonstrated that in addi-
Table 1. Baseline Clinical Characteristics of Study Subjects

<table>
<thead>
<tr>
<th>Clinical and lipid characteristics</th>
<th>Hyperlipidemia (n = 15)</th>
<th>Control (n = 20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (M:F)</td>
<td>8:7</td>
<td>10:10</td>
</tr>
<tr>
<td>Age (years)</td>
<td>65 ± 2.7</td>
<td>60 ± 3.2</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>161 ± 2.6</td>
<td>158 ± 2.4</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>59.5 ± 2.9</td>
<td>61 ± 2.2</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>22.8 ± .077</td>
<td>23.4 ± 0.69</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>139 ± 4.6</td>
<td>136 ± 4.3</td>
</tr>
<tr>
<td>Diastolic blood pressure</td>
<td>83.7 ± 3.2</td>
<td>80.9 ± 2.2</td>
</tr>
<tr>
<td>Total cholesterol (mg/dL)</td>
<td>256 ± 8.5</td>
<td>180 ± 8.4</td>
</tr>
<tr>
<td>LDL cholesterol (mg/dL)</td>
<td>145 ± 2.5</td>
<td>103 ± 7.8</td>
</tr>
<tr>
<td>Triglyceride (mg/dL)</td>
<td>252 ± 14</td>
<td>151 ± 29</td>
</tr>
<tr>
<td>Diabetes</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Smoking</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Hypertension</td>
<td>3</td>
<td>1</td>
</tr>
</tbody>
</table>

BMI indicates body mass index; and LDL, low-density lipoprotein.

...tion to their lipid-lowering effects, statins have many pleiotropic effects, such as inhibiting oxidative stress, improving endothelial function, decreasing vascular inflammation, and enhancing plaque stability. Statins have been reported to improve endothelial function through superoxide dismutase-mediated antioxidant effects.10 Furthermore, cholesterol reduction with pravastatin improves endothelial-dependent vascular function and might cause significant vasodilatation.11-14 Aortic pulse wave velocity appears to be a useful clinical indicator to quantify the magnitude of arteriosclerosis in patients with hyperlipidemia.

A limitation of this study was the small number of subjects. Further study in a greater number of subjects is needed to establish exact clinical significance of the treatment.

In conclusion, the present study documents the novel observation that pravastatin therapy results in a significant reduction of arterial stiffness, and suggests that long-term studies in humans are needed to evaluate the contribution of arterial elasticity to statin-induced vascular remodeling.

REFERENCES


