Clinical research

Impaired myocardial vasodilatation during hyperaemic stress is improved by simvastatin but not by pravastatin in patients with hypercholesterolaemia

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KEYWORDS
Hypercholesterolaemia; Simvastatin; Pravastatin; Coronary circulation; Positron emission tomography

Aims Impaired myocardial vasodilatation during hyperaemic stress with dipyridamole has been documented in hypercholesterolaemics without evidence of ischaemia. This study investigated whether two commonly used hydroxymethylglutaryl coenzyme A reductase inhibitors, simvastatin and pravastatin, are equally effective in restoring myocardial vasodilatation.

Methods and results Forty-four hypercholesterolaemics with a low probability of coronary artery disease and 22 controls were studied. Before and after lipid-lowering therapy with simvastatin (n = 22) or pravastatin (n = 22), myocardial blood flow at rest and during dipyridamole loading was measured using positron emission tomography with $[^{13}\text{N}]$ammonia, and myocardial vasodilatation was assessed. Treatments with simvastatin and pravastatin similarly reduced plasma total cholesterol and plasma low-density lipoprotein cholesterol. Resting myocardial blood flow was comparable in the controls, simvastatin group, and pravastatin group and unchanged after therapy. Myocardial blood flow during dipyridamole loading and myocardial vasodilatation was lower in the two therapy groups before treatment than in the controls. These parameters improved significantly after therapy with simvastatin, whereas no improvement was observed after pravastatin therapy. The per cent change in myocardial vasodilatation after simvastatin therapy was significantly and inversely correlated with per cent changes in plasma lipid fractions.

Conclusion Diminished myocardial vasodilatation in hypercholesterolaemics is improved by simvastatin but not by pravastatin, suggesting differences in vascular effects among statins.

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Introduction

It has been widely recognized that myocardial vasodilatation during hyperaemic stress decreases according to the severity of coronary artery stenosis.1 Myocardial blood flow can be measured noninvasively and quantitatively by positron emission tomography with \[^{13}N\]ammonia.2 The measurement of myocardial blood flow with the administration of dipyridamole or adenosine makes it possible to estimate myocardial vasodilatation during hyperaemic stress and provides important insights into the abnormalities of coronary circulation. Clinical studies using positron emission tomography in hyperlipidaemia have demonstrated decreased myocardial vasodilatation during hyperaemic stress in patients with no evidence of myocardial ischaemia and in myocardial segments perfused by angiographically normal coronary arteries.4,9 This reduction is thought to reflect diffuse coronary artery damage prior to progression to overt coronary artery disease.8–10 Since acute myocardial infarction mostly occurs at sites not previously exhibiting angiographically significant coronary stenosis,11 coronary angiography is insufficient to assess the risk of coronary events. The evaluation of myocardial vasodilatation during hyperaemic stress provides a marker of coronary atherosclerosis that is different from angiographic findings and is expected to contribute to sophisticating strategies to prevent coronary heart disease.12

Studies have demonstrated the effectiveness of lipid-lowering therapy for preventing coronary events13–17 and inducing the regression of coronary artery stenosis.18 Multicentre trials have shown that hydroxymethylglutaryl coenzyme A reductase inhibitors, or statins, aid in preventing ischaemic heart disease.14–17 Statin therapy has been reported to be more effective for reducing the incidence of ischaemic events than percutaneous coronary revascularisation.19 Prevention of coronary events by statins may result, at least in part, from improvement in the diffuse damage to coronary arteries without significant stenosis. It may be inferred that improvement of myocardial vasodilatation during hyperaemic stress may occur in association with improvement of diffuse coronary artery damage after statin therapy. However, studies have shown discrepant results, namely significant improvement20,22 as well as the absence of significant improvement,23,24 in the effects of statins on myocardial vasodilatation in hyperlipidaemia. The statins used in previous studies have varied, as have patient populations, with patients having no evidence of myocardial ischaemia being examined in some studies22,24 and those with ischaemic heart disease being studied in others.20,21,23 Such differences in study design may have contributed to the discrepant results.

We measured myocardial blood flow at rest and during dipyridamole loading in hypercholesterolaemic patients without evidence of myocardial ischaemia to estimate myocardial vasodilatation during hyperaemic stress. Myocardial vasodilatation was evaluated before and after lipid-lowering therapy using two representative hydroxymethylglutaryl coenzyme A reductase inhibitors, simvastatin and pravastatin. This study aimed to clarify the effects of these two statins on impaired myocardial vasodilatation in hypercholesterolaemia and to determine whether or not the effect of the two statins differed.

Methods

Study population

Forty-four patients with hypercholesterolaemia (25 males, 19 females) and 22 control subjects (16 males, 6 females) were studied. The patients were referred from local health service centres to the University of Tokyo hospital for hypercholesterolaemia. Those who had no signs or symptoms of myocardial ischaemia and had not taken lipid-lowering drugs underwent resting electrocardiography and a symptom-limited treadmill test, and patients with normal results were enrolled in the study. Since hyperglycaemia can reduce myocardial vasodilatation during hyperaemic stress,25–27 diabetic patients were excluded to eliminate such an effect from our study. Patients with essential hypertension were also excluded. Among the patients, 23 had hypercholesterolaemia (fasting plasma total cholesterol >232 mg/dl) and 21 had mixed combined hyperlipidaemia (fasting plasma triglycerides over 14 h >200 mg/dl and plasma total cholesterol >232 mg/dl). No patients were on any medication at entry, and only statins were used during the study period. Control subjects were selected from healthy volunteers without a history of heart disease or chronic disease. Evaluation before enrolment consisted of a detailed medical history, physical examinations, laboratory tests, resting electrocardiography, and symptom-limited treadmill testing. Exclusion criteria included hyperlipidaemia, hyperglycaemia, hypertension, abnormal resting electrocardiography, and abnormal symptom-limited treadmill testing. Volunteers with signs or symptoms of myocardial ischaemia and those taking medications also were excluded. The general characteristics of our study subjects are summarised in Table 1. All study subjects were informed of the nature of the study and agreed to participate in the study protocol, which was approved by the local Ethics Committee.

Lipid-lowering therapy

Patients were randomly divided into the simvastatin therapy group (n = 22, 10 mg/day for 17 patients, 5 mg/day for 5 patients) and the pravastatin therapy group (n = 22, 20 mg/day for 17 patients, 10 mg/day for 5 patients) according to the day of their first arrival at our hospital. Simvastatin was prescribed for the patients who first arrived on an even-numbered day, while pravastatin was prescribed for the others. There were no significant differences between the control group and the two therapy groups in age, body weight, height, body mass index, smoking habit, haemoglobin A1c level, systolic blood pressure, diastolic blood pressure, heart rate, or rate-pressure product. The dosage of each drug was decided according to the severity of hypercholesterolaemia. When plasma total cholesterol was 250 mg/dl or more, the dosage of simvastatin was 20 mg/dl and that of pravastatin was 10 mg/day and that of pravastatin was 20 mg/day. When plasma total cholesterol was less than 250 mg/dl, the dosage of simvastatin was 5 mg/day and that of pravastatin was 10 mg/day. No change in medications was made during the course of the study. Plasma lipid fractions were measured two or three times a month during treatment.
Regional myocardial blood flow (ml/min/100 g) at rest and during hyperaemic stress with dipyridamole was measured by positron emission tomography and \([^{13}\text{N}]\)ammonia tracer kinetic model,2,3 before the initiation of lipid-lowering therapy. Lipid-lowering therapy was started immediately after the first measurement, and a second measurement was undertaken 8–12 months after the initiation of therapy. The duration of statin therapy, i.e., the time interval between the first and second measurements, was similar in the two groups (simvastatin, 10.1 ± 1.9 months; pravastatin, 10.2 ± 2.1 months).

Myocardial flow images were obtained using a Headmate IV positron emission tomography scanner (Shimadzu Corp., Kyoto, Japan). After acquiring transmission data for 8 min to correct for photon attenuation, 555–740 MBq (15–20 mCi) of \([^{13}\text{N}]\)ammonia was injected and dynamic positron emission tomography was performed for 2 min (eight 15-s frames), followed by static scanning for 4 min. Fifty-five minutes after the injection of \([^{13}\text{N}]\)ammonia, dipyridamole (0.56 mg/kg) was administered intravenously over a 4-min period. Five minutes after the end of dipyridamole infusion, 555–740 MBq of \([^{13}\text{N}]\)ammonia was injected again, and a second dynamic scan was performed for 2 min followed by static scanning for 4 min. The interval between resting and stress studies was chosen to allow for the decay of tracer radioactivity. Dynamic data were obtained for seven slices and static data for 14 slices. Twenty-four hours before positron emission tomography, xanthine-containing beverages, smoking, and medications were withheld from all study subjects.

### Data analysis

Regional myocardial blood flow was calculated according to the two-compartment, \([^{13}\text{N}]\)ammonia tracer kinetic model,2,3 details of which can be found in our previously published papers.4,5 An operator who was unaware of the clinical information set the regions of interest for all studies. According to the description by Krivokapitch et al.,2 eight segments (two segments each for the septum, anterior wall, lateral wall, and infero-posterior wall) were defined on transaxial images, and a region of interest was selected manually for each segment. To obtain input function, regions of interest were placed in the left ventricular cavity. The same regions of interest were used for the resting and stress images of a single study. Tracer spillover was corrected by least-square nonlinear regression analysis under the assumption that myocardial and left ventricular radioactivity influenced one another. To avoid the influence of the partial volume effect associated with the object’s size, recovery coefficients were applied when calculating regional myocardial blood flow. Wall thicknesses for the septum, anterior wall, lateral wall, and infero-posterior wall were measured by two-dimensional echocardiography by specialists in our hospital, and the mean value was used to determine the recovery coefficient for each subject. The relation between wall thickness and the recovery coefficient was defined from experimental phantom studies in our laboratory. The recovery coefficient was 0.8 when myocardial wall thickness was 10 mm. Myocardial blood flow was determined as the average of regional values.

The myocardial vasodilatation index (MVI) was defined as a marker of myocardial vasodilatation during hyperaemic stress by the following equation:

\[
\text{MVI} = \frac{MBF \text{ during dipyridamole loading} - MBF \text{ at rest}}{MBF \text{ at rest}}
\]

where \(MBF\) is myocardial blood flow. The per cent change in the myocardial vasodilatation index was calculated by the following equation:

\[
\% \text{ Change of MVI} = \frac{100 \times (\text{MVI after therapy} - \text{MVI before therapy})}{\text{MVI before therapy}}
\]

The per cent changes of myocardial blood flow at rest, myocardial blood flow during dipyridamole loading, plasma total cholesterol, plasma low-density lipoprotein cholesterol, and plasma triglycerides were similarly computed. In addition, the

### Table 1  General characteristics of study subjects

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Simvastatin group</th>
<th>Pravastatin group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before therapy</td>
<td>After therapy</td>
<td>Before therapy</td>
</tr>
<tr>
<td>No. (M/F)</td>
<td>22 (16/6)</td>
<td>22 (12/10)</td>
<td>22 (13/9)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>53.7 ± 9.2</td>
<td>51.8 ± 9.1</td>
<td>55.9 ± 9.7</td>
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<tr>
<td>BW</td>
<td>62.0 ± 9.1</td>
<td>58.8 ± 8.6</td>
<td>59.4 ± 10.9</td>
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<tr>
<td>HT</td>
<td>163.6 ± 7.6</td>
<td>158.9 ± 7.9</td>
<td>158.4 ± 9.6</td>
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<tr>
<td>BMI</td>
<td>23.1 ± 2.3</td>
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<td>5/0–10</td>
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<td>Hba1c</td>
<td>5.38 ± 0.27</td>
<td>5.25 ± 0.55</td>
<td>5.23 ± 0.40</td>
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<tr>
<td>SBP at rest</td>
<td>129.3 ± 10.9</td>
<td>132.9 ± 19.5</td>
<td>136.6 ± 18.5</td>
</tr>
<tr>
<td>DBP at rest</td>
<td>75.4 ± 7.1</td>
<td>82.0 ± 13.9</td>
<td>74.4 ± 10.4*</td>
</tr>
<tr>
<td>HR at rest</td>
<td>63.3 ± 8.2</td>
<td>64.9 ± 10.5</td>
<td>64.7 ± 13.8</td>
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<tr>
<td>RPP at rest</td>
<td>868 ± 1168</td>
<td>8624 ± 1988</td>
<td>8342 ± 2639</td>
</tr>
<tr>
<td>SBP with DP</td>
<td>120.0 ± 10.2</td>
<td>123.7 ± 21.7</td>
<td>125.6 ± 19.8</td>
</tr>
<tr>
<td>DBP with DP</td>
<td>69.4 ± 6.6</td>
<td>76.3 ± 17.2</td>
<td>73.5 ± 18.0</td>
</tr>
<tr>
<td>HR with DP</td>
<td>85.8 ± 8.5</td>
<td>81.4 ± 15.5</td>
<td>83.4 ± 18.2</td>
</tr>
<tr>
<td>RPP with DP</td>
<td>10288 ± 1334</td>
<td>10169 ± 2979</td>
<td>10572 ± 3163</td>
</tr>
</tbody>
</table>

Data are presented as means ± standard deviation except for smoking. Smoking data are presented as median/interquartile range.

* p < 0.05 vs. before therapy.
coronary resistance index (CRI) was calculated with the following equation:

\[
\text{CRI} = \frac{\text{MBF during dipyridamole loading}}{\text{MAP during dipyridamole loading}} - \frac{\text{SBP}}{3},
\]

where MAP is mean arterial pressure. Mean arterial pressure was calculated as follows:

\[
\text{MAP} = \frac{(\text{SBP} + \text{DBP}) \times 2}{3},
\]

where SBP is systolic blood pressure and DBP is diastolic blood pressure. The per cent change in the coronary resistance index also was obtained.

Static images of positron emission tomography with \([^{13}\text{N}]\text{ammonia}, \) which represent the distribution of myocardial blood flow, were analysed by visual inspection to assess the presence of regional hypoperfusion. Two specialists who had no information about the subject interpreted the images independently (I.Y., Y.I).

Statistical analysis

Values are expressed as means ± standard deviation. Data obtained before and after treatment for a given therapy group were compared using the Student paired \(t\) test. Differences between two groups were examined with the Student unpaired \(t\) test for parametric distributions and Mann–Whitney test for nonparametric distributions. Comparisons between the groups were made by one-way analysis of variance followed by Kruskal–Wallis test followed by Bonferroni’s Fisher’s least significant difference tests for parametric distributions and Mann–Whitney test for nonparametric distributions. Comparisons between two groups were examined with the Student unpaired \(t\) test. Differences between the groups were compared using the Student paired \(t\) test. Differences

Comparisons between three groups were made by one-way analysis of variance followed by Bonferroni’s method for nonparametric distributions. The per cent change of the myocardial vasodilatation index was compared with the per cent changes of plasma lipid fractions by linear regression analysis. A \(p\) value of less than 0.05 was considered statistically significant.

From previous reports,22 24 the per cent changes of the myocardial vasodilatation index after simvastatin therapy and pravastatin therapy were estimated at 44.1 ± 40.0 and 11.2 ± 40.0, respectively. The sample size calculations using these values indicated that 20 patients would be required for each group in order to detect between-group differences with a type I error of 0.05 (two-tailed) and a power of 80%. In anticipation of a 5% patient dropout rate, it was decided to recruit a total of 44 patients.

Results

Haemodynamic responses to dipyridamole infusion

Before therapy, systolic blood pressure, diastolic blood pressure, heart rate, and the rate-pressure product at rest and during dipyridamole loading did not differ significantly between the control group, simvastatin therapy group, and pravastatin therapy group (Table 1). Diastolic blood pressure at rest was significantly reduced in the simvastatin group after therapy \((p = 0.019)\), but other parameters did not change significantly. Systolic blood pressure, diastolic blood pressure, heart rate, and the rate-pressure product at rest and during dipyridamole loading did not differ significantly between the two therapy groups after treatment and the control group. During dipyridamole loading, no typical chest pain or chest oppression was observed in any subjects.

Plasma lipid fractions before and after lipid-lowering therapy

Before therapy, plasma total cholesterol, plasma low-density lipoprotein cholesterol, and plasma triglycerides did not differ significantly between the simvastatin group and pravastatin group (total cholesterol, \(p = 0.828\); low-density lipoprotein cholesterol, \(p = 0.595\); triglycerides, \(p = 0.837\)) and were significantly higher in both the simvastatin group (total cholesterol, \(p < 0.001\); low-density lipoprotein cholesterol, \(p < 0.001\); triglycerides, \(p < 0.001\)) and pravastatin group (total cholesterol, \(p < 0.001\); low-density lipoprotein cholesterol, \(p < 0.001\); triglycerides, \(p = 0.001\)) than in the control group (Table 2). Plasma high-density lipoprotein cholesterol did not differ significantly between the controls and the two therapy groups before treatment \((p = 0.568)\).

Plasma total cholesterol was significantly reduced after lipid-lowering treatment in both therapy groups \((p < 0.001 for both)\), but was still higher than in the controls (simvastatin, \(p = 0.008\); pravastatin, \(p = 0.006\)). Plasma low-density lipoprotein cholesterol in both groups was significantly reduced after treatment \((p < 0.001 for both)\), to a level comparable to that of the

<table>
<thead>
<tr>
<th>Table 2 Plasma lipid fractions</th>
<th>Control</th>
<th>Simvastatin group</th>
<th>Pravastatin group</th>
</tr>
</thead>
<tbody>
<tr>
<td>TC</td>
<td>Before therapy</td>
<td>After therapy</td>
<td>TC</td>
</tr>
<tr>
<td>TC</td>
<td>194.8 ± 15.4</td>
<td>271.4 ± 40.7****</td>
<td>214.9 ± 29.2****</td>
</tr>
<tr>
<td>LDL</td>
<td>117.3 ± 19.3</td>
<td>178.5 ± 48.9****</td>
<td>126.7 ± 33.7*</td>
</tr>
<tr>
<td>TG</td>
<td>108.6 ± 40.8</td>
<td>205.7 ± 131.4****</td>
<td>165.9 ± 94.6****</td>
</tr>
<tr>
<td>HDL</td>
<td>52.9 ± 16.7</td>
<td>56.3 ± 12.1</td>
<td>56.3 ± 12.4</td>
</tr>
</tbody>
</table>

**TC**, plasma total cholesterol (mg/dl); LDL, plasma low-density lipoprotein cholesterol (mg/dl); TG, plasma triglycerides (mg/dl); HDL, plasma high-density lipoprotein cholesterol (mg/dl).

\(* p < 0.001 vs. before therapy.\)

\(p < 0.05 vs. control.\)

\(p < 0.01 vs. control.\)

\(p < 0.001 vs. control.\)
controls. Plasma triglycerides in both therapy groups
tended to decrease after treatment, but the difference
between levels before and after treatment did not reach
statistical significance (simvastatin, \( p = 0.065 \); pravas-
tatin, \( p = 0.052 \)). Plasma high-density lipoprotein chole-
sterol did not change after therapy (simvastatin, \( p = 0.941 \); pravastatin, \( p = 0.105 \)).
The per cent changes of plasma total cholesterol,
plasma low-density lipoprotein cholesterol, and plasma
triglycerides were \(-19.9 \pm 10.5, -27.1 \pm 14.5, \) and
\(-11.1 \pm 29.6, \) respectively, in the simvastatin therapy
group, and \(-19.7 \pm 8.4, -29.5 \pm 10.1, \) and \(-14.1 \pm 30.8, \) respectively, in the pravastatin therapy group. No sig-
nificant differences were observed between the two
groups (total cholesterol, \( p = 0.925 \); low-density lip-
protein cholesterol, \( p = 0.324 \); triglycerides, \( p = 0.542 \)).

Static positron emission tomography

Static flow images at rest and during dipyridamole load-
ing did not show any regional hypoperfusion in the left
ventricular wall, and occult coronary artery disease was
not evident in any subject of either therapy group or the
control group.

Myocardial blood flow at rest and during
dipyridamole loading

Before therapy, myocardial blood flow at rest (ml/min/
100 g) did not differ significantly between the controls,
simvastatin therapy group, and pravastatin therapy
group (control, 72.6 \pm 17.2; simvastatin, 78.0 \pm 14.1;
pravastatin, 78.2 \pm 14.4; \( p = 0.396 \)). Lipid-lowering
therapy did not alter resting myocardial blood flow in the
simvastatin group (78.2 \pm 12.0, \( p = 0.964 \)) or pravastatin
group (81.7 \pm 17.7, \( p = 0.297 \)) (Fig. 1).

Before therapy, myocardial blood flow during dipy-
ridamole loading was significantly lower in the simva-
statin group (181.0 \pm 49.9, \( p = 0.003 \)) and pravastatin

group (174.7 \pm 71.8, \( p = 0.001 \)) than in the controls
(254.5 \pm 105.8), whereas there was no significant dif-
tance between the two therapy groups (\( p = 0.795 \)).
Myocardial blood flow during dipyridamole loading in the
simvastatin group increased significantly after therapy
(248.7 \pm 103.9, \( p = 0.003 \)), to a level comparable to that
of controls, whereas no significant improvement was
observed in the pravastatin group (195.3 \pm 75.3, 
\( p = 0.131 \)) (Fig. 2). Lipid-lowering therapy significantly
reduced the coronary resistance index (mmHg \times
min \times 100 g/ml) in the simvastatin group (0.560 \pm 0.240
before therapy, 0.439 \pm 0.219 after therapy, \( p = 0.011 \))
but not in the pravastatin group (0.596 \pm 0.210 before
therapy, 0.553 \pm 0.310 after therapy, \( p = 0.340 \)).

Myocardial vasodilatation during hyperaemic
stress

Prior to treatment, the myocardial vasodilatation index
was significantly lower in the simvastatin therapy group
(2.36 \pm 0.67, \( p < 0.001 \)) and pravastatin therapy group
(2.21 \pm 0.72, \( p < 0.001 \)) than in the controls
(3.50 \pm 1.14), but no significant difference was found
between the two therapy groups (\( p = 0.548 \)). The myo-
cardial vasodilatation index increased significantly in the
simvastatin group after treatment (3.18 \pm 1.22, 
\( p = 0.007 \)), but showed no significant change in the
pravastatin group (2.32 \pm 0.64, \( p = 0.410 \)) (Fig. 3). The
myocardial vasodilatation index after simvastatin ther-
apy did not differ significantly from that of the controls
(\( p = 0.309 \)), whereas it was significantly smaller after
pravastatin therapy than in controls (\( p < 0.001 \)).

Per cent changes of myocardial blood flow and
myocardial vasodilatation index

The per cent change of myocardial blood flow at rest did
not differ significantly between the simvastatin therapy

![Fig. 1](https://academic.oup.com/eurheartj/article-abstract/25/8/671/537672/3x6)

**Fig. 1** Myocardial blood flow at rest (MBF at rest) in the simvastatin
therapy group and pravastatin therapy group. Pre = before therapy. Post = after therapy. Bars indicate standard deviations.

![Fig. 2](https://academic.oup.com/eurheartj/article-abstract/25/8/671/537672/5x421)

**Fig. 2** Myocardial blood flow during hyperaemic stress with dipyrid-
amole (MBF with DP) in the simvastatin therapy group and pravastatin
therapy group. Pre = before therapy. Post = after therapy. Bars indicate standard deviations.

![Image](https://academic.oup.com/eurheartj/article-abstract/25/8/671/537672/85x106)
group (2.8 ± 21.3; standard error, 4.5) and pravastatin therapy group (5.7 ± 22.0; standard error, 4.7; p = 0.916) (Fig. 4). The per cent change of myocardial blood flow during dipyridamole loading tended to be larger in the simvastatin group (40.5 ± 56.2; standard error, 12.0) than in the pravastatin group (15.9 ± 34.6; standard error, 7.4), but the difference did not reach statistical significance (p = 0.091). No significant difference in the per cent change of the coronary resistance index was observed between the simvastatin group (−17.5 ± 39.8; standard error, 8.5) and pravastatin group (−8.5 ± 30.7; standard error, 6.6; p = 0.139). The per cent change of the myocardial vasodilatation index in the simvastatin group was 41.3 ± 53.9 (standard error, 11.5), which was significantly larger than the per cent change of the pravastatin group (9.9 ± 28.6; standard error, 6.1; p = 0.029).

The per cent change of the myocardial vasodilatation index was significantly and inversely correlated with per cent changes in plasma total cholesterol (r = −0.583, p = 0.004), plasma low-density lipoprotein cholesterol (r = −0.464, p = 0.030), and plasma triglycerides (r =...
We measured myocardial vasodilatation during hyperaemic stress with dipyridamole in hypercholesterolaemic patients and control subjects. The subjects had no clinical or echocardiographic evidence of myocardial ischaemia and showed no significantly hyperperfused areas on the flow images of positron emission tomography. Positron emission tomography has a high sensitivity and specificity for the diagnosis of ischaemic heart disease.\

The subjects examined in this study appear to have had low probabilities of significant coronary stenosis even though coronary angiography was not done and detailed coronary anatomy was not evaluated.

Lipid-lowering therapy with simvastatin or pravastatin for 8-12 months significantly reduced plasma total cholesterol and plasma low-density lipoprotein cholesterol and caused a nonsignificant decrease in plasma triglycerides. The doses of the statins were relatively low, and the lipid-lowering effect was moderate. The therapeutic effects of the two statins on hyperlipidaemia were similar in the patients studied in this investigation. Before therapy, while myocardial blood flow at rest was comparable between hypercholesterolaemic patients and controls, myocardial blood flow during dipyridamole loading and, consequently, myocardial vasodilatation during hyperaemic stress were significantly reduced in hypercholesterolaemic patients. The patients had low probabilities of significant coronary stenosis, and the reduction in myocardial vasodilatation appears to be attributable to diffuse coronary artery damage. Simvastatin therapy significantly improved myocardial vasodilatation, suggesting a therapeutic effect of simvastatin on diffuse coronary artery damage, whereas pravastatin therapy did not improve myocardial vasodilatation. The per cent change of the myocardial vasodilatation index was significantly larger for simvastatin than for pravastatin. Although the difference in the per cent change of myocardial blood flow during dipyridamole loading and the difference in the per cent change of the coronary resistance index did not reach statistical significance and further validation appears desirable, our observations indicate a difference in the effect on myocardial vasodilatation during hyperaemic stress between the two statins in hypercholesterolaemic patients with no evidence of myocardial ischaemia. Ejashira et al. reported that pravastatin failed to improve the response of angiographically normal coronary arteries to hyperaemic stress in nine patients with coronary artery disease and hypercholesterolaemia. Janatuinen et al. demonstrated that pravastatin did not improve myocardial vasodilatation in 25 young patients with hypercholesterolaemia and no evidence of ischaemia. Baller et al. reported that simvastatin therapy improved myocardial vasodilatation in 23 patients with angina pectoris. Improvement of myocardial vasodilatation after simvastatin therapy also has been reported in 16 patients with familial hypercholesterolaemia and no evidence of myocardial ischaemia. Our present results were consistent with the previous observations and demonstrated that the discrepancy among previous reports in the therapeutic effects of statins on myocardial vasodilatation is ascribable to difference between the two statins.

Although simvastatin and pravastatin improved plasma lipid fractions equally, the effect on myocardial vasodilatation during hyperaemic stress differed between the two drugs. It is suggested that the improvement of myocardial vasodilatation by simvastatin therapy is not a result of reduction in plasma lipid fractions but is caused by some action other than a lipid-lowering effect. Statins have direct beneficial effects on blood vessels beyond lipid lowering, and differences in such cholesterol-independent or pleiotropic effects have been shown between simvastatin, a lipophilic statin, and pravastatin, a hydrophilic statin. Improvement of myocardial vasodilatation during hyperaemic stress may depend on direct vascular effects of statins, and differences in such effects among statins may be responsible for our finding that only simvastatin improved myocardial vasodilatation. Although the mechanisms involved in the improvement of myocardial vasodilatation have not been clarified, our results indicate that statins may act on coronary circulation through mechanisms other than a lipid-lowering effect and that the action may vary among statins. In patients who were treated with simvastatin, improvement of myocardial vasodilatation correlated significantly with lipid-lowering effects. It may be hypothesised that both the increase in vasodilatation and lipid-lowering effect depend in part on a common factor, such as the bioavailability of simvastatin. Further evaluation would be desirable to confirm the relation between the improvement of vasodilatation and lipid-lowering effect for simvastatin therapy and to elucidate the cause of the relation.

The reduction in myocardial vasodilatation during hyperaemic stress without coronary artery stenosis appears to be attributable to diffuse coronary artery damage, including diffuse coronary atherosclerosis and impaired endothelial function. It has been reported that pravastatin therapy improved coronary endothelial function but not vasodilatation during hyperaemic stress in hypercholesterolaemia, suggesting that improvement of endothelial function does not necessarily improve vasodilatation. The improvement of myocardial vasodilatation observed after simvastatin therapy in our study may have resulted from regression of diffuse coronary atherosclerosis, although improvement of endothelial cell function may have also played a role. Migrated smooth muscle cells proliferate abnormally in atherosclerotic lesions. It has been demonstrated that simvastatin but
Simvastatin improved myocardial vasodilatation during hyperaemic stress have not been investigated whether the difference in effect on coronary circulation between simvastatin and pravastatin is specific to dipyridamole or is present for other vasoactive stimuli. It should be noted that our study showed a difference in physiological effect between simvastatin and pravastatin but no difference in clinical consequences. The clinical consequences of improvement of myocardial vasodilatation during hyperaemic stress have not been elucidated, and our results should not influence clinical decision-making at this stage. A multicentre clinical trial appears to be warranted to investigate whether or not the effectiveness for the prevention of coronary events differs between the two statins. In addition, we examined hypercholesterolaemic patients with low probabilities of coronary artery disease; comparison between the statins in overt coronary artery disease was beyond the scope of our study.

Conclusions

Simvastatin improved myocardial vasodilatation during hyperaemic stress with dipyridamole in hypercholesterolaemic patients without evidence of myocardial ischaemia, whereas pravastatin did not. It is suggested that improvement of myocardial vasodilatation produced by simvastatin therapy depends on mechanisms other than the lipid-lowering effect and that the effect on coronary circulation differs between hydroxymethylglutaryl coenzyme A reductase inhibitors.

References


