Effect of Long-Term Cholesterol-Lowering Treatment With HMG-CoA Reductase Inhibitor (Simvastatin) on Myocardial Perfusion Evaluated by Thallium-201 Single Photon Emission Computed Tomography

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Fifteen patients with either angina pectoris or old myocardial infarction, who had positive 201TI single photon emission computed tomography (SPECT) imaging and coronary sclerosis of more than 50%, were treated with an HMG-CoA reductase inhibitor (simvastatin) for more than 1 year. They were compared with an untreated control group (n=25). Total cholesterol decreased 22% and high-density lipoprotein (HDL) increased 9% with simvastatin; both changes were significantly different from those in controls. Long-term simvastatin induced improvement of myocardial perfusion on 201TI SPECT images both during exercise and at rest, which was also significantly different from controls. In addition, the improvement of myocardial perfusion on 201TI SPECT images was clearly related to the improvements in cholesterol values, especially non-HDL cholesterol. Thus, the greater the decrease in nonHDL cholesterol, the greater the improvement in myocardial perfusion at rest or during exercise with long-term treatment using an HMG-CoA reductase inhibitor. These findings indicate that the improvements in cholesterol values caused by HMG-CoA reductase inhibitor therapy are related to improvements of myocardial perfusion seen on 201TI SPECT images. (Jpn Circ J 2000; 64: 177 – 182)

Key Words: Cholesterol; HMG-CoA reductase inhibitor (simvastatin); HDL cholesterol; Myocardial perfusion

Management of risk factors for coronary artery disease, including cholesterol levels, represents a powerful therapeutic strategy in patients with ischemic heart disease (IHD). Several recent studies have indicated that cholesterol reduction is associated with decreased cardiovascular morbidity and mortality in patients with abnormal cholesterol values.1-3 These improvements appear to be due not only to regression of coronary artery sclerosis4,5 but also to enhanced endothelial function6-8. In clinical studies, NO-dependent, acetylcholinestimulated vasodilatation was attenuated after 6 months of cholesterol-lowering treatment9 and forearm vasodilation in response to serotonin increased after 3 months of treatment.10 A recent report stated that only 1 month of treatment could augment both the stimulated and basal NO dilatory function of the endothelium, and also confirmed persistent benefits of HMG-CoA reductase inhibitor therapy.11 Thus, long-term cholesterol reduction with HMG-CoA reductase inhibitors represents an important treatment for patients with IHD, and improvements in perfusion abnormalities both at rest and during exercise can be expected, which may lead to the improved mortality and morbidity. However, no data are available in terms of perfusion improvement as demonstrated with 201TI single photon emission computed tomography (SPECT), which shows both the flow reserve on exercise and hibernating conditions at rest.

In this study, we used 201TI SPECT to document improvements in impaired myocardial perfusion during exercise and at rest after long-term cholesterol-lowering treatment using an HMG-CoA reductase inhibitor (simvastatin).

Methods

The study was conducted in the 5 centers listed in the appendix in compliance with the Medical Research Council of Kyoto University guidelines concerning the protection of the rights and welfare of human subjects. The study received Ethics Committee Approval at all participating centers and all subjects provided written informed consent.

Eligibility

Clinically stable patients of either gender less than 70 years of age who had angina pectoris or myocardial infarction were eligible for inclusion. Criteria for perfusion scintigraphy included positive 201TI scintigraphic imaging either at rest or on exercise with coronary artery narrowing of more than 50%. Total cholesterol (TC) levels of the study patients were more than 220 mg/dl during the observation period (Table I).

Exclusion criteria included drug allergy, severe liver disease, kidney disease, acute and subacute myocardial infarction, pregnancy, and hypercholesterolemia secondary...
to other conditions such as hypothyroidism, obstructive cholelithiasis, pancreatitis, collagen disease, alcoholism and steroid treatment. Patients who had experienced myocardial infarction within the previous 3 months were excluded.

**Study Design**

The study was a nonblind, controlled multicenter trial involving 15 patients treated with simvastatin and 25 untreated patients (controls), followed for an equivalent period. Study inclusion was decided by the chief doctor at each center, because of the strict limitation on insurance coverage of drug prescriptions. The study consisted of a 4-week observation period and a follow-up phase of more than 48 weeks of either treatment with simvastatin (5 mg/day orally) or just observation without treatment. No drug change was allowed during the follow-up period. If treatment failed, the case was withdrawn. The suggested calorie intake was prescribed according to the 'Manual of the Ministry of Health and Welfare, Japan'.

**Baseline Assessment**

Baseline assessment included a physical examination, exercise treadmill test and exercise 201TI SPECT. Patients were not randomized and control patients were enrolled consecutively at each center without special selection. Drugs other than HMG-CoA reductase inhibitors, such as hormonal agents, thyroid drugs and other drugs that affect serum cholesterol levels, were not used during the study period.

**Serum Lipid Examination**

TC, calculated low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglycerides (TG), phospholipids, HDL2 and HDL3 cholesterol, apoproteins including A1, A2, B, C2, C3 and E, lipoprotein(a) (Lp(a)), and lecithin cholesterol acyl transferase (LCAT), hepatic triglyceride lipase (HTGL) and lipoprotein lipase (LPL) were examined.

**Exercise 201TI SPECT**

The exercise 201TI study was performed in both treated and control patients during observation and at study completion in a symptom-limited manner using the Bruce protocol on a treadmill. At the appearance of clinical symptoms, such as ST changes on the ECG, or changes in vital signs, 111 MBq of 201TI was injected 1 min prior to cessation of exercise. Five minutes after exercise was stopped, a SPECT image was taken using the 180-degree rotation method (exercise image). The same method was used at rest and 3 h after the exercise session (resting image).

### Table 1 Clinical Characteristics of 38 Study Patients

<table>
<thead>
<tr>
<th></th>
<th>Simvastatin (n=15)</th>
<th>Control (n=23)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (M/F)</td>
<td>10/5</td>
<td>19/4</td>
<td>NS</td>
</tr>
<tr>
<td>Age (years)</td>
<td>61.7±5.1</td>
<td>66.2±1.6</td>
<td>NS</td>
</tr>
<tr>
<td>BMI</td>
<td>23.4±0.7</td>
<td>23.7±0.4</td>
<td>NS</td>
</tr>
<tr>
<td>OMI</td>
<td>10</td>
<td>18</td>
<td>NS</td>
</tr>
<tr>
<td>AP</td>
<td>8</td>
<td>16</td>
<td>NS</td>
</tr>
<tr>
<td>DM</td>
<td>3</td>
<td>4</td>
<td>NS</td>
</tr>
<tr>
<td>HT</td>
<td>5</td>
<td>3</td>
<td>NS</td>
</tr>
<tr>
<td>1-Vessel Disease</td>
<td>9</td>
<td>15</td>
<td>NS</td>
</tr>
<tr>
<td>2-Vessel Disease</td>
<td>4</td>
<td>5</td>
<td>NS</td>
</tr>
<tr>
<td>3-Vessel Disease</td>
<td>2</td>
<td>3</td>
<td>NS</td>
</tr>
<tr>
<td>TC</td>
<td>239.9±5.4</td>
<td>234.4±12.7</td>
<td>NS</td>
</tr>
<tr>
<td>HDL-C</td>
<td>42.2±2.4</td>
<td>37.7±3.6</td>
<td>NS</td>
</tr>
<tr>
<td>TG</td>
<td>151.9±18.9</td>
<td>174.8±39.3</td>
<td>NS</td>
</tr>
<tr>
<td>non-HDL</td>
<td>197.7±5.6</td>
<td>184.9±9.0</td>
<td>NS</td>
</tr>
<tr>
<td>SBP before</td>
<td>129.5±4.0</td>
<td>134.0±6.4</td>
<td>NS</td>
</tr>
<tr>
<td>SBP after</td>
<td>134.3±4.8</td>
<td>135.0±3.6</td>
<td>NS</td>
</tr>
<tr>
<td>DBP before</td>
<td>72.7±3.0</td>
<td>75.0±2.2</td>
<td>NS</td>
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<tr>
<td>DBP after</td>
<td>73.7±3.0</td>
<td>76.8±2.3</td>
<td>NS</td>
</tr>
<tr>
<td>Interval</td>
<td>53.6±3.3</td>
<td>56.9±7.0</td>
<td>NS</td>
</tr>
</tbody>
</table>

OMI, old myocardial infarction; AP, angina pectoris; DM, diabetes mellitus; HT, hypertension; TC, total cholesterol; HDL/C, HDL cholesterol; TG, triglyceride; nonHDL, nonHDL cholesterol; SBP, systolic blood pressure; before, before treatment; after, after completion of drug treatment.

### Table 2 201TI Defect Scores on Exercised (Stress) and Resting (Delayed) Images

<table>
<thead>
<tr>
<th></th>
<th>Simvastatin</th>
<th>Control</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stress image</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before treatment</td>
<td>15.8±3.6</td>
<td>13.4±3.2</td>
<td>NS</td>
</tr>
<tr>
<td>After treatment</td>
<td>11.7±3.3</td>
<td>14.6±2.0</td>
<td>NS</td>
</tr>
<tr>
<td>Delayed image</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before treatment</td>
<td>13.1±3.4</td>
<td>12.0±2.8</td>
<td>NS</td>
</tr>
<tr>
<td>After treatment</td>
<td>9.7±3.0</td>
<td>12.9±2.2</td>
<td>NS</td>
</tr>
</tbody>
</table>

*p<0.05, **p<0.01.

Fig 1. Scoring method using 4 slices of SPECT (3 short axis and 1 long axis). Slices were divided into 20 segments as shown, and each segment was scored. Total summed scores were compared. LAD, left anterior descending artery region; LCX, left circumflex artery region; RCA, right coronary artery region.
Improvement of Perfusion With HMG CoA Reductase Inhibitor

**Simvastatin Group**

![Graph showing exercise time and pressure-rate product for the Simvastatin Group](image)

**Control Group**

![Graph showing exercise time and pressure-rate product for the Control Group](image)

**Stress image**

- Improved: 80%
- No change: 60%
- Worsened: 40%

**Delayed image**

- Improved: 80%
- No change: 60%
- Worsened: 40%

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**Fig. 2.** Treadmill exercise data. Exercise time (X-axis) and pressure-rate product (Y-axis) are shown during observation (black squares) and follow-up (white squares) phases. (Upper panel) simvastatin group, (Lower) control group.

**Fig. 3.** 

- 201Tl defect changes during exercise (Upper panel) and at rest (Lower panel). (Hatched bar) simvastatin group, (white bar) controls. Chi-square test revealed a statistically significant difference between the groups (p<0.001).

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**Injection method was not used in this study.**

**201Tl Scoring**

A semiquantitative method of scoring was used. Fig.1 shows the segmentation of 4 SPECT slices, namely 3 short axial views and one long axial view, into 20 numbered segments. In each segment, the 201Tl uptake was evaluated by at least 3 cardiologists who had no information about the study. Scoring was as follows: 0, no abnormality; 1, mild reduction of Tl uptake; 2, moderate reduction; and 3, severe reduction or no uptake. Each segment was scored, and the sum of these scores provided the semiquantitative values for exercise or resting scintigraphy. We defined 'improvement' and 'worsening' as a change in total defect score of more than or less than 2, respectively. An intermediate score was defined as 'no change'.

**Statistical Analysis**

The data are expressed as mean±SE. Chi-square test and Student’s t test were used for statistical comparisons of clinical characteristics between treated and untreated groups. Paired t test was applied for statistical analysis of changes in mean pressure-rate product (PRP), exercise time and for comparisons of lipid levels between the 2 groups. The defect scores are presented as median values and were tested with Wilcoxon’s signed-rank test. The parametric one-way analysis of variance (ANOVA) was applied to assess the differences among the lipid values, and post-hoc analysis was performed with Scheffe’s F test. The chi-square test was used for comparing nominal variables between the simvastatin and control groups. A p value less than 0.05 was considered statistically significant.

**Results**

Out of the 18 patients enrolled in this study, 3 dropped out: 1 patient was found to have familial hypercholesterolemia, and 2 failed to take the drug as directed. The 15 remaining patients completed the protocol without any cardiac events. Twenty-three patients were enrolled as controls, and all of them were judged eligible by the chief doctor of their hospital.

Two patients developed cardiac events in the control group: one with unstable angina and one with heart failure. Both were treated as required and were not withdrawn. No events occurred in the treatment group.

The clinical characteristics of the 38 study patients are shown in Table 1. The mean age was 61.7±2.1 in the simvastatin group and 66.2±1.6 in the controls (NS) and there were no differences in underlying diseases, number of stenotic coronary arteries (>75%), or blood pressure. Cholesterol and TG levels also showed no differences at baseline between the simvastatin and control groups. The observation period was 53.6±3.3 weeks in the treatment group and 56.9±7.0 in the control group, showing no statistically significant difference. Coronary intervention therapy was not performed in either group during this study.

**Fig. 2** shows the exercise perfusion scintigraphy data. In...
Fig 4. Changes in lipid values before and after the follow-up period are shown in the simvastatin (hatched bar) and control groups (white bar). All 4 parameters improved in the simvastatin group but not in the control group. 1st TI, control data when first 201I study was done; 2nd TI, follow-up data when 2nd 201I study was done. **, p<0.01; *, p<0.05.

Fig 5. Improvements in 4 lipid levels are compared with 201I-SPECT images. Improvements in both exercise and resting images are closely related with improved values (Δ mg) of TC, HDL-C, nonHDL-C, and TG. When ‘no change’ or ‘worsening’ images were considered at the same time, TC was the best predictor of improvement in the image. dotted bar, improved; hatched bar, no change; white bar, worsened.
the simvastatin group, exercise time improved from 465±46 to 476±42 s, and PRP improved from (234±17) × 10² to (255±18) × 10², with no significant difference. In the control group, exercise time decreased from 473±29 to 447±23 s, and PRP increased from 202±9 to 206±12, with no significant difference. Although these values did not differ significantly between the groups, the simvastatin group tended to show improved exercise time and PRP. 201TI defect score data (Table 2) showed that 73% of the exercise images and 67% of the resting images indicated improvement. The chi-square comparison is shown in Fig.3. The proportional improvement showed a significant difference between the simvastatin and control groups in both the exercise and resting images (p<0.001).

Lipid data including TC, HDL-C, non-HDL-cholesterol (non-HDL-C) and TG are summarized in Fig.4. TC significantly decreased with simvastatin from 239.9±5.4 to 187.8± 6.5 mg/dl (p<0.01). The control group showed increased TC (from 224.0±12.7 to 229.0±8.5 mg/dl). HDL-C also significantly improved with simvastatin, from 42.2±2.4 to 46.3±3.4 mg/dl over 1 year, but this parameter did not change in the control group (from 37.7±1.4 to 38.7±2.2 mg/dl). Non-HDL-C dropped from 197.7±5.6 to 146.5±5.7 mg/dl with simvastatin (p<0.05), whereas the control group showed increased non-HDL-C over the year (from 184.9±9.0 to 194.3±8.8 mg/dl). TG values showed much greater variation in both the treated and untreated groups; however, the simvastatin group showed a clear decrease over the year (from 151.9±18.9 to 115.3±15.8 mg/dl, vs from 174.8±39.3 to 200.0±46.3 mg/dl for controls). In summary, the group treated with simvastatin for 1 year demonstrated clear differences from the control group in cholesterol, HDL-C and non-HDL-C (p<0.01).

Fig.5 shows the comparison between reduced lipid levels and improvements in 201TI score data, in both exercise and resting images, which clearly demonstrates that improvement in either the exercise or resting scintigraphic image is closely related to cholesterol improvement, especially a decrease in non-HDL-C (p<0.05). HDL2, HDL3, apoproteins and lipid enzymes, including LCAT, HTGL and LPL, did not show significant differences between the groups in this study.

Discussion

In this small study, long-term treatment with simvastatin induced clear improvements in 201TI SPECT images both during exercise and at rest. The changes were significantly different from follow-up data in controls. In addition, the improvements shown in the 201TI SPECT images were clearly related to the improvements in lipid levels, especially non-HDL-C. Thus, the greater the decrease in non-HDL-C or TC, the greater the improvement in myocardial perfusion at rest or during exercise after long-term treatment with an HMG-CoA reductase inhibitor.

The Scandinavian Simvastatin Survival Study (4S) demonstrated that the survival of patients with angina pectoris or old myocardial infarction improved with long-term (5.4 years) cholesterol-lowering treatment with simvastatin. In the 4S study, cholesterol decreased 25%, LDL-C dropped 35%, TG improved 10% and HDL increased by 8% compared with control values. Our study also showed similar improvements in these values. Mortality was reported to be decreased 42% in 4S, but our study was too short to observe mortality or morbidity rates; however, it is likely that a 70% improvement in perfusion would contribute to increased survival.

Cardiac events may be prevented by several factors in response to lowering of cholesterol. Plaque stabilization and protection against disruption12-14 reduced monocyte chemotaxis or smooth muscle cell migration and proliferation15,16 reduced platelet thrombus formation17 and, most importantly, improved endothelial function are probably responsible for the lowered risk. Studies of the human coronary vascular bed indicate that hypercholesterolemia impairs endothelial function and the degree of impairment correlates with the serum cholesterol concentration18-20. Several studies also reported out that endothelial function improves with lowering of serum cholesterol.21-24 Positron emission tomography (PET) studies showed that flow reserve also improves with cholesterol-lowering treatment21,22. From these findings, it seems logical to expect considerable improvement with effective cholesterol-lowering treatment. Our present data indicated that the flow reserve improved to a greater extent with cholesterol-lowering treatment, which may be reasonable if the improvement in flow reserve during exercise is associated with improved endothelial function. In spite of improved flow reserve, the exercise tolerance in the treatment group of the present study did not reach statistical difference. Relatively good exercise tolerance at the baseline and no active training of peripheral muscle could be the reasons. However, our results indicate that an improvement of exercise tolerance, in association with a total therapeutic regimen including life style, which will be followed by good quality of life.

To our surprise, improvement in the exercise image was associated with improvement in the resting image. The resting 201TI image normally improves within 3 months of a myocardial infarction.4 Our study group did not include patients with such recent myocardial infarction. Thus, the resting image improvement might indicate improvement related to hibernation or repeated stunting. However, we still have no data concerning the natural consequences of repetitive limitation of flow reserve when an adequate reserve is necessary.

We also have no data about the consequences of improved flow reserve in that situation or in myocardial hibernation. However, it is possible that improvements in the endothelium-dependent flow of the epicardium and the microcirculation will be reflected in the resting image.4 A recent paper reported that hypercholesterolemia elicits endothelial dysfunction in coronary conduit and resistance vessels in humans that precedes angiographically visible atherosclerotic lesions in large coronary arteries.11 Coronary vasomotor tone within the coronary circulation may predispose these patients to myocardial ischemia. Resting flow might be improved by relaxing the coronary tone. Some reports suggest that repetitive stunting leads to hibernation5,26 Limited flow reserve due to endothelial dysfunction may readily lead to subclinical ischemia and, consequently, to decreased resting flow. Thus, either by endothelial improvement or coronary tone, it might be possible to recover resting flow, which would otherwise not normalize without treatment27.

The limited flow reserve visualized by thallium or perfusion tracer is related to the incidence of cardiac events or mortality28,29. For this reason, improved perfusion and reserve is associated with a good outcome.

Frost and colleagues studied the association between
serum lipids and coronary artery disease (CAD) in individuals 60 years of age or older in an attempt to identify whether the previously defined association between serum lipids and CAD progression in middle-aged men is also true in older individuals.38

HDL-cholesterol and TG levels were not significantly related to CAD. In fasting participants, elevated nonHDL or LDL-C was associated with a 30–35% higher CAD event rate. Thus, serum lipids, especially LDL, are CAD risk factors in older as well as younger subjects. Thus, in people of any age who have HDL, cholesterol-lowering treatment may be necessary to improve perfusion and thus mortality.

Study Limitations

The present study was non-randomized, and the control group was selected semi-randomly during the same period, with the final decision on inclusion made by the respective hospital doctors. In spite of the multicenter design, we could not enroll a large number of patients because of the cost of the imaging studies. However, the data clearly showed differences between the treated and untreated groups. The follow-up period also showed some difference between the 2 groups.

Clinical Implications

This study clearly demonstrated that cholesterol values are related to myocardial perfusion both during exercise and at rest in patients receiving chronic cholesterol-lowering treatment. From this viewpoint, reducing cholesterol values is especially important in patients with IHD. The National Cholesterol Education Program recommends a cholesterol value less than 200mg/dl in IHD patients39 The results of this study contribute to an understanding of why cardiac events are less common in patients with improved cholesterol values due to HMG-CoA reductase inhibitor treatment.

References

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