Statins Induce the Regression of Left Ventricular Mass in Patients With Angina

Hiroaki Nishikawa, MD; Shin-ichiro Miura, MD; Bo Zhang, PhD; Hideki Shimomura, MD*; Hidekazu Arai, MD*; Yoshihiro Tsuchiya, MD; Kunihiro Matsuo, MD; Keijiro Saku, MD

Background There is evidence that statins induce the regression of cardiac hypertrophy in a transgenic rabbit model of hypertrophic cardiomyopathy.

Methods and Results The association between treatment with statins and the regression of cardiac mass (left ventricular mass index, LVMI) was investigated in a case–control study using transthoracic echocardiography in 304 patients with angina who underwent coronary angiography. Those who received pravastatin or simvastatin were defined as cases (n=66), and age, sex and body mass index-matched controls (n=127) were selected. The cases showed a significant decrease in LVMI compared with the controls. Although the cases included a significantly higher percentage of patients with hypertension and calcium antagonist (CaA) treatment than the controls, there were no relationships between LVMI and either hypertension or CaA treatment. Because the cases had a significantly higher number of stenosed vessels than the controls, LVMI for each number of stenosed vessels was analyzed, and a significant interaction effect between the association of LVMI with statin and the number of stenosed vessels was found.

Conclusions Treatment with statins was associated with a lower cardiac mass in patients with angina, suggesting that this is one of the drugs’ pleiotropic effects. (Circ J 2004; 68: 121–125)

Key Words: Echocardiography; Left ventricular mass index; Statins

Cardiovascular disease (CAD) is still the most frequent cause of death in the Western world. Heart failure is the predominant long-term outcome of all forms of CAD. Cardiac hypertrophy and interstitial fibrosis, the common responses of the heart to all forms of heart injury, are the major determinants of the morbidity and mortality from CAD.

Statins, which are potent inhibitors of 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase (HMG-CoA), inhibit cholesterol biosynthesis. Major studies of statins have demonstrated that lowering the cholesterol concentration reduces the risk of coronary events in patients without known CAD and reduces both coronary events and total mortality in patients with stable CAD.

Recent reports have shown that statins have several pleiotropic effects, including the promotion of endothelial angiogenesis in addition to antithrombotic effects and anti-inflammatory effects, and they also improve endothelial dysfunction and promote smooth muscle cell migration and proliferation, suggesting that they may have more beneficial effects in the setting of CAD.

The regression of cardiac hypertrophy may also be beneficial in patients with CAD. A recent preclinical study showed that simvastatin induced the regression of cardiac hypertrophy in vivo in a transgenic rabbit model of human hypertrophic cardiomyopathy. Moreover, statins have been shown to inhibit angiotensin II-mediated myocyte hypertrophy and to block intracellular signaling molecules that have been implicated in cardiac hypertrophy.

In addition, Hasegawa et al reported that statin prevented the development of cardiac hypertrophy and heart failure in rats. Although the beneficial effects of statins in humans have not yet been examined, this regression of cardiac hypertrophy may be helpful in patients with CAD.

Therefore, we hypothesized that the use of statins may be associated with a significant regression of left ventricular mass (LVM) in humans. In the present case–control study, we assessed the LVM by transthoracic echocardiography in patients with angina who received statin therapy and compared the results with those from patients who did not receive statin therapy.

Methods

Patients The subjects included 304 patients with angina who underwent coronary angiography. Those who received pravastatin or simvastatin were defined as cases (n=66, F/M: 26/40, age: 65±11 years), and age, sex and body mass index (BMI)-matched controls (n=127, F/M: 52/75, age: 66±9 years) were selected. Patients with old myocardial infarction and/or bypass surgery were excluded. Patients with acute myocardial infarction (within 3 weeks of onset), unstable angina, heart failure (Killip ≥II, New York Heart Association ≥II), vascular disease (aortitis treatment with prednisolone) or hepatic dysfunction (viral and nonviral, transaminases more than 3-fold the normal value) were also excluded.
excluded from the study. Cases were selected from among patients who underwent diagnostic coronary angiography for suspected or known coronary atherosclerosis or for other reasons (mostly atypical chest pain) at Fukuoka University Hospital from 1998 to 2001. The Ethics Committee of Fukuoka University Hospital approved this study and informed consent was obtained from each patient. Patients with total cholesterol (TC) >220 mg/dl or triglyceride (TG) >150 mg/dl were considered to have hyperlipidemia. Patients with systolic or diastolic blood pressure >140 mmHg or 90 mmHg, respectively, or who were under antihypertensive treatment were considered to have hypertension (HT). Patients who were being treated for diabetes mellitus (DM) or who had symptoms of DM and a fasting glucose concentration ≥126 mg/dl were considered to have DM. Otherwise, the results of a 75-g oral glucose tolerance test were used to diagnose DM. None of the patients was receiving hormone replacement therapy.

### Coronary Angiography

Coronary angiograms were recorded and divided into 15 segments according to the classification of the American Heart Association Grading Committee. The presence of stenosis was determined using a computer-assisted coronary angiography analysis system after the direct intracoronary injection of isosorbide dinitrate, as described previously.\(^13\) Arterial stenosis that produced more than 50% luminal narrowing was considered significant.

### Determination of Serum Lipids

Blood was drawn in the morning after an overnight fast at the time of coronary angiography. Serum TC, TG and high density lipoprotein-cholesterol were determined enzymatically as described previously.\(^19\)

### Transthoracic Echocardiography

Echocardiography was performed before coronary angiography upon hospitalization. An experienced sonographer obtained all echocardiographic data, which was interpreted by an experienced staff echocardiographer. Comprehensive examinations were performed on all of the study patients, including M-mode, 2-dimensional, conventional Doppler, and color Doppler echocardiography, at the time of coronary angiography. The LVM were calculated as \(1.04 \times \left(\frac{(LV \text{ internal dimension at end-diastole + interventricular septal thickness + LV posterior wall thickness})^3 - (LV \text{ internal dimension at end-diastole})^3}{13.6}\right) - 13.6\), according to the method of Devereux et al\(^{20}\) and the LVM index (LVMI) was adjusted for body surface area.

### Statistical Analysis

Statistical analysis was performed using the SAS (Statistical Analysis System) Software Package (Version 6.12, SAS Institute Inc, Cary, NC, USA) at Fukuoka University (Fukuoka, Japan). Categorical variables such as gender

---

### Table 1 Clinical Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Controls (n=127)</th>
<th>Cases (n=62)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>65±11</td>
<td>66±9</td>
<td>0.895</td>
</tr>
<tr>
<td>F/M, %</td>
<td>41/59</td>
<td>39/64</td>
<td>0.787</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>24±3</td>
<td>24±3</td>
<td>0.101</td>
</tr>
<tr>
<td>HT, %</td>
<td>53</td>
<td>71</td>
<td>0.018*</td>
</tr>
<tr>
<td>DM, %</td>
<td>27</td>
<td>33</td>
<td>0.358</td>
</tr>
<tr>
<td>Smoking, %</td>
<td>48</td>
<td>56</td>
<td>0.352</td>
</tr>
<tr>
<td>Serum lipids and lipoprotein, mg/dl</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TC</td>
<td>181±34</td>
<td>200±31</td>
<td>0.002*</td>
</tr>
<tr>
<td>TG</td>
<td>132±82</td>
<td>159±91</td>
<td>0.053</td>
</tr>
<tr>
<td>HDL-C</td>
<td>50±15</td>
<td>47±13</td>
<td>0.261</td>
</tr>
<tr>
<td>LDL-C</td>
<td>105±29</td>
<td>121±29</td>
<td>0.003*</td>
</tr>
<tr>
<td>PTCA, %</td>
<td>30</td>
<td>29</td>
<td>0.870</td>
</tr>
<tr>
<td>Stenosed vessels</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0V/1V/2V/3V, %</td>
<td>54/30/12/4</td>
<td>39/23/17/21</td>
<td>0.001*</td>
</tr>
<tr>
<td>Medication</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACEI, %</td>
<td>23</td>
<td>21</td>
<td>0.819</td>
</tr>
<tr>
<td>ARB, %</td>
<td>18</td>
<td>21</td>
<td>0.682</td>
</tr>
<tr>
<td>CaA, %</td>
<td>38</td>
<td>56</td>
<td>0.014*</td>
</tr>
<tr>
<td>BB, %</td>
<td>9</td>
<td>14</td>
<td>0.365</td>
</tr>
<tr>
<td>ISDN, %</td>
<td>90</td>
<td>90</td>
<td>0.900</td>
</tr>
<tr>
<td>Diuretics, %</td>
<td>18</td>
<td>11</td>
<td>0.531</td>
</tr>
</tbody>
</table>

Values are shown as mean±SD. BMI, body mass index; HT, hypertension; DM, diabetes mellitus; OMI, old myocardial infarction; TC, total cholesterol; TG, triglycerides; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol; PTCA, percutaneous transluminal coronary angioplasty; ACEI, angiotensin converting enzyme; ARB, angiotensin II type 1 receptor antagonist; CaA, calcium antagonist; BB, &-blocker; ISDN, isosorbide dinitrate. *p<0.05.

### Table 2 Echocardiography in the Cases and Controls

<table>
<thead>
<tr>
<th></th>
<th>Controls (n=127)</th>
<th>Cases (n=62)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IVS, mm</td>
<td>10.4±3.0</td>
<td>9.7±1.8</td>
<td>0.029*</td>
</tr>
<tr>
<td>LVPW, mm</td>
<td>10.2±2.0</td>
<td>9.9±1.6</td>
<td>0.098</td>
</tr>
<tr>
<td>LVDD, mm</td>
<td>49.7±8.4</td>
<td>47.3±6.3</td>
<td>0.028*</td>
</tr>
<tr>
<td>LDVs, mm</td>
<td>32.5±10.0</td>
<td>30.5±6.0</td>
<td>0.105</td>
</tr>
<tr>
<td>LV, g</td>
<td>238±94</td>
<td>205±59</td>
<td>0.002*</td>
</tr>
<tr>
<td>LVMI, g/m²</td>
<td>149±59</td>
<td>127±34</td>
<td>0.002*</td>
</tr>
<tr>
<td>EF, %</td>
<td>63±16</td>
<td>64±12</td>
<td>0.948</td>
</tr>
</tbody>
</table>

IVS, interventricular septum; LVPW, left ventricular posterior wall; LVDD, left ventricular dimension at end-diastole; LDVs, left ventricular dimension at end-systole; LV, left ventricular mass; LVMI, LVMI index; EF, left ventricular ejection fraction. Values are shown as mean±SD. *p<0.05.
Statins and LV Mass

Circulation Journal Vol.68, February 2004

were compared between cases and controls by a chi-square analysis. Differences between groups were examined by an unpaired t test or Wilcoxon’s rank-sum test. The association between LVMI and statin was adjusted for hypertension, medication with Ca antagonist, and the number of stenosed vessels by an analysis of covariance (ANCOVA) using the GLM (general linear model) procedure. The significance of the interaction effects between the association of LVMI with statin and adjusting variables was also examined by ANCOVA. A p value of less than 5% was considered to be significant unless otherwise indicated.

Results

Patient Characteristics

As shown in Table 1, although the cases did not differ from the controls in age, sex, BMI etc, there were significantly higher values of TC and low density lipoprotein-cholesterol, more HT and calcium antagonist (CaA) treatment and a lower number of stenosed vessels than in the controls. There was no difference in the average duration of medical treatment, except for statin treatment, between the 2 groups. None of the patients received digitalis. The average duration of statin administration was 31±22 months in the cases. The statin-treated patients were presumed to have been taking medication for a sufficient duration, because early initiation of statin treatment in patients with acute myocardial infarction has been associated with a reduced 1-year mortality rate.21

LV Hypertrophy Regression

As shown in Table 2, the cases showed a significantly lower LVMI (127±34 g/m²) in addition to interventricular septum and left ventricular dimension at end-diastole values compared with the controls (149±59 g/m²). Because there were differences in the percentages of patients with HT and CaA treatment and in the number of stenosed vessels between the groups, we adjusted the LVMI according to these factors.

Effects of HT and CaA Treatment on LVMI

Although there was no difference in LVMI between subjects with and without HT in the controls, the cases with HT had a significantly lower LVMI than the controls with HT, and the cases without HT tended to have a lower LVMI than the controls without HT (Fig 1A). We also compared LVMI between subjects with and without CaA treatment. Although statin treatment (112±31 g/m²) was associated with a significantly lower LVMI than no treatment (152±67 g/m²) in subjects without CaA treatment (Fig 1B), LV hypertrophy with statins was not significantly lower than that without statins in subjects with CaA treatment.

Effect of the Number of Stenosed Vessels on the Association Between Cases and Controls

Because the cases had significantly more stenosed vessels than the controls, we compared LVMI between cases and controls according to the number of stenosed vessels. There were no differences in the clinical characteristics in Table 1 between the cases and controls. As shown in Fig 2, the cases had significantly lower LVMI than the controls after adjusting for the number of stenosed vessels, as assessed by ANCOVA (p<0.05).

Discussion

Because a recent study indicated that statin prevented the development of cardiac hypertrophy in rats,22 we used...
transthoracic echocardiography to examine whether the use of statins is associated with a significant regression of LVM in humans. Our results are consistent with the hypothesis that the use of statins is associated with a significantly lower LVM value. This is the first comprehensive analysis of the role of the statin-induced regression of LVM independent of its lipid-lowering action. The observed beneficial effects of statins in patients with LV hypertrophy are consistent with the effects of statins in the prevention of angiotensin II-17 or noradrenaline-induced myocyte hypertrophy23 and pressure-overload-induced hypertrophy in rats.

The mechanism by which statins induce the regression of hypertrophy is likely to involve downregulation of the levels of activated ERK1/2, the predominant stress-responsive intracellular signaling kinase involved in modulating cardiac hypertrophy. Various upstream regulators, including Ras-dependent and Ras-independent pathways, could activate ERK1/2. Because statins induce the regression of load-induced cardiac hypertrophy by reducing the activity of angiotensin-converting enzyme and the cardiac content of angiotensin II,24 they also have pleiotropic effects that interact with the effects of the renin–angiotensin–aldosterone system pathway. In addition, statins inhibit the synthesis of the isoprenoid intermediates in cholesterol biosynthesis, farnesylpyrophosphate and geranylgeranylpyrophosphate, which are used in the post-translation modification of Ras and Rho proteins, respectively, by isoprenyl transferases.25 This modification step is thought to be essential for the maturation, membrane localization, and subsequent activation of small GTP-binding proteins.26 Oi et al reported that statins may prevent angiotensin II-induced cardiac hypertrophy through the Ras molecule, which is an upstream signaling regulator for ERK1/2.23 Ras has also been shown to induce migration through a Ras pathway. Collectively, Ras and Rho molecules, translocation of which to the cell membrane is blocked by statins, play a role in cell motility and survival, including hypertrophy.

The LVMI in the controls was 149±59 g/m². Palmieri et al28 reported that LVMI in hypertensive patients was 135±25 g/m². In addition, Ichihara et al29 showed that LVMI in controls with normal LV geometry was 95±14 g/m², whereas that in eccentric and concentric hypertrophy patients was 138±26 g/m² and 158±38 g/m², respectively. The LVMI value in the controls in the present study can be considered LV hypertrophy, although only 53% of the controls were hypertensive.

In the present study, CaA treatment masked the statin-induced regression of LV hypertrophy in the cases. Generally, intracellular Ca²⁺ levels are elevated by various hypertrophic stimuli and Ca²⁺ has been reported to play a critical role in the development of cardiac hypertrophy.30 Because long-acting nifedipine (CaA) induces the regression of left ventricular hypertrophy in hypertensive animals and patients,31,32 combination therapy with statin and CaA should induce a greater regression of hypertrophy. More detailed investigations will be required to clarify this point.

Hypertrophy is the common response of the heart to all forms of injury and is a major determinant of mortality and morbidity. Thus, our findings have broader implications for the treatment and prevention of all forms of cardiovascular disease. Statins have a well-established safety profile and the treatment and prevention of all forms of cardiovascular disease. Statins have a well-established safety profile and the treatment and prevention of all forms of cardiovascular disease. Statins have a well-established safety profile and the treatment and prevention of all forms of cardiovascular disease. Statins have a well-established safety profile and the treatment and prevention of all forms of cardiovascular disease. Statins have a well-established safety profile and the treatment and prevention of all forms of cardiovascular disease.

Conclusion

This is the first study to demonstrate that statins, which are agents with pleiotropic effects, may induce the regression of LVM in patients with angina. These findings suggest a new option for the treatment and prevention of cardiac hypertrophy in humans with angina or any form of cardiovascular disease.

Acknowledgments

This work was supported by a grant-in-aid from the Ministry of Education, Science and Culture of Japan (No.12670712), and by research grants from the Central Research Institute of Fukuoka University (No. 026004), Uehara Memorial Foundation (2002), the Clinical Research Foundation (2001), Fukuoka University School of Medicine, the Eboshi Association (2001) and the Japan Research Foundation for Clinical Pharmacology (2002).

References

12. Patel R, Naghie SF, Tsybouleva N, Abdellatif M, Lautucia S,


