Platelet-Dependent Thrombin Generation in Patients With Hyperlipidemia

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Objectives. We evaluated coagulability as determined by platelet-dependent thrombin generation in hypercholesterolemic patients before and after treatment with pravastatin and in hypertriglyceridemic patients to investigate the usefulness of coagulability as an index of atherosclerosis and to determine the importance of treating hyperlipidemia.

Background. An understanding of the interaction between platelets and the plasma coagulation system is important for clarifying the mechanism of the procoagulant process.

Methods. We assessed coagulability in 58 patients with hypercholesterolemia (serum total cholesterol level \( \geq 220 \text{ mg/dl} \), age 56.5 \( \pm \) 1.5 years [mean \( \pm \) SEM]), 37 patients with hypertriglyceridemia (serum triglyceride level \( \geq 200 \text{ mg/dl} \), age 59.5 \( \pm \) 1.7 years), 13 patients with hypercholesterolemia plus hypertriglyceridemia (age 51.4 \( \pm \) 3.1 years) and 75 normal subjects (age 52.2 \( \pm \) 1.7 years). We also studied platelet-dependent thrombin generation in patients with hypercholesterolemia before and after treatment with pravastatin. Calcium chloride was added to 0.5 ml of platelet-rich plasma (150 \( \times \) 10\(^3\) /liter) to initiate coagulation. Ten microliters of the sample was transferred into 90 \( \mu \)l of 3.8% sodium citrate at 10-min intervals for 30 min. A chromogenic substrate, S-2238, was added to each sample, and absorbance was measured spectrophotometrically at a wavelength of 405 nm to determine thrombin generation.

Results. Platelet-dependent thrombin generation was increased in patients with hypercholesterolemia and patients with hypercholesterolemia plus hypertriglyceridemia \((p < 0.01)\) compared with patients with hypertriglyceridemia and control subjects. Treatment with pravastatin normalized thrombin generation.

Conclusions. Hypercholesterolemia, but not hypertriglyceridemia, was associated with increased platelet-dependent thrombin generation. Pravastatin normalized the generation of thrombin.

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Hyperlipidemia is a risk factor for atherosclerotic disease and is often associated with myocardial infarction and cerebrovascular disorders (1). The coagulation system has been proposed as a possible mechanism of thrombogenesis and atherosclerosis in patients with hyperlipidemia. Some studies have demonstrated increased coagulation activity and platelet function in patients with hyperlipidemia (2–10), but others have produced conflicting results (11–16). Thus, the roles of coagulation factors and platelets in hyperlipidemia remain to be clarified. Previous studies have measured coagulation activity and platelet function without examining their interactions. Aronson et al. (17) have developed an experimental system for measuring the platelet-dependent generation of thrombin to assess the interaction between coagulation factors and platelets. In the present study, we measure the platelet-dependent generation of thrombin in patients with hypercholesterolemia to evaluate the prothrombotic state in hyperlipidemic patients. We also studied the effects of pravastatin, a lipid-lowering agent, on thrombin generation to determine the relation between thrombin generation and hypercholesterolemia and to evaluate the usefulness of the agent for resolving the prothrombotic state in patients with hyperlipidemia.

Methods

Subjects. We studied 58 patients with hypercholesterolemia (total serum cholesterol level \( \geq 220 \text{ mg/dl} \), 75 normal subjects matched for age and gender (serum total cholesterol level <220 mg/dl), 37 patients with hypertriglyceridemia (serum triglyceride level \( \geq 200 \text{ mg/dl} \), 3 patients with hypercholesterolemia plus hypertriglyceridemia (Table 1). All subjects had normal thyroid, hepatic and renal function, and none had underlying diseases, such as ischemic heart disease, heart failure, inflammatory disease, malignant tumors and diabetes mellitus. Subjects received no medications known to affect platelet or coagulation function or the metabolism of lipids in the 2 weeks before blood collection. Pravastatin (15 mg/day) was administered to

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patients with hypercholesterolemia for at least 1 month, and thrombin generation was compared before and after treatment. Blood was collected from fasting subjects at 9 AM after they had rested for at least 1 h. Smokers were requested to abstain from smoking for at least 2 h before blood collection. Informed consent was obtained from all subjects.

**Measurement of thrombin generation.** Thrombin generation was measured according to the method of Aronson et al. (17), with slight modifications. Venous blood (3.8% sodium citrate/blood 1:9) collected from patients and normal subjects was centrifuged at 1,500 g for 15 min to obtain platelet-poor plasma (PPP). The platelet count in the PRP was determined with a Coulter counter confirmed that the sample was not contaminated by other cells. PRP aliquots (0.5 ml) were placed into round-bottomed polypropylene tubes (12 × 75 mm), and 20 µl of 1 mol/liter calcium chloride was added to initiate clotting; glass tubes were not used because they would activate the intrinsic pathway of coagulation cascade. Samples (10 µl) were added to the wells of a microtiter plate containing 90 µl of 3.8% sodium citrate at 10-min intervals for 30 min. Color was developed for 2 min by the addition of 50 µl of 0.5 mmol/liter S-2238 (H-D-Phe-Arg-NH₂-NO₂-HCl, a thrombin-specific substrate; Dai-ichi Kagaku Yakuhin, Tokyo, Japan) in 1 mol/liter Tris (pH 8.1). The absorbance of the released color product was measured spectrophotometrically at a wavelength of 405 nm using a Vmax microtiter plate reader (Easy Reader, EAR 340AT, SLT Lab Instruments GmbH, Vienna, Austria). Measurements were obtained in triplicate at each time point. The amount of thrombin generation was calculated from a standard curve.

**Effect of pravastatin on thrombin generation in vitro.** The effect of pravastatin on thrombin generation was investigated by measuring platelet-dependent thrombin generation after incubating PRP obtained from normal subjects (n = 4) with pravastatin for 10 min. Pravastatin sodium (Sankyo Co., Ltd., Tokyo, Japan) was dissolved in physiologic saline and added to PRP in concentrations of 10, 100 and 1,000 ng/ml (the serum level of pravastatin in the clinical setting is ~20 to 50 ng/ml) (18). Physiologic saline was used as the control vehicle.

**Effects of pravastatin on platelet aggregability, prostaglandin production, phospholipids, lipoprotein(a) and platelet activity in patients with hypercholesterolemia.** We investigated the effects of pravastatin in 15 patients with hypercholesterolemia not accompanied by hypertriglyceridemia and in 13 age- and gender-matched normal subjects (Table 2). We assessed the effects of pravastatin on subfractions of low and high density lipoprotein cholesterol and investigated its effect on platelet aggregability by measuring platelet aggregation in response to 3 µg/ml of collagen (MC Medical Co., Ltd., Tokyo, Japan), 1 µmol/liter of adenosine diphosphate (Sigma) and 1 µmol/liter of epinephrine (Dai-ichi Pharmaceuticals, Inc., Tokyo, Japan), according to the method described by Born (19). Prostaglandin production was assessed by measuring plasma

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**Table 1. Clinical Characteristics of Study Subjects**

<table>
<thead>
<tr>
<th></th>
<th>Normal Group (n = 75)</th>
<th>Hyper-Chol Group (n = 58)</th>
<th>Hyper-TG Group (n = 37)</th>
<th>Hyper-Chol+ Hyper-TG Group (n = 13)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Male/female</strong></td>
<td>34/41</td>
<td>24/34</td>
<td>24/13</td>
<td>8/5</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td>52.2 ± 1.7</td>
<td>56.5 ± 1.5</td>
<td>59.5 ± 1.7</td>
<td>51.4 ± 3.1</td>
</tr>
<tr>
<td><strong>T-Chol (mg/dl)</strong></td>
<td>183.0 ± 3.8</td>
<td>272.8 ± 4.8*</td>
<td>219.1 ± 4.1†</td>
<td>203.9 ± 2.7</td>
</tr>
<tr>
<td><strong>TG (mg/dl)</strong></td>
<td>105.2 ± 5.9</td>
<td>162.9 ± 14.2*</td>
<td>140.4 ± 12.1</td>
<td>303.5 ± 24.5*</td>
</tr>
<tr>
<td><strong>HDL-Chol</strong></td>
<td>58.6 ± 2.8</td>
<td>54.2 ± 2.0</td>
<td>54.6 ± 1.7</td>
<td>46.7 ± 2.2*</td>
</tr>
<tr>
<td><strong>LDL-Chol</strong></td>
<td>115.3 ± 4.9</td>
<td>189.3 ± 5.1*</td>
<td>136.4 ± 4.5†</td>
<td>108.6 ± 6.9*</td>
</tr>
<tr>
<td><strong>TAT (ng/ml)</strong></td>
<td>2.4 ± 0.3</td>
<td>2.6 ± 0.5</td>
<td>2.1 ± 0.4</td>
<td>2.4 ± 0.3</td>
</tr>
<tr>
<td><strong>PIC (µg/ml)</strong></td>
<td>0.9 ± 0.1</td>
<td>0.8 ± 0.1</td>
<td>0.9 ± 0.1</td>
<td>0.9 ± 0.1</td>
</tr>
<tr>
<td><strong>t-PA-Ag (ng/ml)</strong></td>
<td>3.1 ± 0.8</td>
<td>3.2 ± 0.9</td>
<td>2.9 ± 0.7</td>
<td>3.1 ± 0.8</td>
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</tbody>
</table>

*p < 0.01 versus normal group. †p < 0.01 versus before treatment. Data presented are mean value ± SEM. HDL-Chol = high density lipoprotein cholesterol; Hyper-Chol = hypercholesterolemic; Hyper-TG = hypertriglyceridemic; LDL-Chol = low density lipoprotein cholesterol; PIC = plasmin-alpha2- plasmin complex; TAT = thrombin-antithrombin III complex; T-Chol = total cholesterol; TG = triglycerides; t-PA-Ag = tissue-type plasminogen activator antigen.
Table 2. Effect of Pravastatin on Platelet Aggregability, Prostaglandin Production and Platelet Activity in Hypercholesterolemic Patients

<table>
<thead>
<tr>
<th></th>
<th>Normal Group (n = 13)</th>
<th>Hyper-Chol Group (n = 15)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Before Treatment</td>
<td>After Treatment</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male/female</td>
<td>11/2</td>
<td>12/3</td>
</tr>
<tr>
<td>Age</td>
<td>45.4 ± 3.1</td>
<td>46.1 ± 3.8</td>
</tr>
<tr>
<td>T-Chol (mg/dl)</td>
<td>192.4 ± 5.7</td>
<td>250.0 ± 6.8*</td>
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<tr>
<td>TG (mg/dl)</td>
<td>138.9 ± 7.1</td>
<td>152.6 ± 6.3</td>
</tr>
<tr>
<td>HDL-Chol (mg/dl)</td>
<td>49.3 ± 2.7</td>
<td>37.8 ± 2.4*</td>
</tr>
<tr>
<td>Subfraction 2</td>
<td>34 ± 3</td>
<td>16 ± 1*</td>
</tr>
<tr>
<td>Subfraction 3</td>
<td>19 ± 2</td>
<td>14 ± 1</td>
</tr>
<tr>
<td>LDL-Chol (mg/dl)</td>
<td>113.8 ± 6.5</td>
<td>170.6 ± 11.7*</td>
</tr>
<tr>
<td>Subfraction L</td>
<td>76 ± 10</td>
<td>133 ± 13*</td>
</tr>
<tr>
<td>Subfraction S</td>
<td>32 ± 6</td>
<td>38 ± 12</td>
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<tr>
<td>Lipoprotein(a) (mg/dl)</td>
<td>16.1 ± 4.7</td>
<td>16.0 ± 4.6</td>
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<tr>
<td>Phospholipid (mg/dl)</td>
<td>195.4 ± 3.5</td>
<td>277.5 ± 6.0</td>
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<tr>
<td>Platelet aggregation</td>
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<tr>
<td>ADP (%)</td>
<td>77.8 ± 5.3</td>
<td>60.0 ± 7.8</td>
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<tr>
<td>Collagen (%)</td>
<td>85.6 ± 4.5</td>
<td>78.7 ± 8.8</td>
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<tr>
<td>Epinephrine (%)</td>
<td>75.0 ± 7.0</td>
<td>77.5 ± 5.9</td>
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<tr>
<td>Platelet activity</td>
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<tr>
<td>Beta-thrombo (ng/ml)</td>
<td>2.4 ± 0.3</td>
<td>58.4 ± 14.6</td>
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<td>PF-4 (pg/ml)</td>
<td>0.9 ± 0.1</td>
<td>19.3 ± 7.7</td>
</tr>
<tr>
<td>TX-B2 (pg/ml)</td>
<td>3.1 ± 0.8</td>
<td>12.0 ± 1.5</td>
</tr>
<tr>
<td>6-keto-PGF1alpha (pg/ml)</td>
<td>3.1 ± 0.8</td>
<td>8.1 ± 2.6</td>
</tr>
</tbody>
</table>

*p < 0.01 versus normal subjects. †p < 0.01 versus pretreatment. Data presented are mean value ± SEM. ADP = adenosine diphosphate; Beta-thrombo = beta-thromboglobulin; L = large; PF-4 = platelet factor 4; PGF1alpha = prostaglandin F1alpha; S = small; TX-B2 = thromboxane B2; other abbreviations as in Table 1.

levels of thromboxane B2 (TX-B2) and 6-keto-prostaglandin F1alpha (6-keto-PGF1alpha), according to the method described by Powell (20). Platelet activity was determined by measuring the serum levels of beta-thromboglobulin (beta-TG) and platelet factor 4 (PF-4), according to the method described by Takahashi et al. (21).

Other markers of coagulation and fibrinolysis. Plasma levels of thrombin-antithrombin III complex and plasmin-alpha2-plasmin inhibitor complex were measured by enzyme immunoassays using commercially available kits (Enzygnost-TAT, Behringwerke AG, Marburg, Germany and PIC-test, Teijin, Japan). The tissue-type plasminogen activator antigen (t-PA–Ag) level was measured by a solid plasma enzyme immunoassay using a commercially available kit (ELISA-tPA, Technoclone, Austria). Measurements were obtained in hyperlipidemic patients and control subjects.

Statistical analysis. Results are shown as the mean value ± standard error (SEM). Data were analyzed by repeated-measures analysis of variance for thrombin generation, and analysis of variance for other variables. When a significant difference was observed, the Bonferroni/Dunn method was used for multiple comparisons. A p value <0.01 was accepted as indicating statistical significance. Statistical calculations were performed using StatView-J (version 4.02, Abacus Concepts, Inc.).

Results

Platelet-dependent thrombin generation. Platelet-dependent thrombin generation was significantly increased in patients with hypercholesterolemia and those with hypercholesterolemia plus hypertriglyceridemia compared with those with hypercholesterolemia and those with hypercholesterolemia plus hypertriglyceridemia, or between men and women (control group: 132 ± 29 mIU/ml vs. 137 ± 26 mIU/ml; patients with hypercholesterolemia: 379 ± 46 mIU/ml vs. 371 ± 50 mIU/ml; patients with hypertriglyceridemia: 246 ± 44 mIU/ml vs. 295 ± 71 mIU/ml, respectively). Pravastatin reduced thrombin generation in patients with hypercholesterolemia to the control level (Fig. 2). Thrombin generation peaked at the time of clot formation (568 ± 20 mIU/ml) and remained high thereafter. Clotting time after the addition of calcium chloride was significantly shorter in patients before pravastatin administration than in control subjects and patients after pravastatin administration (control 67 ± 4 min; pretreatment 37 ± 4 min [p < 0.01 vs. control and posttreatment groups]; posttreatment 59 ± 5 min).

Effects of pravastatin on thrombin generation in vitro. Pravastatin had no effect on thrombin generation in vitro. Mean thrombin level 30 min after addition of calcium chloride was 69 ± 4 mIU/ml in control experiments, 86 ± 15 mIU/ml in the presence of 10 ng/ml of pravastatin, 67 ± 16 mIU/ml in the presence of 100 ng/ml of pravastatin and 63 ± 10 mIU/ml in the presence of 1,000 ng/ml of pravastatin. There were no significant differences among groups, indicating that pravasta-
The serum level of HDL, subfraction 2 (HDL-2) cholesterol tended to become closer to that in control subjects than in control subjects (squares) \( p < 0.01 \). Thrombin generation did not have direct effect on platelet-dependent thrombin generation.

**Effects of pravastatin on platelet aggregability, prostaglandin production and platelet activity in patients with hypercholesterolemia.** There was no significant difference in platelet aggregability between pretreatment and posttreatment groups (Table 2). There was no significant difference in platelet activity assessed by measurement of plasma levels of beta-TG and PF-4, or in prostaglandin production, assessed by measurement of plasma levels of TX-B\(_2\) and 6-keto-PGF\(_{1\alpha}\).普洛伐他汀 did not have direct effect on platelet aggregability.

**Figure 2.** Platelet-dependent thrombin generation in patients with hypercholesterolemia treated with pravastatin. Platelet-dependent thrombin generation was higher in patients with pretreatment (circles) than in control subjects (squares) \( *p < 0.01 \). Thrombin generation did not have direct effect on platelet-dependent thrombin generation.

**Effects of pravastatin on platelet aggregability, prostaglandin production and platelet activity in patients with hypercholesterolemia.** There was no significant difference in platelet aggregability between pretreatment and posttreatment groups (Table 2). There was no significant difference in platelet activity assessed by measurement of plasma levels of beta-TG and PF-4, or in prostaglandin production, assessed by measurement of plasma levels of TX-B\(_2\) and 6-keto-PGF\(_{1\alpha}\).普洛伐他汀 did not have direct effect on platelet aggregability.

**Other coagulation and fibrinolytic markers.** There were no significant differences in the plasma levels of thrombin–antithrombin III complex, plasmin-alpha\(_{2}\)-plasmin inhibitor complex and t-PA–Ag among control subjects, patients with hypercholesterolemia, patients with hypertriglyceridemia and patients with hypercholesterolemia plus hypertriglyceridemia. There were also no significant differences in these markers after treatment with pravastatin in patients with hypercholesterolemia.

**Discussion**

Hyperlipidemia is a risk factor for ischemic heart disease, suggesting that hypercoagulability may play a role in patients with hyperlipidemia. However, previous studies (11–16,22–25) using conventional methods of evaluating coagulation factors and platelets, including measurement of coagulation markers and platelet aggregability, have yielded conflicting results. Thrombus formation results from the interaction between platelets and various coagulation factors. Coagulation Factor X is activated on platelet surfaces, and platelet factor 3 accelerates the conversion of prothrombin to thrombin (26,27). Thrombin generated on activated platelets stimulates the release of Factor Va from alpha-granules. Factor Va and Factor Xa then convert prothrombin to thrombin, markedly amplifying the coagulation cascade on the platelet membrane (28). To investigate the interaction between coagulation factors and platelets, we used the method described by Aronson et al. (17) to measure platelet-dependent thrombin generation in patients with various types of hyperlipidemia.

**Platelet-dependent thrombin generation in patients with hyperlipidemia.** In the present study, platelet-dependent thrombin generation was increased in patients with hypercholesterolemia and those with hypercholesterolemia plus hypertriglyceridemia. Thrombin generation was not increased in patients with hypertriglyceridemia. Hypertriglyceridemia and hypercholesterolemia did not have synergistic effects on platelet-dependent thrombin generation. These results indicate that hypercholesterolemia, but not hypertriglyceridemia, was associated with increased thrombin generation in patients with hyperlipidemia. No or little thrombin generation was observed within 30 min in calcified PPP of control subjects and patients with hypercholesterolemia (control subjects: 75 ± 8 mIU/ml; patients 82 ± 6 mIU/ml at 30 min after addition of calcium chloride, n = 12). These data are consistent with the results of the previous study (17), confirming that platelets are involved in thrombin generation in this system.

**Effects of pravastatin on platelet-dependent thrombin generation.** Pravastatin normalized platelet-dependent thrombin generation in association with a reduction in the serum level of cholesterol, confirming that hypercholesterolemia was associated with increased platelet-dependent thrombin generation. Pravastatin did not affect the plasma levels of other lipoproteins, such as lipoprotein(a) and phospholipids, which is consistent with the results of previous studies (29,30), and suggests that lipoprotein(a) and phospholipids are not associated with platelet-dependent thrombin generation.

**Mechanisms of increased thrombin generation in patients with hypercholesterolemia.** Some studies have shown increased platelet reactivity in patients with hypercholesterolemia (31–33), but others have shown conflicting results (8,34). Previous studies (35,36) have shown that LDL cholesterol increases platelet reactivity by stimulating phosphoinositide turnover and increasing the cytosolic calcium concentration. In the present study, we investigated the hypothesis that hypercholesterolemia increased platelet reactivity. There were no significant differences in platelet aggregability or plasma levels of PF-4, beta-TG, TX-B\(_2\) and 6-keto-PGF\(_{1\alpha}\) indexes of platelet reactivity, between control subjects and patients with hypercholesterolemia or before and after pravastatin treatment in patients with hypercholesterolemia. However, we could not conclude from these data that platelet aggregability
or platelet activity was not increased in patients with hypercholesterolemia for the following reasons: 1) the concentration of the agonists used here was high enough to induce near-maximal aggregation, and it was difficult to differentiate aggregable platelets from normal ones; 2) variables such as PF-4, beta-TG and TX-B could be increased easily by platelet activation during blood collection, suggesting that these variables were unreliable as markers for platelet activity. Next, we investigated another hypothesis that alterations in the subfractions of LDL cholesterol or HDL cholesterol might have decreased thrombin generation. Previous studies have shown that HDL-2 cholesterol decreased platelet aggregability (37) and that small, dense LDL cholesterol increased an atherogenicity (38). In the present study, the serum level of HDL-2 cholesterol was significantly increased in patients with hypercholesterolemia after treatment with pravastatin. But this change in HDL-2 cholesterol level was not reflected in platelet aggregability because platelet aggregability was not changed after treatment with pravastatin. Furthermore, there was no significant difference in the serum level of small, dense LDL cholesterol between pretreatment and posttreatment groups, suggesting that small, dense LDL cholesterol was not responsible for the change in thrombin generation. One proposed mechanism is that alterations in the lipid–protein matrix and a rearrangement of the lipid bilayer of platelets may stimulate Factor Xa-induced conversion of prothrombin to thrombin in patients with hypercholesterolemia (39). Further studies are needed to investigate this possibility. Thus, we must assume that the precise mechanisms of the increase in platelet-dependent thrombin generation associated with hypercholesterolemia still remain unclear.

Study limitations. We used the method of Aronson et al. (17) to assess hypercoagulability in patients with hypercholesterolemia. This method is based on the measurement of thrombin generated by the addition of Ca$^{2+}$ ions to PRP. The mechanism underlying increased platelet-dependent thrombin generation in patients with hypercholesterolemia could not be determined for the reasons described in the discussion section. Also, whether a plasma factor is involved could not be determined because we did not conduct mixing experiments using a mixture of control platelets plus patients’ plasma or a mixture of patients’ platelets plus control plasma. Endothelial cells, which modulate the prothrombotic state in vessels by producing various proteins, including thrombomodulin, plasminogen activator inhibitor-1 and tissue-type plasminogen activator are not present in this system, and thus, we did not examine the interaction between endothelial cells and platelets. Other important factors, such as shear stress and whole-blood fluidity, were also not considered. Further studies are needed to evaluate these factors.

Conclusions. Platelet-dependent thrombin generation was increased in patients with hypercholesterolemia, indicating that hypercholesterolemia is associated with hypercoagulability through the interaction between platelets and coagulation factors. Increased thrombin generation in patients with hypercholesterolemia was normalized by treatment with pravastatin, suggesting that pravastatin may be useful for the prevention of thrombotic complications in hypercholesterolemic patients.

References