Captopril Reduced Plasminogen Activator Inhibitor Activity in Patients With Acute Myocardial Infarction

Yasushi Moriyama, MD; Hisao Ogawa, MD*; Shuich Oshima, MD; Keiji Takazoe, MD; Yoshio Honda, MD; Osamu Hirashima, MD; Hidekazu Arai, MD; Tomohiro Sakamoto, MD*; Hitoshi Sumida, MD*; Hisakazu Suefuji, MD*; Koichi Kaikita, MD*; Hirofumi Yasue, MD*

Recent clinical trials have demonstrated that the administration of angiotensin-converting enzyme (ACE) inhibitors to patients with myocardial infarction reduces the incidence of recurrent myocardial infarction. It has also been reported that an elevated level of plasminogen activator inhibitor (PAI) appears to constitute a marker of the risk of recurrent coronary thrombosis. To determine whether the ACE inhibitor captopril reduces plasma PAI inhibitor activity, we measured changes in plasma PAI activity (IU/ml), tissue plasminogen activator (t-PA) antigen (ng/ml), and serum ACE activity (IU/L) in 14 survivors of myocardial infarction receiving captopril therapy (37.5 mg daily) and compared them with the values in 15 placebo-treated patients chosen at random. Blood sampling was performed at 07.00 h. In the captopril-treated group, serum ACE activity decreased significantly, from 14.0±0.8 to 11.5±1.2 IU/L 24 h after captopril therapy (p<0.01), and those of PAI activity and t-PA antigen also decreased significantly – from 11.9±2.8 to 5.5±2.2 IU/ml (p<0.02) and from 9.9±1.0 to 7.5±0.9 ng/ml (p<0.05), respectively 48 h after captopril therapy. However, the levels of ACE activity, PAI activity, and t-PA antigen remained unchanged during the study period in the placebo group. Thus, our data indicate that the administration of captopril to patients with acute myocardial infarction may result in a reduced frequency of recurrent coronary thrombosis by increasing fibrinolytic capacity.

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Key Words: Captopril; Plasminogen activator inhibitor; Myocardial infarction

Recent clinical trials indicate that the administration of angiotensin-converting enzyme (ACE) inhibitors reduces recurrent myocardial infarction in patients with left ventricular dysfunction after myocardial infarction.1–2 However, the mechanism of this newly recognized effect of ACE inhibition is not clear. It has been reported that ACE inhibitors may regulate bradykinin, which can increase the production of prostacyclin, endothelium-derived relaxing factor, and tissue plasminogen activator (t-PA)3 and that angiotensin II (ANG II) effects a direct increase in plasminogen activator inhibitor 1 (PAI-1)4.

There is an increasing body of evidence to indicate that coronary thrombosis plays an important role in the pathogenesis of myocardial infarction.5–6 Furthermore, thrombus formation has been suggested to be related to decreased fibrinolysis? The central component of the fibrinolytic system is plasmin, which dissolves fibrin or thrombus, and which is converted from plasminogen by t-PA5. In blood, however, t-PA is rapidly inhibited by plasminogen activator inhibitors (PAlS), mainly PAI-17 Thus, the fibrinolytic function of the blood is determined by the balance between t-PA and PAlS. Furthermore, it has been reported that elevated levels of PAI-1 and t-PA antigen appear to constitute a marker of the risk for coronary thrombosis and that PAI, in particular, is a marker of recurrent coronary thrombosis.8–16 Wright et al17 have also

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Division of Cardiology, Fukuoka TokusyuKai Hospital, Fukuoka, Japan, and *Kumamoto University School of Medicine, Kumamoto, Japan
Mailing address: Hisao Ogawa, MD, Division of Cardiology Kumamoto University Medical School, 1-1-1 Honjo, Kumamoto 860, Kumamoto, Japan
demonstrated that treatment with captopril for 4 weeks is associated with a significant decrease in the levels of t-PA antigen and PAI activity during the chronic period in patients with uncomplicated myocardial infarction. However, it is not known whether captopril induces changes in the levels of these factors during the subacute phase of the disease or during hospitalization for acute myocardial infarction.

We hypothesized that prior administration of the ACE inhibitor captopril to patients with acute myocardial infarction might result in a reduction in plasma levels of PAI-1, as occurs in the chronic phase. We examined the levels of plasma PAI activity, t-PA antigen, and serum ACE activity before and after captopril therapy in hospitalized patients with acute myocardial infarction.

Methods

Study Population

This study was a prospective, randomized, placebo-controlled trial in patients with myocardial infarction. We studied 29 patients for 12–25 days (mean 16.5 days) after the onset of myocardial infarction. The patients were randomly assigned to the study groups (14 in the captopril group and 15 in the placebo group). Pain was associated with at least one of the following features: elevation of the ST segment in 2 or more continuous electrocardiographic leads; new, pathologic Q-waves; or elevated plasma levels of enzymes indicating myocardial damage. Patients were excluded from the study if their blood pressure was less than 100/60 mmHg. Patients were also excluded if they had any of the following: a need for vasopressor treatment for blood pressure support; hemodynamically severe valvular stenosis; untreated third-degree atrioventricular block; a history of angioedema or sensitivity to ACE inhibitors or the use of such drugs within 1 week before the infarction; clinically severe renal, hepatic, or hematologic disorders; a history of cerebral transient ischemic attacks related to reduction in blood pressure within the preceding 6 months; or life-threatening conditions other than myocardial infarction. All patients received standard therapy, including nitrates, calcium channel blockers, thrombolytic agents, coronary angioplasty, aspirin, diuretics, and anticoagulants. Any treatment with thrombolytic agent or coronary angioplasty was completed before administration of captopril or placebo. Treatment was initiated with 37.5 mg of oral captopril daily (one 12.5-mg tablet at 06.00, 12.00 and 18.00 h).

Captopril administration was stopped if the systolic blood pressure fell to 90 mmHg or if the diastolic pressure fell to 60 mmHg. No patients exhibited a marked hypotensive response. Written informed consent was obtained from each patient, and the study was performed in accordance with the guidelines approved by the Kumamoto University School of Medicine Ethics Committee.

Blood Samples and Assays

Blood sampling was undertaken at 07.00 h with patients in the fasting state because plasma PAI activity and t-PA antigen show a significant circadian variation. Blood was withdrawn from the antecubital vein using a 21-gauge needle (to achieve clean venipuncture without stasis) by specially trained persons before the administration of captopril or placebo, and on days 1 and 2 after administration. The first 3 ml of blood was discarded, and then 4.5 ml of blood for assay of PAI activity and t-PA antigen was drawn directly into a glass tube containing 0.5 ml of sodium citrate (0.13 mol/L, pH 7.5). Blood sampling for measurement of ACE activity was performed at the same time. All blood samples were immediately centrifuged at 3000 rpm for 15 min at 4°C, and aliquots of samples were immediately stored at −80°C until used. PAI activity was determined by a chromogenic substrate assay with the Spectrolyze/PL reagent kit (Biopool, Umeå, Sweden). The results are expressed in IU/ml. The intra-assay and interassay coefficient of variation are 9.4% and 11.4%, respectively. The normal PAI activity level in our laboratory (n=33) is 5.2±0.5 IU/ml (mean±SEM).

t-PA antigen levels were measured with a commercial enzyme-linked immunosorbent assay kit (Diagnostica Stago, Francoville, France) using the sandwich method. The results are expressed in ng/ml. The intra-assay and interassay coefficient of variation for this assay are 2.4 and 4.7%, respectively. The normal value for t-PA antigen in our laboratory (n=35) is 5.8±0.3 ng/ml (mean±SEM).

Serum ACE activity was measured by colorimetry using a commercially available kit, ACE color (Fujirebio, Tokyo). The results are expressed in IU/L. The intra-assay and inter-assay coefficient of variation of this method are 7.8% and 14.3%, respectively. The normal value for ACE activity in our laboratory (n=19) is 14.5±0.87 IU/L (mean±SEM).

Statistical Analyses

The clinical and angiographic characteristics of the captopril- and placebo-treated subjects were compared using the unpaired Student’s t test for continuous data and the 2 test for group data. The statistical significance of serial changes in plasma PAI activity, t-PA
Table 1 Characteristics of the Study Groups

<table>
<thead>
<tr>
<th></th>
<th>Captopril (n=14)</th>
<th>Placebo (n=15)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>61.6±11.2</td>
<td>65.3±11.2</td>
<td>NS</td>
</tr>
<tr>
<td>Range</td>
<td>39–76</td>
<td>38–77</td>
<td></td>
</tr>
<tr>
<td>Sex (male/female)</td>
<td>10/4</td>
<td>12/3</td>
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</tr>
<tr>
<td>Previous MI</td>
<td>4</td>
<td>4</td>
<td>NS</td>
</tr>
<tr>
<td>Hypertension</td>
<td>6</td>
<td>7</td>
<td>NS</td>
</tr>
<tr>
<td>Smokers</td>
<td>11</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>3</td>
<td>4</td>
<td>NS</td>
</tr>
<tr>
<td>Serum cholesterol (mg/dl)</td>
<td>187.5±34.2</td>
<td>197.5±43.9</td>
<td>NS</td>
</tr>
<tr>
<td>HDL-cholesterol (mg/dl)</td>
<td>39.8±12.9</td>
<td>41.9±13.3</td>
<td>NS</td>
</tr>
<tr>
<td>Triglyceride</td>
<td>140.8±102.5</td>
<td>183.5±183.5</td>
<td>NS</td>
</tr>
<tr>
<td>EF (%)</td>
<td>49.7±14.1</td>
<td>55.9±11.7</td>
<td>NS</td>
</tr>
<tr>
<td>Infarction site</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Anterior</td>
<td>6</td>
<td>6</td>
<td>NS</td>
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<tr>
<td>Infero lateral</td>
<td>8</td>
<td>9</td>
<td>NS</td>
</tr>
<tr>
<td>Q-wave infarction</td>
<td>10</td>
<td>10</td>
<td>NS</td>
</tr>
<tr>
<td>Thrombolytic therapy</td>
<td>6</td>
<td>7</td>
<td>NS</td>
</tr>
<tr>
<td>Direct or rescue PTCA</td>
<td>9</td>
<td>10</td>
<td>NS</td>
</tr>
</tbody>
</table>

EF, ejection fraction; HDL, high-density lipoprotein; MI, myocardial infarction; PTCA, percutaneous transluminal coronary angioplasty. Values are means ± SEM.

Table 2 Changes in Systolic and Diastolic Blood Pressure in the 2 Groups

<table>
<thead>
<tr>
<th>Group</th>
<th>Baseline</th>
<th>Day 1</th>
<th>Day 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic BP (mmHg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Captopril</td>
<td>125.4±5.7</td>
<td>116.9±5.4</td>
<td>121.1±5.6</td>
</tr>
<tr>
<td>Placebo</td>
<td>118.2±5.7</td>
<td>119.7±6.2</td>
<td>120±5.5</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Captopril</td>
<td>70.8±2.1</td>
<td>65.7±2.8</td>
<td>71.7±3.6</td>
</tr>
<tr>
<td>Placebo</td>
<td>69.2±2.5</td>
<td>70.8±2.8</td>
<td>72.2±1.8</td>
</tr>
</tbody>
</table>

BP, blood pressure, Values are means ± SEM.

antigen, and serum ACE activity was evaluated using analysis of variance for repeated measurements. Blood pressure and heart rate for 3 days were also evaluated using analysis of variance for repeated measurements. Probability levels of less than 0.05 were considered significant. Data are expressed as means ± SEM.

Results

Patients Characteristics and Clinical Outcomes (Tables 1 and 2)

There was no significant difference in patient characteristics and clinical outcomes between the captopril-treated group and the placebo-treated group, as shown in Table 1. Nor was there any significant difference between the 2 groups in terms of changes in blood pressure, although the systolic and diastolic blood pressure were slightly decreased on day 1 in the captopril-treated group (Table 2).

Changes in Plasma t-PA Antigen, Plasma PAI Activity, and Serum ACE Activity in the 2 Groups (Figs 1 and 2)

The level of t-PA antigen decreased significantly from 9.9±1.0 to 7.5±0.9 ng/ml on day 2 in the captopril-treated group (p<0.05) [median reduction 18%; 95% confidence interval (CI) 3% to -32%] but remained unchanged in the placebo-treated group (Fig 1). ACE activity decreased significantly (p<0.01) from 14.0±0.8 to 11.5±1.2 IU/L on day 1 after captopril administration (median 10%, 95% CI 16% to -27%) but remained unchanged in the placebo group (Fig 2). PAI activity also significantly (p<0.02) decreased from 11.9±2.8 to 5.5±2.2 IU/ml on day 2 in the captopril group(56%−, -34% to -79%) (Fig 3). It remained unchanged in the placebo group.

Discussion

ACE inhibitors are beneficial in patients with severe
heart failure because they reduce mortality and improve left ventricular function. Experimental and clinical studies in animals have shown that ACE inhibitors have an advantageous effect on the remodeling of the myocardium after myocardial infarction. Furthermore, ACE inhibitors also have a beneficial effect on acute ischemia. The effects of ACE inhibitors on the myocardium appear to be multifactorial and may include an anti-ischemic effect in the treatment of acute heart failure.

In addition, the results of the SAVE trial have demonstrated that the administration of captopril to patients with left ventricular dysfunction after myocardial infarction reduces the incidence of recurrent myocardial infarction by approximately 25%. However, the mechanism of this newly recognized effect...
of ACE inhibition is not clear. Ridker et al\(^4\) have shown that infusion of ANG II results in a rapid increase in circulating levels of PAI-1, a risk marker for recurrent coronary thrombosis. The activity of the fibrinolytic system is reflected in the circulating levels of t-PA and its most physiologically important inhibitor, PAI-1.\(^2\) Thus, fibrinolytic function in blood is determined by the balance between t-PA and PAIs.

Measured levels of t-PA antigen include inactive complexes of t-PA with PAI-1. It has also been reported that there is an approximately linear relation between t-PA antigen and PAI activity.\(^2\) Thus, the higher levels of t-PA antigen which are associated with high levels of PAI activity may reflect decreased active circulating levels of t-PA and low t-PA activity. In practice, increased levels of t-PA antigen have been shown to be a marker of coronary thrombosis.\(^12\)–\(^16\) It has been reported that elevated PAI-1 activities reflecting low t-PA activities and low fibrinolytic activity appear to constitute a marker of the risk of coronary thrombosis and an increased risk of reinfarction.\(^10\),\(^11\) These findings suggest that a low PAI-1 activity and a low level of t-PA antigen may result in an improvement in fibrinolytic capacity and thus a reduced risk of reinfarction.

Wright et al\(^17\) also have demonstrated that treatment with captopril for 4 weeks is associated with a significant decrease in the level of t-PA antigen and PAI activity during the chronic period (at least 12 weeks after the initial event) in patients with uncomplicated myocardial infarction. Thus, the object of the present investigation was to determine whether the ACE inhibitor captopril rapidly (within 48 h after administration) reduces plasma levels of PAI activity and t-PA antigen during the subacute period (at least 12 days after the onset of myocardial infarction), as it does in the chronic phase. We found that PAI activity and t-PA antigen were significantly decreased 48 h after captopril therapy. PAI activity was reduced more markedly in our study (by 56%) than in the study of Wright et al (17% reduction). This might be due to differences in the timing of the start of the studies, the duration of the studies, the dose of captopril administered (37.5 mg/day in our study vs 75 mg/day in the study by Wright et al) or the race of the subjects.

In this study blood samples were drawn more than 12 days after the onset of myocardial infarction because it has been suggested that fibrinolytic variables are disturbed only in the first few days after infarction and are stable after 1 week.\(^3\) The earlier administration of an ACE inhibitor for the treatment of acute myocardial infarction is controversial.\(^3\)–\(^3\)

As recent studies\(^4\),\(^3\) and our data suggest, an additional action of ACE inhibition may be to improve endogenous fibrinolytic function among patients at high risk for recurrent ischemic events. Such a potential relation between the renin-angiotensin system and endogenous fibrinolytic function might help to explain the observation that patients with high-renin essential hypertension appear to be at greater risk for coronary thrombus than do patients with similar levels of hypertension but lower plasma renin activity.\(^2\) In addition,
Captopril has been shown to inhibit platelet aggregation and thereby reduce the release of platelet-derived growth factor, one of the agents known to enhance endothelial PAI-1 synthesis.5

In conclusion, our data indicate that captopril administration may cause a rapid increase in fibrinolytic capacity during the subacute phase of acute myocardial infarction as well as during the chronic phase. These findings suggest that earlier administration of ACE inhibitor to patients with acute myocardial infarction might reduce the risk of reinfarction. The optimum timing of start of administration and the optimum dose of captopril require further investigation.

Acknowledgments

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