Angiotensin-Converting Enzyme Inhibitor Promotes Coronary Collateral Circulation in Patients With Coronary Artery Disease

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Previous studies have suggested that angiotensin-converting enzyme inhibitors (ACEI) promote collateral circulation in ischemic limbs of rabbits. The present study was designed to determine the association between treatment with ACEI and the development of coronary collateral circulation, as assessed by the Rentrop Score, in patients with coronary artery disease (CAD) in a case–control study. Subjects included 456 patients with angina who underwent coronary angiography. Those who had one (1-V), two (2-V) or three (3-V) significantly stenosed vessels, and who received only ACEI without any other anti-hypertensive medication were defined as cases (n=33), and age, sex and body mass index-matched subjects (n=56) were selected as controls. Among 1-V patients, but not 2-V or 3-V patients, the cases included a higher percentage of patients with Rentrop Score of at least 1 than the controls, suggesting that ACEI was associated with coronary collateral circulation. Patients with 1-V disease who were treated with ACEI were most likely [odds ratio (confidence interval): 6.1 (1.4–30.1)] to develop collateral circulation, as assessed by a multiple logistic regression analysis. Therefore, treatment with ACEI was associated with the development of collateral circulation in patients with CAD, suggesting that such an action is associated with bradykinin production by ACEI. (Circ J 2003; 67: 535–538)

Key Words: Angiotensin-converting enzyme inhibitors (ACEI); Bradykinin; Collateral circulation; Stenosed vessels

C oronary artery disease (CAD) is still the most frequent cause of death in Western countries. The improved survival of patients with acute coronary syndrome (ACS), whether treated medically or with revascularization techniques, has led to an increase in the number of patients with chronic CAD. The stimulation of collateral artery development (arteriogenesis) and/or capillary network growth (angiogenesis) may be beneficial in these patients.

Angiotensin-converting enzyme (ACE) is a dipeptidyl carboxypeptidase that converts inactive angiotensin I (Ang I) to angiotensin II (Ang II) and inactivates bradykinin (BK). ACE inhibition targeting the kininase-mediated inactivation of BK may increase local nitrous oxide (NO) production, and the clinical application of drugs that inhibit ACE activity has been shown to exert a favourable effect on endothelial dysfunction.

ACE inhibitors (ACEI) have been reported to increase capillary density in rat limb muscle,[6] sciatic nerve[7] and coronary microvasculature[4,5]. In addition, ACE inhibition with quinaprilat promotes angiogenesis in a rabbit model of hindlimb ischemia. Recently, BK, in synergy with interleukin-1 has been shown to enhance the angiogenic process in rat subcutaneous-sponge granuloma[8] and the local delivery of tissue kallikrein gene has been shown to induce angiogenesis in both ischemic and normoperfused skeletal muscle.[9]

We hypothesized that the use of ACEI may be associated with a significant progression of coronary collateral circulation, although there is no clear evidence to show that ACEI has similar beneficial effects in humans. Accordingly, in the present case–control study, we investigated coronary collateral circulation, assessed by the Rentrop Score, in patients with CAD who received ACEI therapy.

Methods

Study Patients

The subjects were 452 patients with angina who underwent coronary angiography. They included patients who had one (1-V), two (2-V) or three (3-V) significantly stenosed coronary arteries (>50% luminal narrowing) as defined by coronary angiography. Patients with statin treatment were excluded from this study. Those who did and did not receive ACEI drugs as the only anti-hypertensive treatment were defined as cases (n=33, F/M: 8/25, age: 67±8 years) and age, sex and body mass index-matched controls (n=56, F/M: 16/40, age: 68±12 years), respectively. The duration of ACEI treatment was 31±24 months. Each group included 2 patients with bypass surgery. 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 2002. The ethics committee of Fukuoka University Hospital approved this study and
informed consent was obtained from each patient. Patients with acute myocardial infarction (within 3 weeks of onset), heart failure, vascular disease (aortitis treated by prednisolone) or hepatic dysfunction (viral or nonviral, transaminases more than 3-fold the normal value) were excluded from the study. Patients with total cholesterol (TC) >220 mg/dl or triglyceride (TG) >150 mg/dl were considered to have hyperlipidemia (HL). Patients with systolic or diastolic blood pressure >140 mmHg or <90 mmHg 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 or old myocardial infarction (OMI) did not. There was no difference between the 2 groups with respect to age, sex, body mass index (BMI), prevalence of HT, DM or old myocardial infarction (OMI). Baseline concentrations of TG and HDL-C were similar between the 2 groups.

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 direct intracoronary injection of isosorbide dinitrate, as described previously. Arterial narrowing that produced more than 50% luminal narrowing was considered significant. Coronary collateral circulation was graded according to the Rentrop Score as the next step.

Determination of Serum Lipid Concentrations

Blood was drawn in the morning after an overnight fast and serum concentration of TC, TG and high density lipoprotein-cholesterol (HDL-C) were determined enzymatically as described previously.

### Table 1 Baseline Characteristics of Controls and Cases

<table>
<thead>
<tr>
<th></th>
<th>Controls (n=56)</th>
<th>Cases (n=33)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>68±12</td>
<td>67±8</td>
<td>NS</td>
</tr>
<tr>
<td>F/M</td>
<td>16/40</td>
<td>8/25</td>
<td>NS</td>
</tr>
<tr>
<td>BMI, kg·m⁻²</td>
<td>24±3</td>
<td>23±2</td>
<td>NS</td>
</tr>
<tr>
<td>HT, %</td>
<td>4/1</td>
<td>1/5</td>
<td>NS</td>
</tr>
<tr>
<td>DM, %</td>
<td>32</td>
<td>44</td>
<td>NS</td>
</tr>
<tr>
<td>OMI, %</td>
<td>33</td>
<td>48</td>
<td>NS</td>
</tr>
<tr>
<td>Smoking, %</td>
<td>34</td>
<td>48</td>
<td>NS</td>
</tr>
<tr>
<td>PTCA, %</td>
<td>54</td>
<td>48</td>
<td>NS</td>
</tr>
<tr>
<td>Serum lipid profile, mg/dl</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TC</td>
<td>189±32</td>
<td>187±32</td>
<td>NS</td>
</tr>
<tr>
<td>TG</td>
<td>137±70</td>
<td>141±90</td>
<td>NS</td>
</tr>
<tr>
<td>HDL-C</td>
<td>48±16</td>
<td>44±12</td>
<td>NS</td>
</tr>
<tr>
<td>LDL-C</td>
<td>112±29</td>
<td>114±28</td>
<td>NS</td>
</tr>
</tbody>
</table>

Values are shown as mean±SD. BMI, body mass index; HT, hypertension; DM, diabetes mellitus; OMI, old myocardial infarction; PTCA, percutaneous transluminal coronary angioplasty; TC, total cholesterol; TG, triglycerides; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol. NS, not significant.

### Table 2 Stenosed Vessels, Rentrop Score and Cardiac Function in the Controls and Cases

<table>
<thead>
<tr>
<th></th>
<th>Controls (n=56)</th>
<th>Cases (n=33)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stenosed vessels</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-V/2-V/3-V, %</td>
<td>48/30/21</td>
<td>36/42/21</td>
<td>NS</td>
</tr>
<tr>
<td>Rentrop score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0/1/2/3, %</td>
<td>66/5/17/10</td>
<td>42/9/30/18</td>
<td>p&lt;0.05</td>
</tr>
<tr>
<td>Cardiac function</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CI, L·min⁻¹·m⁻²</td>
<td>2.8±0.8</td>
<td>2.8±0.6</td>
<td>NS</td>
</tr>
<tr>
<td>EF, %</td>
<td>61±13</td>
<td>55±17</td>
<td>NS</td>
</tr>
</tbody>
</table>

Values are shown as mean±SD. CI, cardiac index; EF, ejection fraction; NS, not significant.

### Transthoracic Echocardiography

An experienced sonographer, with the assistance of an experienced staff echocardiographer, obtained all echocardiographic data. Comprehensive examinations were performed on all of the study patients, including M-mode, ejection fraction (EF), 2-dimensional, conventional Doppler, and color Doppler echocardiography.

### Statistical Analysis

Statistical analysis was performed using the SAS software package (version 6.12, Statistical Analysis System, SAS Institute Inc, Cary, NC, USA) at Fukuoka University (Fukuoka, Japan). Categorical and continuous variables in cases and controls were compared by a chi-square analysis and an analysis of variance, respectively. Relationships between variables were tested by Pearson and Spearman correlations. Associations among the Rentrop Score, number of diseased vessels, and case–control status were examined by logistic regression analysis. We calculated 95% confidence intervals for the odds ratios.

### Results

### Patient Demographics

Baseline clinical characteristics of the cases and controls are shown in Table 1. Among the 89 patients, 33 (37%) received treatment with ACEI and the remaining 56 (63%) did not. There was no difference between the 2 groups with respect to age, sex, body mass index (BMI), prevalence of HT, DM or old myocardial infarction (OMI). Baseline concentrations of TG and HDL-C were similar between the groups.

All patients in both groups had at least one significantly stenosed vessel. Patients with OMI, who had undergone percutaneous transluminal coronary angioplasty during the acute phase of myocardial infarction, were re-evaluated by coronary angiography at 6 months after the initial attack. There was no difference in the percentage of patients with unstable angina pectoris between groups (controls 11% vs cases 9%). The development of collateral coronary circulation was associated with the strength and duration of angina. Although we did not have enough information to analyze the precondition state as a retrospective study, we matched the baseline characteristics of the groups using as many factors as possible.

The cases included a higher percentage of patients with a Rentrop Score ≥1 than the controls (Table 2). Therefore, we adjusted the number of stenosed vessels to the Rentrop Score as the next step.
ACEI and Collateral Circulation

Relation Between Collateral Circulation and Number of Stenosed Vessels

Because collateral circulation develops in the advanced stages of coronary atherosclerosis; it was assessed according to the percentage of patients with Rentrop Score ≥1 among those with 1-V, 2-V or 3-V. As shown in Fig 1A, the percentage of patients with a Rentrop Score ≥1 among cases was significantly higher than that in controls among 1-V patients, but not 2-V or 3-V patients, suggesting that ACEI treatment was associated with coronary collateral circulation in 1-V disease patients.

Effects of Collateral Circulation on Statin Treatment

Fig 1B shows the odds ratio for each combination of ACEI treatment (controls and cases) and the number of stenosed vessels (1-V and 2-V + 3-V). As shown, patients with 1-V disease who were treated with ACEI showed significantly higher relative development of collateral circulation than patients with 1-V disease who were not treated with ACEI, and patients with 2-V + 3-V disease showed similar development in both groups. These results suggest that ACEI treatment is useful for collateral development in the mild degree of CAD, such as 1-V disease.

Discussion

Based on a recent study that indicated that ACE inhibition with quinaprilat promotes angiogenesis in a rabbit model of hindlimb ischemia; we studied whether the use of ACEI is associated with a significant development of coronary collateral circulation in humans. Our finding in the first comprehensive analysis of the role of ACEI-induced coronary collateral circulation is consistent with other clinical studies that have shown that ACEI therapy rapidly improves endothelial function, including collateral blood flow, independent of its anti-hypertensive action.

The ACEI captopril, but not quinaprilat, has a sulfhydryl group that has been implicated in a variety of effects including inhibition of neovascularization in the rat cornea. This inhibition has been shown not to result from reduced enzymatic ACE activity, but instead appeared to result from captopril inhibition of Zn2+-dependent metalloproteinase activity that endothelial cells need to respond to an angiogenic stimulus. Because none of the cases received captopril, collateral circulation developed with the use of ACEI in this study.

The duration of ACEI treatment ranged from 3 to 120 months (30±24 months). Treatment with quinaprilat for 40 days promoted angiogenesis while inhibiting ACE activity in a rabbit model of hindlimb ischemia. Silvestre et al also reported that ACE inhibition with perindopril for 28 days had a proangiogenic effect in a mouse model of hindlimb ischemia. We can not directly compare the collateral circulation in an animal model of hindlimb ischemia to that in a human coronary artery. Because ACEI treatment for 3 months was enough to block ACE activity in humans, ACEI-treated patients were presumed to have been receiving medication for a sufficient duration.

ACEI blocks Ang II-induced signalling by inhibiting Ang II production. Although Ang II has previously been reported to induce a concentration- and time-dependent increase in vascular endothelial growth factor (VEGF) expression by vascular smooth muscle cells as well as endothelial cells; hypoxia in the ischemic limb was sufficiently potent to upregulate VEGF expression independently of Ang II levels. There is insufficient evidence to support the notion that the renin–angiotensin system has a direct endogenous angiogenic effect.

The finding in previous animal experiments that the adaptation to chronic experimental occlusion can proceed via either an arteriogenenic pathway or a predominantly angiogenic pathway indicates that multiple occlusions in the human heart may give rise to a mixed arteriogenenic/type of adaptation, which is the development of collateral circulation. The process of arteriogenesis is mediated by shear stress-stimulated monocyte chemoattractant protein-1 (MCP-1). Because BK stimulated the release of MCP-1, BK might promote arteriogenesis through MCP-1. Angiogenesis involves the sprouting of endothelial cells by the induction of VEGF and nitric oxide synthetase (NOS). The proangiogenic effect of ACE inhibition with upregulation of eNOS is mediated by B2 receptor. In addition, we recently reported that in an in vitro model of human coronary artery endothelial cell tube formation, stimulation of the B2 receptor by BK led to the transactivation of KDR/Flk-1, VEGF receptor, as well as to eNOS activation, which induced angiogenesis. Therefore, ACEI may induce angiogenesis through BK-induced NO synthesis. These findings suggest that ACEI therapy could also be useful in CAD patients with normal blood pressure.

Our study was a nonrandomized, retrospective, observational study and we simply examined the association between ACEI and coronary collateral circulation. A large randomized controlled trial of ACEI in patients with CAD is warranted to evaluate the potential benefits of these agents.

In conclusion, our study provides initial observational evidence to suggest that treatment with ACEI is associated

Fig 1. (A) Relationship between the percentage of patients with Rentrop Score ≥1 and the number of stenosed vessels in the controls and cases. (B) Odds ratios for the association of each combination of statin (1-V or 2-V + 3-V) and status (control or case) with collateral development as assessed by the multiple logistic regression analysis. Odds ratios and 95% confidence intervals are shown.
with a significant promotion of coronary collateral circulation in patients with CAD. The results suggest that ACEI therapy may help prevent acute coronary syndrome.

Acknowledgments

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References


