Long-Term Treatment With Perindopril Ameliorates Dobutamine-Induced Myocardial Ischemia in Patients With Coronary Artery Disease

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ABSTRACT—The present study was designed to examine whether long-term blockade of angiotensin-converting enzyme (ACE) with perindopril ameliorates dobutamine-induced myocardial ischemia in patients with coronary artery disease (CAD). Twelve patients with proven CAD were randomly divided in two groups; one group received perindopril (8 mg/day, p.o.) for 3 months and another group served as a control. To evaluate anti-ischemic effects of perindopril, dobutamine stress echocardiography was performed before and 3 months after the treatment in a double-blind manner. Long-term treatment with perindopril significantly ameliorated the dobutamine-induced myocardial ischemia, as evaluated by time to the onset of symptoms, magnitude of electrocardiographic ST-segment changes, and left ventricular wall motion score (all \( P < 0.05 \)). The treatment significantly decreased serum ACE activities (\( P < 0.01 \)) and increased plasma bradykinin concentrations (\( P < 0.05 \)). The extent of reduction of left ventricular wall motion score by perindopril was closely correlated with that of inhibition of serum ACE activities (\( P < 0.01 \)) and with that of increase in plasma bradykinin concentrations (\( P < 0.05 \)). By contrast, no such beneficial changes were noted in the control group. These results provide the first evidence that long-term treatment with perindopril exerts anti-ischemic effects on the myocardial ischemia induced by increased myocardial oxygen demand in patients with CAD.

Keywords: Angiotensin-converting enzyme inhibitor, Coronary artery disease, Dobutamine stress echocardiography, Myocardial ischemia, Perindopril

Angiotensin-converting enzyme (ACE) inhibitors have been widely used in the treatment of hypertension and heart failure. Recently, blockade of the renin-angiotensin system with ACE inhibitors has been proved to be effective in reducing the risk of major cardiovascular events, including worsening angina, myocardial infarction, coronary revascularization (angioplasty or bypass surgery), cardiac arrest and death from cardiovascular causes (1). The beneficial effects of ACE inhibitors have also been noted in a wide spectrum of patients with coronary artery disease (CAD), irrespective of the presence or absence of left ventricular dysfunction, coronary risk factors, or concomitant use of medication (1). Despite such accumulating evidence, the mechanisms of actions for it remain to be fully elucidated, and it is still controversial whether blockade of ACE ameliorates myocardial ischemia per se in patients with CAD (2).

It has been reported that treatment with ACE inhibitors exerts beneficial effects on myocardial ischemia during treadmill exercise testing in patients with CAD (3, 4). However, exercise tolerance during treadmill testing is determined both by cardiac factors (e.g., coronary circulatory or left ventricular function) and by non-cardiac factors (e.g., peripheral arterial or pulmonary function). Thus, the beneficial effects of ACE inhibitors could in part be due to their non-cardiac effects. No study has ever addressed the direct effects of ACE inhibitors on myocardial ischemia in patients with CAD.

Dobutamine stress echocardiography (DSE) is the most sensitive method for detecting myocardial ischemia in patients with CAD clinically (5, 6). In the presence of
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CAD, the increased myocardial oxygen demand by continuous intravenous infusion of dobutamine is associated with an inadequate increase in coronary blood flow, resulting in myocardial ischemia with abnormal left ventricular wall motion that can be detected directly by cross-sectional echocardiography with high sensitivity (85%) and specificity (93%) (7, 8). The present study was therefore designed to examine whether or not long-term blockade of ACE with perindopril ameliorates the myocardial ischemia during DSE in patients with CAD.

MATERIALS AND METHODS

Subjects

DSE was carried out in 33 consecutive patients, and a positive result was obtained in 19 patients. Among them, 12 patients with CAD proved by coronary arteriography, who consented to participation in the study, were enrolled. All patients gave a written informed consent. The study protocol was approved by the Human Research Committee at the University of Occupational and Environmental Health. No patient received ACE inhibitors, angiotensin type-1 receptor antagonists or 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors before the examination. The clinical characteristics of the patients are shown in Table 1.

Study protocol

The patients were randomly divided in two groups by the envelope method; one group received perindopril (8 mg/day, p.o.) for 3 months, and another group served as a control. To evaluate the degree of myocardial ischemia, DSE was performed before and 3 months after the treatment with perindopril in a double-blind manner. Time to the onset of symptoms, electrocardiographic ST-segment depression and left ventricular wall motion score were examined as markers of dobutamine-induced myocardial ischemia (9). The effects of the perindopril treatment were compared at the maximal comparable stage of DSE, which was the maximal level that the same patient achieved in two examinations (9).

DSE

DSE was carried out at the same time of day (from 9:00 AM) in all patients. One patient in the control group was receiving a β-adrenergic receptor blocking agent, which was discontinued one day before the examination (9). No patient received verapamil, which could suppress the heart rate response to dobutamine. The presence of unstable angina, profound anemia, electrolyte imbalance, or uncontrolled hypertension (systolic blood pressure >190 mmHg or diastolic blood pressure >100 mmHg, or both) was regarded as a contraindication for DSE.

The patients were in the left lateral decubitus position throughout the study. They were asked to report the onset of chest pain or discomfort or both during the examination. Dobutamine was administered intravenously by an infusion pump. The starting dose of dobutamine was 5 μg·kg⁻¹·min⁻¹, and the dose of dobutamine was increased in a stepwise manner to 10, 20, 30 and 40 μg·kg⁻¹·min⁻¹ every 4 min. Then 0.5 to 1.0 mg atropine was injected until one of the following general end points was reached: target heart rate (85% of age-predicted maximal heart rate), peak dose of dobutamine, ischemic ECG changes (>1 mm

| Patient number | Age (yr)/Gender | Coronary artery disease | Old myocardial infarction | LVEF (%) | Risk factor |
|----------------|-----------------|-------------------------|---------------------------|----------|------------|
| **Control group** | |
| 1 | 50/M | 2VD | Yes (inferior) | 59 | HL, DM |
| 2 | 83/F | 3VD | Yes (lateral) | 40 | HL |
| 3 | 75/M | 1VD | No | 63 | HT |
| 4 | 71/M | 3VD | Yes (anteroseptal) | 44 | DM |
| 5 | 62/M | 3VD | Yes (inferior) | 65 | DM |
| 6 | 82/M | 2VD | Yes (posterior) | 61 | DM |
| **Perindopril group** | |
| 1 | 76/F | 1VD | No | 45 | HT, HL |
| 2 | 61/F | 3VD | Yes (inferolateral) | 56 | DM |
| 3 | 71/M | 3VD | Yes (anteroseptal) | 46 | DM |
| 4 | 61/M | 1VD | No | 64 | DM, HT |
| 5 | 48/M | 2VD | Yes (anteroseptal) | 51 | HL |
| 6 | 63/F | 3VD | No | 71 | HT, HL |

HL, hyperlipidemia; DM, diabetes mellitus; HT, hypertension; LVEF, left ventricular ejection fraction; VD, vessel disease.
ST-segment depression or elevation in more than two leads), severe hypertension (systolic blood pressure >220 mmHg or diastolic blood pressure >110 mmHg, or both), hypotension (>20 mmHg decrease in systolic blood pressure), chest pain or patient refusal to continue. When the patient experienced only mild chest discomfort or dyspnea without any of the end points mentioned above, the dobutamine infusion was continued until an end point was reached.

Two-dimensional echocardiograms were obtained at rest, 3 min after dobutamine infusion at each stage, and 10 min after the end of the dobutamine infusion. Echocardiographic images included parasternal long-axis, parasternal short-axis, apical two-chamber and apical four-chamber views; they were stored on both a digitized format (Cine View version 5.14; TomTec Imaging, Inc., Place, CO, USA) and S-VHS videotapes (Fujifilm, Tokyo) for off-line analysis.

Twelve-lead electrocardiograms were recorded at each stage (Cardiofax V ECAPS12; Nihon Kohden, Tokyo) and the patient was continuously monitored by three-lead electrocardiograms during the examination. Blood pressure was measured at each stage with a cuff manometer in the right or left arm opposite to the dobutamine infusion side. Time to the onset of symptoms (chest pain, chest discomfort or dyspnea) was also recorded. ST-segment depression was measured at 0.08 s after the J point, and ST elevation was measured at 0.02 s after the J point. The sum of ST shifts was calculated by summing the ST depressions or elevations in 12-lead electrocardiograms.

We have previously confirmed that our DSE is reproducible to detect the presence of CAD with a sensitivity of 85% and a specificity of 93% (7).

Analysis of DSE

Echocardiograms were independently interpreted in a blind manner by two experienced cardiologists familiar with the analysis of left ventricular wall motion (7, 9). Left ventricular wall motion was analyzed in a 16-segment model as suggested by the American Society of Echocardiography by using a quad-screen format (10). Wall motion was scored in the following manner: normal = 1, mild hypokinesia = 1.5, moderate hypokinesia = 2, severe hypokinesia = 2.5, akinesia = 3, and dyskinesia = 4. Hyperdynamic wall motion was regarded as a normal response to dobutamine (8). The segments at which no wall motion abnormality was seen in both examinations before and after 3 months varied even in the same patient. Thus, the changes in the wall motion score or the ST-segment level from the low-dose dobutamine stage to the maximal comparable stage of DSE, which is the maximal level that the same patient could achieve in both examinations, was determined to evaluate the effects of perindopril.

The mean value of the changes in the wall motion score was used for off-line analysis.

Measurements of serum ACE activities and plasma bradykinin concentrations

Venous blood sampling was carried out at 8:30 AM under fasting condition before DSE. The samples were immediately centrifuged at 3,000 rpm, 4°C for 15 min and the supernatants were stored at −80°C. Serum ACE activities were measured by the Kasahara method (11) and plasma bradykinin concentrations were determined by a radioimmunoassay (12).

Drugs

Dobutamine chloride was obtained from Shionogi Pharmaceutical Co., Ltd. (Osaka), atropine sulfate from Tanabe Pharmaceutical Co., Ltd. (Tokyo) and perindopril from Dai-ichi Pharmaceutical Co., Ltd. (Tokyo).

Statistical analyses

Results are expressed as the mean value ± S.E.M. Throughout the text, n means the number of patients. Results were analyzed with a paired t-test, unpaired t-test, chi-square test or analysis of variance where appropriate. If a significant F value was found in the analysis of variance, the Scheffe’s test for multiple comparisons was used to identify the differences among groups. The values were considered to be statistically different when P was less than 0.05.

RESULTS

Patient characteristics

Clinical characteristics, including age, gender, number of significantly stenotic coronary arteries (more than 75% stenosis by American Heart Association classification) (13), history of old myocardial infarction (14), left ventricular ejection fraction calculated by left ventriculogram and the presence of coronary risk factors, were comparable between the control and the perindopril groups (Table 1). All patients received aspirin and nitrates. No adverse effect was noted in the perindopril group.

End point of DSE

Among the 24 DSE examinations, dobutamine infusion was stopped because of chest pain in 4, achievement of the peak dose of dobutamine in 5, ischemic ST-segment
changes in 2, and appearance of wall motion abnormalities in 13. Thus, the maximal stage of DSE (as expressed by the dobutamine dose or by atropine injection) was 10 (n = 0), 20 (n = 2), 30 (n = 3) and 40 (n = 13) μg · kg⁻¹ · min⁻¹ of dobutamine and atropine injection (n = 6). The patients reported that the dobutamine-induced chest pain was similar to that experienced in their daily life.

**Hemodynamic variables**

No significant difference was noted between the two groups for heart rate, blood pressure or rate-pressure product at each stage of DSE before and 3 months after the study (Table 2). The long-term treatment with perindopril did not significantly change those hemodynamic variables (Table 2).

**Symptoms, electrocardiographic changes, and wall motion abnormalities**

The long-term treatment with perindopril significantly prolonged the time to the onset of symptoms by an average

| Table 2. Hemodynamic variables before and 3 months after the study |
|-------------------------|-------------------------|
|                         | Before                  | After 3 months          |
|                         | rest low dose high dose | rest low dose high dose |
| Control group           |                         |                         |
| HR                     | 55 ± 3                  | 63 ± 7                  |
| Systolic BP            | 125 ± 7                 | 123 ± 5                 |
| Diastolic BP           | 74 ± 3                  | 75 ± 2                  |
| RPP                    | 6.965 ± 610 11.568 ± 1,109 | 7.335 ± 643 11.843 ± 659 |
| Perindopril group      |                         |                         |
| HR                     | 58 ± 5                  | 64 ± 3                  |
| Systolic BP            | 127 ± 8                 | 127 ± 5                 |
| Diastolic BP           | 78 ± 6                  | 72 ± 3                  |
| RPP                    | 7.908 ± 1,155 11.012 ± 1,132 | 8.004 ± 244 11.189 ± 586 |

HR, heart rate; BP, blood pressure; RPP, rate-pressure product.

**Fig. 1.** Time to the onset of symptoms during DSE. The long-term treatment with perindopril significantly prolonged the onset of symptoms during DSE. One of 6 control patients was asymptomatic.

**Fig. 2.** Summed ST-segment changes during DSE. The long-term treatment with perindopril significantly reduced the magnitude of summed ST-segment changes at the maximum comparable stage of DSE.
of 36% \((P<0.05)\) (Fig. 1). The treatment also significantly reduced the magnitude of summed ST-segment changes at the maximum comparable stage of DSE by an average of 42% \((P<0.05)\) (Fig. 2). Furthermore, the treatment significantly ameliorated the worsening of left ventricular wall motion score at the maximum comparable stage of DSE by an average of 39% \((P<0.05)\) (Fig. 3). In contrast, no such beneficial changes were noted in the control group (Figs. 1–3).

The beneficial effects of perindopril on dobutamine-induced myocardial ischemia were observed regardless of the presence or absence of baseline wall motion abnormalities (data not shown).

Relation between left ventricular wall motion score and serum ACE activities or plasma bradykinin concentrations

The long-term treatment with perindopril significantly decreased serum ACE activities \((P<0.01)\) and increased plasma bradykinin concentrations \((P<0.05)\) (Table 3). In contrast, these values did not change in the control group (Table 3).

The extent of reduction of left ventricular wall motion score by perindopril was significantly correlated with that of the inhibition of serum ACE activities \((r = 0.96, P<0.01)\) (Fig. 4, left panel) and with that of the increase in plasma bradykinin concentrations \((r = 0.82, P<0.05)\) (Fig. 4, right panel).

| Table 3. Serum ACE activities and plasma bradykinin concentrations before and 3 months after the study |
|-----------------------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Control group | Perindopril group | Control group | Perindopril group | Control group | Perindopril group | Control group | Perindopril group | Control group | Perindopril group |
| Before | After 3 months | \(P\ value\) | Before | After 3 months | \(P\ value\) | Before | After 3 months | \(P\ value\) | Before | After 3 months | \(P\ value\) |
| ACE | 10.0 ± 1.6 | 10.1 ± 1.9 | n.s. | 12.7 ± 1.2 | 2.4 ± 0.6 | <0.01 | 16.9 ± 5.6 | 112.8 ± 26.9 | <0.05 |
| Bradykinin | 54.6 ± 23.9 | 100.9 ± 41.1 | n.s. | 16.9 ± 5.6 | 112.8 ± 26.9 | <0.05 |

ACE, angiotensin-converting enzyme; n.s., not significant.

Fig. 3. Left ventricular wall motion score at the maximum comparable stage of DSE. The long-term treatment with perindopril significantly ameliorated the worsening of the left ventricular wall motion score at the maximum comparable stage of DSE.

Fig. 4. Correlation between the extent of reduction of the left ventricular wall motion score and that of the inhibition of serum ACE activities (left panel) or that of the increase in plasma bradykinin concentrations (right panel) in the perindopril group.
DISCUSSION

In the present study, we demonstrated that the long-term treatment with perindopril prolonged the time to the onset of symptoms and reduced the magnitude of electrocardiographic ST-segment changes and the left ventricular wall motion score in the DSE test. This is, to our knowledge, the first direct evidence that long-term blockade of ACE ameliorates the myocardial ischemia induced by increased myocardial oxygen demand in patients with CAD.

DSE examination

Dobutamine is a synthetic catecholamine and has effects on β₁-, β₂- and α₁-adrenergic receptors (15, 16). Dobutamine increases myocardial oxygen demand by increasing heart rate and myocardial contractility primarily due to β₂-adrenergic receptor stimulation (15, 16). Because the β₂- and α₁-adrenergic agonist activities of dobutamine are milder than its β₁-adrenergic activity and because dobutamine-induced vasodilatation via β₂-adrenergic receptor and vasoconstriction via α₁-adrenergic receptor are balanced in peripheral vasculature, dobutamine infusion has minimal effects on blood pressure (15). In the presence of CAD, the increased myocardial oxygen demand by dobutamine is associated with an inadequate increase in coronary blood flow, resulting in myocardial ischemia and abnormal left ventricular wall motion that can be detected directly by cross-sectional echocardiography with high sensitivity (85%) and specificity (93%) (7, 8).

Characteristics of Perindopril

Perindopril is a long-acting ACE inhibitor with a high peak/trough ratio (87–100%) (17). Perindopril possesses high tissue binding affinity and indeed has been demonstrated to inhibit endothelial and adventitial ACE activities of the internal mammary artery of patients with CAD (18). Although other ACE inhibitors improved vascular remodelling (the ratio of media thickness to lumen diameter) in humans, the dose used exceeded the clinically recommended dose (2–4 times higher) (19, 20). Recent studies have shown that perindopril repairs vascular remodelling of the resistant vessels of hypertensive patients at a clinical dosage (21, 22). Based on these promising data, the European trial on reduction of cardiac events with perindopril in patients with stable CAD (EUROPA), which is proposed to recruit more than 10,000 patients, is now ongoing (23).

Anti-ischemic effects of perindopril

Biochemical studies reported that 90–99% of ACE in the body is found in local tissues, including blood vessels, the heart, and the kidney, while only 1–10% is found in circulating blood (24). ACE is upregulated under atherosclerotic and/or ischemic conditions, thereby increasing tissue angiotensin II production (2, 25). Thus, inhibition of the local tissue ACE activity is important for the vascular effects of ACE inhibitors.

In patients with CAD, treatment with perindopril for 3 months significantly improved dobutamine-induced anginal symptoms, electrocardiographic findings and left ventricular wall motions. By contrast, no such beneficial changes were noted in the control group. These results indicate that perindopril has anti-ischemic effects on the myocardial ischemia induced by increased myocardial oxygen demand.

Although the precise mechanisms for the anti-ischemic effects of perindopril are unclear, it may be due to the following vasculoprotective properties. First, angiotensin II is a potent vasoconstrictor (26), and thus perindopril may dilate the coronary vasculature, thereby increasing coronary blood flow. Second, angiotensin II produces superoxide anions via stimulation of NADH/NADPH oxidase of smooth muscle cells (27), and thus perindopril may protect the inactivation of endothelium-derived nitric oxide by superoxide anions. Third, angiotensin II induces smooth muscle cell proliferation (2, 25), and thus perindopril may have anti-atherogenic effects, as previously noted in a regression of atherosclerotic changes in human coronary arterioles (21, 22). Fourth, the inhibitory effects of ACE inhibitors on angiotensin II-induced thrombogenesis, sympathetic nerve activation, endothelin release and plaque instability may also be involved (2, 25). In the present study, the efficacy of perindopril was confirmed by the 81% inhibition of plasma ACE activities, which resulted in its anti-ischemic effects.

It is known that ACE degrades the local and circulating levels of bradykinin into inactive peptide and that the inhibition of ACE by its inhibitors leads to an increase in bradykinin levels (28). Indeed, the long-term treatment with perindopril significantly increased plasma bradykinin concentrations in the present study. Bradykinin stimulates vascular endothelium to release several relaxing factors, such as nitric oxide, prostacyclin and endothelium-derived hyperpolarizing factor, via the bradykinin B₂ receptor (29–32). It has been demonstrated that endothelium-dependent vasodilatation mediated by ACE inhibitors is indeed related to an increase in vascular bradykinin levels in healthy humans (33). In addition, perindopril has been shown to improve impaired flow-mediated coronary vasodilatation in patients with essential hypertension (34) and reverse endothelial dysfunction in patients with heart failure (35). Endothelial production of nitric oxide by bradykinin also has other beneficial effects on vascular integrity, by inhibiting platelet aggregation (36), neutrophil adhesion (37) and vascular smooth muscle mitogenesis (38), all of which may result in the anti-atherogenic actions of the kinin. The possible involvement of plasma bradykinin in the anti-
ischemic effect of perindopril is also supported by the present finding that the extent of perindopril-induced increase in plasma bradykinin concentrations is closely correlated with the reduction of left ventricular wall motion score. Thus, increased bradykinin concentrations would explain in part the anti-ischemic effects of perindopril.

A direct protective effect against cardiac myocytes may also be involved in the beneficial effect of perindopril. Angiotensin II stimulates cardiac hypertrophy via induction of protooncogene and growth factor expression, whereas bradykinin has an inhibitory effect on cardiac hypertrophy through NO and prostacycline generation. It is therefore likely that inhibition of angiotensin II production and elevation of bradykinin concentrations by perindopril could exert cardioprotective effects on ventricular remodeling in the ischemic myocardium.

In the present study, there was no significant difference in the markers of myocardial oxygen demand (e.g., blood pressure, heart rate, or rate-pressure product) between the control and perindopril groups. Therefore, the long-term treatment with perindopril appears to reduce myocardial ischemia without altering myocardial oxygen demand.

Even single administration of ACE inhibitors has been reported to improve exercise-induced myocardial ischemia in patients with CAD (3) and endothelial dysfunction in patients with essential hypertension (34). However, in most studies that showed a regression of arteriosclerotic vascular lesions, administration of ACE inhibitors was carried out for more than 6 months (19–23). In a preliminary study, we examined the effect of the perindopril treatment for 1 and 3 months. We noted that the perindopril treatment for 3 months, but not that for 1 month (data not shown), significantly improved dobutamine-induced myocardial ischemia in patients with CAD. Therefore, we treated our patients with perindopril for 3 months to demonstrate its anti-ischemic effect by DSE.

We were able to demonstrate that long-term blockade of ACE with perindopril ameliorates dobutamine-induced myocardial ischemia. Our findings may contribute to the better understanding of the beneficial effects of ACE blockade for the treatment of CAD.

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