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Effect of L-Arginine on Acetylcholine-Induced Endothelium-Dependent Vasodilation Differs Between the Coronary and Forearm Vasculatures in Humans

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Objectives. **The goal of this study was to determine whether the effect of L-arginine on endothelium-dependent vasodilation evoked with acetylcholine differs between the coronary and forearm vasculatures in humans.**

Background. **Administration of L-arginine, a substrate in the production of endothelium-derived nitric oxide, may stimulate the release of nitric oxide.**

Methods. **Seven patients with normal coronary angiograms and seven with mild coronary artery disease and hypertension underwent coronary arteriography and an intracoronary Doppler catheter technique, and the diameter of the large epicardial coronary artery and coronary blood flow were measured. Forearm blood flow was measured by use of a strain gauge plethysmograph.**

Results. **Before L-arginine administration, acetylcholine (1 to 30 μg/min) increased coronary blood flow with modest vasoconstriction of a large coronary artery. Acetylcholine (4 to 24 μg/min) also increased forearm blood flow. The acetylcholine-induced increases in coronary and forearm blood flow were significantly less in patients with coronary artery disease than in control patients. Intracoronary infusion of L-arginine at 50 mg/min did not alter responses of the large coronary artery diameter or coronary blood flow to acetylcholine in either group. In contrast, L-arginine at 10 mg/min significantly ($p < 0.01$) augmented the forearm blood flow response to acetylcholine (4 to 24 μg/min) to a similar extent in the two groups.**

Conclusions. **The effect of L-arginine on acetylcholine-induced vasodilation differs between the coronary and forearm vasculatures in humans. It is suggested that impaired acetylcholine-induced coronary and forearm vasodilation in patients with coronary artery disease and hypertension may not be related to a limited availability of L-arginine.**

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Recent studies (1–7) in animals and humans have demonstrated that the vascular endothelium plays an important role in the regulation of regional blood flow by releasing endothelium-derived relaxing factors. It has been shown (8) that nitric oxide is a major component of endothelium-derived relaxing factor and is synthesized from an amino acid, L-arginine, in endothelial cells. It has also been shown (1,2) that the endothelium-dependent vasodilator mechanisms differ among the vascular beds and species.

It has been reported (9,10) that intravenous administration of L-arginine, a substrate of nitric oxide production, reduced arterial pressure, possibly by means of vasodilation of peripheral resistance vessels in humans. We showed (11) that intra-arterial infusion of L-arginine at large doses caused forearm vasodilation and that L-arginine at low doses augmented endothelium-dependent forearm vasodilation evoked with acetylcholine in healthy human subjects. These findings suggest that administering an increased concentration of the substrate of nitric oxide synthesis, L-arginine, facilitates release of nitric oxide in the peripheral vasculature of healthy humans.

In contrast, Drexler et al. (12) demonstrated that intracoronary infusion of L-arginine did not alter vasomotor responses of large and resistance coronary arteries to acetylcholine in patients with no hypercholesterolemia. These previous findings may suggest that the effect of L-arginine on acetylcholine-induced vasodilation may differ between the peripheral and coronary vasculature in humans. However, whether the effect of L-arginine on endothelium-dependent vasodilation differs between the peripheral and coronary vasculature in humans has not been determined because no study has examined its effect in the two vasculatures in the same subjects.

We (5–7) and other investigators (12–19) have demonstrated that hypercholesterolemia as well as other risk factors for atherosclerosis are associated with impaired endothelium-dependent vasodilation in the peripheral or coronary vasculature in animals and humans. It has been shown (12,20–25) that defective endothelium-dependent vasodilation caused by low-

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Table 1. Patient Characteristics

Pt No.	Age (yr)/ Gender	Serum Cholesterol Level (mg/dl)	Smoking	HT	Drugs
Control Patients With a Normal Coronary Angiogram					
1	56/F	204	–	–	D
2	54/M	224	–	–	D, N
3	54/M	178	+	–	—
4	46/M	148	+	–	Nif, N
5	40/M	189	+	–	D
6	69/F	190	–	–	Nif
7	59/M	221	+	–	D
Mean ± SD	54 ± 9	193 ± 26			
Patients With Coronary Artery Disease					
1	64/M	260	+	+	D, N
2	62/M	254	+	+	D, Nif
3	59/M	178	+	+	Nic
4	65/M	264	–	–	B
5	63/F	180	+	+	Nif, Nic
6	66/M	147	+	+	—
7	68/M	159	+	+	—
Mean ± SD	64 ± 3*	206 ± 51			

*p = 0.02 versus control patients with a normal coronary angiogram. B = beta-blocker; D = diltiazem; F = female; HT = arterial hypertension; M = male; N = nitrate; Nic = nisorandil; Nif = nifedipine; Pt = patient; + = yes; – = no.

density lipoprotein or hypercholesterolemia is reversed by supplementation with L-arginine. On the basis of these previous results, it is proposed that the limited availability of L-arginine for synthesis of endothelium-derived nitric oxide or an enhanced inactivation of endothelium-derived nitric oxide is a cause of defective endothelium-dependent vasodilation in hypercholesterolemia or an early stage of atherosclerosis (26–30). However, it is not known whether local administration of L-arginine improves endothelium-dependent vasodilation in patients with mild coronary artery disease or risk factors other than hypercholesterolemia.

We aimed to determine whether the effect of local administration of L-arginine on endothelium-dependent vasodilation evoked with acetylcholine differs between the coronary and forearm vasculatures in humans. In addition, we examined whether impaired acetylcholine-induced vasodilation in patients with coronary artery disease is related to a limited availability of L-arginine.

Methods

Study patients. The study included 14 patients undergoing diagnostic coronary arteriography for investigation of coronary artery disease who were classified into two groups on the basis of coronary arteriographic findings (Table 1). Group 1 (control patients with normal coronary angiograms) included seven patients who had atypical chest pain and angiographically normal coronary arteries without wall irregularities in any of three major coronary arteries. Coronary arteriography was done in these patients to exclude the possibility of coronary vasospasm as a cause of atypical chest pain. All patients had a normal exercise test and negative findings on thallium myocardial scintigraphy stress tests. None had arterial hypertension or diabetes mellitus. Group 2 (patients with coronary artery disease) included seven patients with lumen irregularities (≤30% stenosis) in the left anterior descending coronary artery. Three patients had mild, and four had significant, stenosis (≤40% and >76% diameter stenosis, respectively) in the left circumflex or right coronary artery.

Study protocol. Coronary and forearm blood flow responses to drugs were measured in each patient. Antianginal and antihypertensive medications (Table 1) were discontinued at least 24 h before the coronary or forearm blood flow study. Cardiac catheterization was performed with patients in the fasting state after administration of 5 mg of oral diazepam. After completion of diagnostic coronary arteriography, the coronary blood flow study was carried out by one investigator (K.E.) who used an intracoronary Doppler catheter technique (5–7). On a different day, before or after the coronary blood flow study, the forearm blood flow study was performed by two investigators (Y.H. and T.I.) with use of a strain gauge plethysmograph. These two studies were done within 5 days. The study protocol was approved by the institutional committee on human research, and written informed consent was obtained from each patient.

Quantitative coronary arteriography. The diameter and cross-sectional area at the proximal segment of left anterior descending coronary artery were determined using a validated cinevideodensitometric analysis system, as previously described (5–7). After selection of the view that allowed the best visualization of the left anterior descending coronary artery, coronary angiograms were recorded with a Siemens cineangiographic system. The angle of view and the distance from the X-ray focus to the object and that from the object to the image intensifier were kept constant during the study.

An end-diastolic frame was selected on a cineprojector, and the image of the arterial segment of interest was digitized and analyzed with the videodensitometric analysis system. The diameter of the segment of interest (2 mm in length) was measured three times, and the average value was used for analysis. Two or more branch points were determined to allow assessment of serial changes in the diameter of the same arterial site in response to drugs. The size of a Judkins catheter was used for calibrating the arterial diameter in millimeters.

Measurements of coronary blood flow velocity and blood flow. A 8F angioplasty-guiding catheter was introduced into the left main coronary artery by a femoral approach. A 3F Doppler flow velocity catheter (model DC-201, Miller Instruments) was introduced into the proximal left anterior descending coronary artery. Blood flow velocity signals were obtained using a Millar DC-101 velocimeter. Coronary blood flow was estimated from the product of the mean coronary blood flow velocity and the cross-sectional area of the proximal left anterior descending coronary artery segment distal to the tip of the Doppler catheter, as previously described (5–7).

Table 2. Vasomotor Response of the Large Epicardial Coronary Artery Diameter to Acetylcholine Before and During L-Arginine Infusion

	Acetylcholine (μg/min)				
	Baseline	1	3	10	30
Coronary Artery Diameter (mm) in Control Patients With a Normal Coronary Angiogram					
Before L-arginine infusion	2.6 ± 0.2	2.7 ± 0.3	2.7 ± 0.4	2.6 ± 0.4	2.3 ± 0.4*
During L-arginine infusion	2.6 ± 0.6	2.8 ± 0.7	2.6 ± 0.5	2.6 ± 0.5	2.3 ± 0.5*
Coronary Artery Diameter (mm) in Patients With Coronary Artery Disease					
Before L-arginine infusion	2.6 ± 0.7	2.6 ± 1.0	2.5 ± 0.9	2.6 ± 0.8	2.4 ± 1.0*
During L-arginine infusion	2.8 ± 0.8	2.7 ± 0.8	2.6 ± 0.7	2.5 ± 0.9	2.4 ± 0.7*

*$p < 0.05$ versus control value. Data presented are mean value ± SD.

After completion of the diagnostic catheterization, the following studies were performed: 1) Papaverine (10 mg/5 ml) was injected through the lumen of the guiding catheter. 2) Acetylcholine at graded doses of 1, 3, 10 and 30 μg/min (for 2 min at each dose) was infused through the Doppler catheter. 3) After recovery from the effect of acetylcholine, L-arginine (50 mg/min) was infused through the guiding catheter. Ten minutes later, acetylcholine infusion was repeated while L-arginine was simultaneously infused. We selected this dose of L-arginine for the coronary blood flow study because at doses of ≥100 mg/min, L-arginine increased basal coronary blood flow in the preliminary studies (data not shown).

Measurements of forearm blood flow. Studies were done with the subjects in the supine position. Forearm blood flow was measured by use of a mercury-in-silastic strain gauge plethysmograph and the venous occlusion technique (11,14). The strain gauge was placed ~5 cm below the antecubital crease. The pressure in the venous occlusion or congesting cuff was 40 mm Hg. Circulation to the hand was arrested during determination of forearm blood flow by inflating a cuff around the wrist to a pressure that was suprasystolic. Forearm blood flow was taken as the average of at least four flow measurements made at 15-s intervals. The brachial artery was cannulated with a 20-gauge catheter for drug infusion and measurement of arterial pressure. Arterial pressure was recorded by connecting the arterial line to a pressure transducer with a three-way stopcock.

After the placement of a cannula and a strain gauge plethysmograph, at least 15 min was allowed for the subjects to become accustomed to the study conditions before the beginning of the protocol. The arterial line was kept open by infusing heparinized saline solution before drug infusion.

We examined forearm vasodilating responses to intraarterial infusions of acetylcholine and sodium nitroprusside. Acetylcholine (4, 8, 16 and 24 μg/min) and sodium nitroprusside (0.2, 0.4, 0.8 and 1.6 μg/min) were infused for 2 min at each dose. The order of the series of drug infusion was alternated. Forearm blood flow was measured continuously in the ipsilateral arm during drug infusion. Because forearm blood flow reached a steady state by 1 min after starting infusion of each drug, we used the last 1 min of measurements during drug infusion of each dose for analysis. After recovery, intraarterial infusion of L-arginine at 10 mg/min was started. Ten minutes after starting infusion of L-arginine, forearm vasodilating responses to acetylcholine and sodium nitroprusside were examined while L-arginine was simultaneously infused. We selected this dose of L-arginine for the forearm blood flow study because infusion of L-arginine at doses of ≥20 mg/min increased, but 10 mg/min did not increase basal forearm blood flow (11).

Measurement of plasma L-arginine levels. During cardiac catheterization, a 7F catheter was inserted into the coronary sinus vein, and blood was withdrawn at the baseline condition and 10 min after intracoronary L-arginine infusion at 50 mg/min for determination of plasma arginine levels in coronary sinus blood. During the forearm blood flow study, venous blood was drawn from an antecubital vein of the ipsilateral forearm before and 10 min after L-arginine at 10 mg/min. Plasma arginine levels were measured with an amino acid analyzer at a commercial laboratory (SRL, Tokyo, Japan).

Statistical analysis. Data are expressed as mean value ± SD, except for the figures. For comparisons of the dose–response relation with acetylcholine or sodium nitroprusside before and after L-arginine, two-way analysis of variance for repeated measures was used. Serial changes in blood flow and hemodynamic variables in response to drugs at the graded doses were compared using one-way analysis of variance. Paired data were compared by Student t test; $p < 0.05$ was considered significant.

Results

Patient characteristics. Table 1 shows clinical characteristics of the study patients. Mean ages ($p = 0.02$) and incidence of arterial hypertension ($p < 0.01$) were significantly higher in patients with coronary artery disease than in control patients. Mean serum total cholesterol level did not differ between the two groups. None of the patients in either group had diabetes mellitus.

Effects of L-arginine on coronary artery diameter and coronary blood flow. Table 2 shows the changes in the diameter of the large epicardial coronary artery, arterial pressure

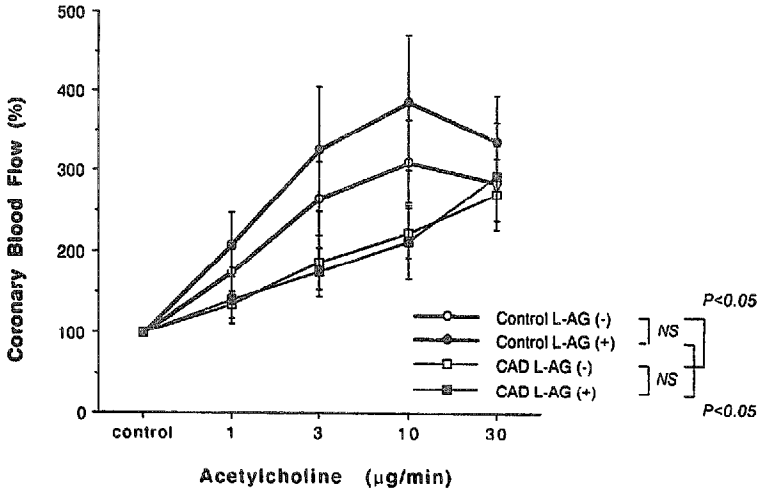

Figure 1. Acetylcholine-induced increases in coronary blood flow before and during infusion of L-arginine (L-AG) in control patients and patients with coronary artery disease (CAD). The percent increases from the baseline value (expressed as 100%) are presented. Data are mean value ± SE.

and heart rate in response to intracoronary infusion of acetylcholine before and during simultaneous infusion of L-arginine at 50 mg/min. The baseline arterial diameter (2.6 ± 0.2 and 2.6 ± 0.7 mm, p = NS), arterial pressure (82 ± 7 and 90 ± 10 mm Hg, $p < 0.05$) and heart rate (69 ± 7 and 74 ± 12 beats/min, p = NS) did not differ between control patients and patients with coronary artery disease, respectively. Before L-arginine, the large coronary artery diameter slightly but significantly decreased ($p < 0.05$) at the high dose (30 μg/min) of acetylcholine in control patients as well as in patients with coronary artery disease. The responses of the large coronary artery diameter to acetylcholine were similar between the two groups. The infusion of L-arginine did not alter the baseline arterial diameter, arterial pressure, heart rate or their responses to acetylcholine in either group.

Acetylcholine significantly ($p < 0.01$) increased coronary blood flow in a dose-dependent manner in the two groups (Fig. 1). Before L-arginine infusion, the percent increases in coronary blood flow evoked with acetylcholine were significantly smaller ($p < 0.05$) in patients with coronary artery disease than in control patients. The percent increase in coronary blood flow evoked with papaverine was comparable between the two groups (481 ± 30% in group 1, 446 ± 49% in group 2, p = NS). L-Arginine infusion did not alter the coronary blood flow responses to acetylcholine in either group ($p > 0.1$).

Effects of L-arginine on forearm blood flow response. Mean arterial pressure (84 ± 8 mm Hg in control patients, 88 ± 9 mm Hg in patients with coronary artery disease) and heart rate (64 ± 5 beats/min in control patients, 64 ± 2 beats/min in patients with coronary artery disease) at the forearm blood flow study were comparable to those at the coronary blood flow study (Table 3). Figure 2 shows the percent increase in forearm blood flow evoked with acetylcholine before and during L-arginine infusion. Before L-arginine, the dose-dependent increases in forearm blood flow evoked with acetylcholine were significantly smaller ($p < 0.01$) in patients with coronary artery disease than in control patients, but the forearm blood flow responses to sodium nitroprusside were comparable between the two groups (Table 4). Infusion of L-arginine at 10 mg/min did not alter basal arterial pressure and heart rate or their responses to acetylcholine or nitroprusside. L-Arginine significantly augmented ($p < 0.01$) the forearm blood flow responses to acetylcholine in the two groups, although it did not alter the forearm blood flow responses to sodium nitroprusside in either group. During L-arginine infusion,

Table 3. Forearm Blood Flow Response to Acetylcholine Before and During L-Arginine Infusion

		Acetylcholine (μg/min)			
	Baseline	4	8	16	28
Forearm Blood Flow (ml/min per 100 ml) in Control Patients With a Normal Coronary Angiogram					
Before L-arginine infusion	4.4 ± 1.5	9.2 ± 5.3*	18.8 ± 10.1*	29.6 ± 19.7*	33.0 ± 19.9*
During L-arginine infusion†	3.9 ± 1.2	19.0 ± 11.3*	30.3 ± 20.1*	37.7 ± 23.3*	36.0 ± 24.9*
Forearm Blood Flow (ml/min per 100 ml) in Patients With Coronary Artery Disease					
Before L-arginine infusion	2.7 ± 1.1	5.3 ± 3.8*	8.7 ± 5.6*	13.3 ± 8.5*	11.8 ± 9.6*
During L-arginine infusion†	2.9 ± 1.1	7.4 ± 4.3*	12.2 ± 8.1*	21.3 ± 9.3*	22.5 ± 14.0*

*$p < 0.01$ versus control value. †$p < 0.01$ versus before L-arginine by analysis of variance. Data presented are mean value ± SD.

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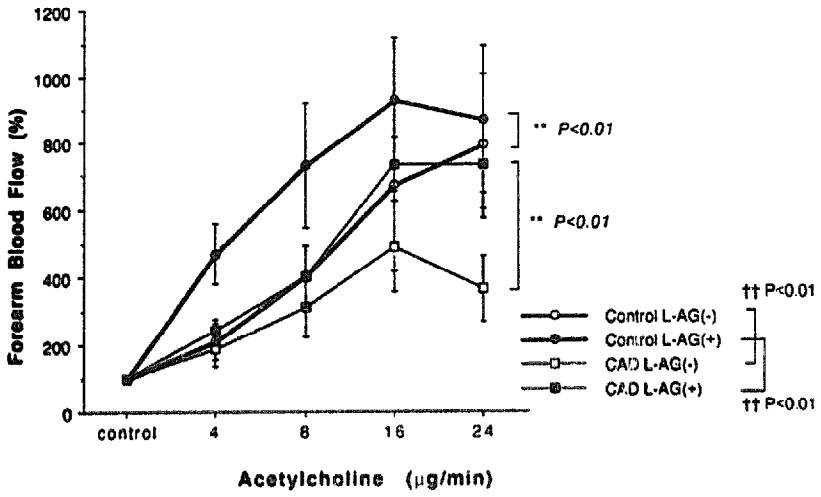

Figure 2. Acetylcholine-induced increases in forearm blood flow before and during infusion of L-arginine (L-AG) in control patients and patients with coronary artery disease (CAD). The percent increases from the baseline value (expressed as 100%) are presented. Data are mean value ± SE. **$p < 0.01$ before and after L-arginine infusion by analysis of variance. ††$p < 0.01$ between patients with and without coronary artery disease by analysis of variance.

acetylcholine-induced increases in forearm blood flow were still smaller ($p < 0.01$) in patients with coronary artery disease than in control patients.

Plasma L-arginine levels. The basal plasma arginine level in the coronary sinus was 111 ± 22 nmol/ml in control patients (n = 6) and 100 ± 23 nmol/ml in patients with coronary artery disease (n = 6, p = NS). Intracoronary infusion of L-arginine at 50 mg/min increased the plasma arginine level in the coronary sinus from 106 ± 10 to 1,063 ± 257 nmol/ml ($p < 0.01$) (n = 4 [3 patients with coronary artery disease and 1 control patient]).

Intraarterial infusion of L-arginine at 10 mg/min increased the plasma arginine level in an ipsilateral antecubital vein from 110 ± 10 to 1,146 ± 220 nmol/ml ($p < 0.05$) (n = 4 [2 control patients and 2 patients with coronary artery disease]).

Discussion

The major findings of this study are that intracoronary L-arginine at 50 mg/min did not alter acetylcholine-induced changes in the diameter of large epicardial coronary artery or coronary blood flow in either control patients or patients with coronary artery disease, whereas intraarterial infusion of L-arginine at 10 mg/min augmented acetylcholine-induced increases in forearm blood flow to a similar extent in the two groups. These results indicate that the effect of L-arginine on endothelium-dependent vasodilation with acetylcholine differs between the coronary and forearm vasculature.

Effects of L-arginine on acetylcholine-induced coronary vasomotion. In patients with and without coronary artery disease, acetylcholine did not cause vasodilation of large epicardial coronary artery, and the drug at the high dose caused modest but significant vasoconstriction. The degrees of vasoconstriction of large coronary artery evoked with acetylcholine were not statistically different between the two groups. The results are consistent with the previous findings, because it has been shown that intracoronary infusion of acetylcholine causes vasoconstriction of angiographically normal segments of large epicardial coronary arteries in patients who have risk factors for coronary atherosclerosis or in patients with atherosclerotic lesions elsewhere in other coronary arteries (5,6,13,31–33). Our control patients had risk factors, such as age ≥50 years, smoking or mild hypercholesterolemia, all of

Table 4. Forearm Blood Flow Response to Sodium Nitroprusside Before and During L-Arginine Infusion

		Sodium Nitroprusside (μg/min)			
	Baseline	0.2	0.4	0.8	1.6
Forearm Blood Flow (ml/min per 100 ml) in Control Patients With a Normal Coronary Angiogram					
Before L-arginine infusion	4.7 ± 1.8	5.6 ± 1.8	8.0 ± 2.2*	10.5 ± 2.8*	14.0 ± 3.9*
During L-arginine infusion	4.6 ± 1.2	6.4 ± 2.3	7.6 ± 3.3*	8.3 ± 3.4*	12.8 ± 5.8*
Forearm Blood Flow (ml/min per 100 ml) in Patients With Coronary Artery Disease					
Before L-arginine infusion	2.7 ± 1.1	5.3 ± 3.8	8.7 ± 5.6*	13.3 ± 8.5*	11.8 ± 9.6*
During L-arginine infusion	3.6 ± 1.8	4.8 ± 1.9	5.5 ± 1.9†	7.3 ± 2.3*	10.0 ± 3.0*

*$p < 0.05$, †$p < 0.01$ versus control value. Data presented are mean value ± SD.

which were associated with attenuated endothelium-dependent vasodilation of large coronary artery (5–7,12,13,17,19,31,32). In contrast to the response of the large coronary artery to acetylcholine, acetylcholine increased coronary blood flow in a dose-dependent manner in control patients and in patients with coronary artery disease. However, the increases in coronary blood flow evoked with acetylcholine were less in patients with coronary artery disease than in control patients. The coronary blood flow response to papaverine was similar between the two groups. These results are also consistent with the previous findings that the increase in coronary blood flow evoked with acetylcholine is impaired by the presence of coronary risk factors and upstream atherosclerotic lesions (5,6,12).

Our results demonstrated that infusion of L-arginine at 50 mg/min did not alter responses of large epicardial coronary artery to acetylcholine in either control patients or patients with coronary artery disease. This finding is in agreement with that of Drexler et al. (12), who showed that intracoronary L-arginine at 160 μmol/min had no effect on vasomotor responses of the large epicardial coronary artery to acetylcholine (0.036, 0.36 and 3.6 μg/min) in patients with and without hypercholesterolemia. The dose of L-arginine that we infused into the coronary artery (50 mg/min) was similar to that used by Drexler et al. Dubois-Rande et al. (34) demonstrated that intracoronary L-arginine at 25 mg/min attenuated vasoconstriction of the large coronary arteries evoked with acetylcholine at higher doses (10^{-6} and 5×10^{-6} mol/liter) in patients who had hypercholesterolemia and diffuse lumen narrowing in the study artery. They suggested that less vasoconstriction of the large coronary artery evoked with acetylcholine after L-arginine might have resulted from an increased release of endothelium-derived relaxing factor by L-arginine. The difference in patients, such as the degree of atherosclerotic changes, the serum cholesterol level or the doses of acetylcholine or L-arginine used, might have accounted for the different results between these studies.

Our results also indicated that L-arginine at 50 mg/min did not improve the coronary blood flow response to acetylcholine in either control patients or patients with coronary artery disease. Of note is that infusion of L-arginine into the brachial artery at 10 mg/min significantly augmented forearm blood flow responses to acetylcholine in the same patients. It is unlikely that the dose of intracoronary L-arginine was inadequate, because the magnitude of the increase in plasma arginine levels in coronary vein during intracoronary infusion of L-arginine was identical to that in antecubital vein during infusion of L-arginine to the brachial artery.

Our results showing no effect of L-arginine on the coronary blood flow response to acetylcholine differ from those of Drexler et al. (12), who demonstrated that intracoronary administration of L-arginine significantly improved the coronary blood flow response to acetylcholine in patients with hypercholesterolemia. Drexler et al. concluded that L-arginine improved endothelial dysfunction at the level of resistance vessels by increasing the production of endothelium-derived nitric oxide. A major difference between our study and the study by Drexler et al. (12) is that Drexler et al. compared the effect of L-arginine between patients with and without hypercholesterolemia, whereas we compared its effect between patients with and without coronary artery disease. Importantly, mean serum cholesterol level did not differ between our control patients and patients with coronary artery disease. Therefore, it appears that the beneficial effects of L-arginine on endothelium-dependent coronary vasodilation evoked with acetylcholine may be confined to the coronary microcirculation in patients with hypercholesterolemia. In this study, the coronary blood flow response to acetylcholine after supplementation with L-arginine was still less in patients with coronary artery disease than in control patients, which suggests that the mechanisms of impaired acetylcholine-induced vasodilation of the resistance coronary artery in the presence of an upstream coronary artery lesion are not related to a limited availability of L-arginine.

It has been assumed that acetylcholine increases coronary blood flow largely by the muscarinic receptor-mediated release of endothelium-derived relaxing factors such as nitric oxide in humans (35,36). This assumption is based on the finding that the acetylcholine-induced increase in coronary blood flow was attenuated by methylene blue (36), which inhibits the cyclic guanosine monophosphate pathway. However, Lefroy et al. (37) found that the coronary blood flow response to acetylcholine, which was assessed indirectly by the changes in oxygen saturation of coronary venous blood, was not altered by intracoronary infusion of N^G-monomethyl-L-arginine, an inhibitor of nitric oxide synthesis, suggesting that acetylcholine-induced vasodilation of the resistance coronary artery may not be mediated by endothelium-derived nitric oxide. If so, it is possible that acetylcholine-induced increases in coronary blood flow are not altered by L-arginine supplementation, as presented in this study. Further studies are needed to elucidate the mechanism involved in the acetylcholine-induced vasodilation of the coronary vascular bed in humans.

Effects of L-arginine on the acetylcholine-induced forearm vasodilation. The forearm blood flow response to acetylcholine was attenuated significantly more in patients with coronary artery disease than in control patients, whereas the forearm blood flow response to sodium nitroprusside was comparable between the two groups. These findings may be accounted for by the presence of risk factors such as hypertension, which are known to be associated with impaired endothelium-dependent vasodilation in the human forearm (14–16). Hypertension was present in six of seven patients with coronary artery disease but in none of the control patients.

The results of the present study indicate that infusion of L-arginine at 10 mg/min into the brachial artery significantly augmented the forearm blood flow response to acetylcholine but did not augment the response to nitroprusside in control patients as well as in patients with coronary artery disease and hypertension. These results suggest that L-arginine facilitated nitric oxide synthesis in the endothelial cells of forearm resistance vessels and thus augmented the forearm blood flow

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response to acetylcholine in these patients. The magnitude of L-arginine-induced augmentation of forearm vasodilation evoked with acetylcholine was similar between the two groups, and after L-arginine, the increases in forearm blood flow with acetylcholine were still smaller in patients with coronary artery disease than those in control patients (Fig. 2). Our results differ from those of Panza et al. (38), who demonstrated that acetylcholine-induced forearm vasodilation was not altered by intraarterial infusion of L-arginine at 40 μmol/min (a similar dose to that used in this study) in hypertensive patients. The different results between our study and the study of Panza et al. (38) may have resulted from different patients studied (patients with mild hypertension [mean blood pressure 90 mm Hg] in this study vs. patients with long-lasting hypertension [148 mm Hg] treated for ≥5 years in the study of Panza et al. [38]). These results suggest that the mechanism responsible for the impaired endothelium-dependent forearm vasodilation in our patients with coronary artery disease and hypertension may not be related to a limited availability of L-arginine.

Conclusions. It is clear from the results of this study that the effect of local infusion of L-arginine on acetylcholine-induced vasodilation differs between the coronary and forearm vasculatures in both control patients and in patients with coronary artery disease and hypertension. These results are consistent with the suggestion that endothelium-dependent vasodilator mechanisms differ among vascular beds. Although we did not explore the mechanism responsible for the difference in this study, it is plausible to speculate that the mechanism may be related to the different stages of vascular disease process between the coronary and forearm vasculature, because it is conceivable that structural changes may be less in forearm vasculature than in coronary vasculature.

Our results also suggest that the mechanism responsible for the impaired acetylcholine-induced vasodilation of coronary and peripheral microcirculation in patients with coronary artery disease and hypertension may not be related to limited availability of L-arginine.

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