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Effect of Acetylcholine on the Highly Stenotic Coronary Artery: Difference Between the Constrictor Response of the Infarct-Related Coronary Artery and That of the Noninfarct-Related Artery

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To examine the constrictor response of the infarct-related stenotic coronary artery in comparison with that of noninfarct-related stenotic arteries, acetylcholine in maximal doses of 100 μg for the left and 50 μg for the right coronary artery was injected into the 16 infarct-related coronary arteries of 16 patients with previous myocardial infarction (group 1) and into 19 stenotic coronary arteries of 16 patients with stable angina without myocardial infarction (group 2). Acetylcholine's effects on lumen diameter and area were quantitatively analyzed at the stenotic segment and its proximal segment without significant stenosis.

Acetylcholine decreased lumen diameter and area at the stenotic segments from 0.72 ± 0.18 to 0.18 ± 0.33 mm and from 0.45 ± 0.22 to 0.10 ± 0.22 mm², respectively, in group 1 (both $p < 0.01$) and from 0.75 ± 0.22 to 0.49 ± 0.30 mm and 0.48 ± 0.29 to 0.26 ± 0.23 mm², respectively, in group 2 (both $p < 0.01$). Acetylcholine decreased the diameter and area at the proximal segment from 2.71 ± 0.75 to 2.38 ± 0.6 mm and from 6.18 ± 3.4 to 4.71 ± 2.23 mm², respectively, in group 1 (both $p < 0.01$) and from 2.31 ± 0.67 to 1.95 ± 0.59 mm and from 4.5 ± 2.97 to 3.22 ± 1.96 mm², respectively, in group 2 (both $p < 0.01$). The changes in diameter and area at the stenotic segment in group 1 were significantly greater than those in group 2 (both $p < 0.01$); there were no significant differences between groups in the changes at the proximal segment. Total or subtotal occlusion of the stenotic artery was induced in 11 (69%) patients in group 1 compared with 4 (21%) patients in group 2 ($p < 0.01$ group 1 vs. group 2).

It is concluded that the constrictor response to acetylcholine of the stenotic segment of the infarct-related coronary artery is enhanced as compared with that of noninfarct-related arteries.

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Occlusion of the coronary artery by an intraluminal thrombus has been angiographically demonstrated in the early phase of acute myocardial infarction (1,2). The mechanism of the occlusive thrombus formation is still controversial and rupture of the atheromatous plaque and a subsequent platelet aggregation (3,4) or occlusive vasoconstriction (or coronary spasm) superimposed on the atherosclerotic lesion (5,6), or both, has been proposed (7,8) as a triggering mechanism for the thrombus formation. Approximately 75% of the stenotic coronary artery has an eccentric residual lumen with potential for active or passive vasomotion by an arc of normal arterial wall partially surrounding the lumen (9). Previous studies have examined quantitatively the constrictor response of the stenotic coronary artery in response to dynamic (10) or static exercise (11,12) and to a vasoactive substance such as acetylcholine (13–15) in patients with angina pectoris. Coronary spasm has been shown (16) to be inducible in some patients with recent myocardial infarction. However, the constrictor response of the infarct-related stenotic coronary artery in comparison with that of the noninfarct-related stenotic artery has not been analyzed quantitatively.

We (14) and other investigators (13,17) have shown that intracoronary administration of acetylcholine, an endothelium-dependent vasodilator (17), causes vasodilation in arteries without atherosclerosis and vasoconstriction in arteries with atherosclerosis. In the present study, incremental doses of acetylcholine were injected into the highly stenotic coronary artery of patients with a previous myocardial infarction (group 1) and patients with stable angina without a previous infarction (group 2). By comparing its effects on lumen diameter and area of the stenotic coronary artery in the two groups, we examined whether the constrictor response of the infarct-related coronary artery is enhanced as compared with that of noninfarct-related coronary arteries.

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Table 1. Patient Profiles and Angiographic Characteristics of Stenotic Lesions

Patient No.	Age (yr)/ Gender	Location of MI	Time From MI Onset (mo)	Characteristics of Stenotic Lesion		
				Site*	Type	Length (mm)
Group 1						
1	62/M	Anterior	1	S6	Eccentric	3
2	50/M	Inferior	19	S1	Concentric	5
3	54/M	Lateral	3	S13	Concentric	6
4	55/M	Lateral	3	S12	Concentric	<3
5	56/M	Anterior	6	S7	Concentric	3
6	56/M	Inferior	2	S2	Eccentric	5
7	46/M	Anterior	1.5	S7	Eccentric	3
8	63/M	Anterior	2	S8	Eccentric	10
9	63/M	Anterior	24	S7	Concentric	4
10	72/F	Inferior	1.2	S2	Eccentric	11
11	74/F	Inferior	1	S1	Eccentric	6
12	56/M	Anterior	3	S6	Eccentric	<3
13	58/M	Inferior	2	S2	Eccentric	9
14	59/M	Anterior	1	S6	Eccentric	4
15	48/M	Anterior	1	S7	Eccentric	6
16	71/M	Inferior	1	S1	Eccentric	<3
Group 2						
17	61/F	—	—	S3	Concentric	3
18	52/M	—	—	S7	Concentric	<3
19	63/M	—	—	S2	Eccentric	4
				S6	Concentric	3
20	44/M	—	—	S6	Eccentric	3
21	58/M	—	—	S6	Eccentric	5
22	62/M	—	—	S6	Eccentric	3
				S11	Eccentric	3
23	55/M	—	—	S11	Eccentric	4
24	60/M	—	—	S2	Eccentric	3
25	62/M	—	—	S6	Eccentric	3
26	65/F	—	—	S12	Concentric	3
27	62/M	—	—	S7	Eccentric	3
28	58/M	—	—	S7	Eccentric	6
29	63/M	—	—	S7	Concentric	3
				S11	Concentric	<3
30	60/M	—	—	S13	Eccentric	10
31	35/M	—	—	S4	Concentric	4
32	68/F	—	—	S2	Concentric	3

*S1 to S13 indicate the segments of the coronary arteries as defined by the AHA Committee Report (18). F = female; Group 1 = 16 patients with prior myocardial infarction; Group 2 = 16 patients with stable angina without prior infarction; M = male; MI = myocardial infarction.

Methods

Study patients (Table 1). The study group comprised 32 consecutive patients who 1) had one or more fixed, high grade stenoses in a coronary artery other than the left main trunk, and 2) did not have either congestive heart failure or unstable angina at the time of cardiac catheterization. Patients with total occlusion in the three major coronary artery branches were excluded from study. The study patients were classified into two groups according to the presence or absence of previous myocardial infarction in the territory perfused by the stenotic coronary artery.

Group 1 comprised 16 patients with onset of a prior myocardial infarction 25 to 725 days before the angiographic study; 14 of the 16 were male and 2 female; the mean age was 59 years (range 46 to 74). No patient underwent thrombolytic therapy during the acute phase of the prior infarction. Within 1 month before the onset of infarction, nine patients had had new episodes of angina (rest and effort angina in seven patients and rest angina alone in two), but none had taken antianginal medicine. One patient had had effort angina 2 years before the onset of infarction but had been free of angina, without medication, during the 6 months preceding the onset of infarction. The remaining six patients had never experienced an anginal attack before the acute infarction. The site of infarction was anterior in eight patients, inferior in six and lateral in two. The diagnosis and site of myocardial infarction were based on the electrocardiographic (ECG) changes during the acute phase (i.e., ST segment elevation and development of abnormal Q waves). In 13 (81%) of the 16 patients, thallium-201 myocardial scintigraphy with or without exercise testing was performed during the chronic phase of the disease and all patients showed a perfusion defect without redistribution in the territory perfused by the stenotic coronary artery. All patients showed a wall motion abnormality in the territory perfused by the stenotic artery on the left ventriculogram.

Group 2 comprised 16 patients with stable effort angina and no previous myocardial infarction; 13 of the 16 were male and 3 female; the mean age was 58 years (range 35 to 68). No patient had had angina at rest and none had evidence of myocardial infarction on the ECG at rest. Exercise thallium-201 myocardial scintigraphic examination was performed in 12 (75%) of the 16 patients and a perfusion defect was demonstrated in the territory perfused by the stenotic coronary artery or arteries immediately after exercise in all patients. However, no perfusion defect was present at the redistribution phase in any patient.

In both groups of patients, all medications were withdrawn ≥72 h before the study; the exception was sublingual nitroglycerin, which was also withdrawn ≥6 h before the study. No patient had experienced rest angina after interruption of antianginal medicines. No patient had allergy, active peptic ulcer, chronic obstructive lung disease or any other serious diseases. The study was performed during diagnostic cardiac catheterization and written informed consent was obtained from all patients before the study. The study was in agreement with the guidelines approved by the ethics committee at our institution.

Angiographic examination and study protocol. Coronary arteriography was performed with the Sones technique in the morning while the patient was in the fasting state. A tripolar electrode catheter (USCI) was inserted into the right ventricular apex by way of the right femoral vein and was connected to a temporary pacemaker set at a rate of 40 to 50 beats/min. Coronary arteriograms were taken in the right anterior oblique projection for the left coronary artery and in the left anterior oblique projection for the right coronary

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artery. The relations among focal spot, patient and height of the imaging tube were kept constant during the study.

Study protocol. After baseline left and right coronary arteriography, intracoronary injection of acetylcholine was performed. When the highly stenotic lesion was in the left coronary artery, incremental doses of acetylcholine (20, 50 and 100 μg) were injected into that artery; when the lesion was in the right coronary artery, incremental doses of acetylcholine (20 and 50 μg) were injected into that artery. Injection continued until total or subtotal occlusion of the artery was induced or ischemic ST segment changes with or without associated chest pain developed or the maximal dose of acetylcholine (100 μg for the left and 50 μg for the right coronary artery) was given. The details of the method of acetylcholine injection were reported previously (19,20). The duration of injection of each dose of acetylcholine was 20 s and the interval between injections was 5 min. A coronary arteriogram was performed 1 min after completion of acetylcholine injection. The timing of arteriography was based on the previously reported documentation (20) of coronary spasm in patients with variant angina by arteriography performed approximately 1 min after acetylcholine injection. When acetylcholine-induced occlusion did not resolve spontaneously within 5 min or hemodynamic instability due to myocardial ischemia developed, nitroglycerin (100 to 200 μg) was injected into the coronary artery involved. The arteriograms were obtained from multiple projections after administration of sublingual nitroglycerin and the morphology and degree of the coronary artery lesion were determined. Three ECG leads (I, aVF and V_1 or V_4) and arterial blood pressure were continuously monitored on an oscilloscope during the study. In addition, six ECG leads (I, II, aVF, V1, V_3 and V_5) were continuously recorded during acetylcholine injection and for the following 3 min.

Quantitative coronary arteriography. Measurement of lumen diameter and area of the coronary artery was performed quantitatively with the aid of a computer-assisted coronary angiography analysis system. End-diastolic cinefilms most clearly visualizing the stenotic lesion were videodigitized and stored in the cardiac image analysis system (Cardio 500, Kontron Instruments). Automated contour detection was performed by a geometric edge differentiation technique similar to the method described by Reiber et al. (21). In brief, after interactive delineation of a centerline within the vessel segment to be measured, the computer automatically generates scanlines perpendicular to the centerline. The first and second derivative function of the densograms along each scanline are then computed, and the contour point is defined as 60% of the distance between the extrema of the first and second derivative. With use of the detected edge points, the computer then automatically generates a refined centerline of the vessel segment, and the edge detection algorithm is repeated. A smoothing procedure is applied to each of the detected contours by evaluating features of the local neighborhood and averaging them. Calibration is achieved by measuring a magnification factor based on the known size of the angiographic catheter.

Measurements were performed by two investigators. If the investigators did not agree with part of the detected contours, especially in the stenotic lesion, they discussed where the proper positions were and corrected the positions interactively with the cursor. The arterial segment that was not considered to be parallel to the image intensifier was excluded from the analysis.

The method of quantitative angiography was validated in phantom studies. The accuracy and precision of this method were determined from analysis of cinefilms of an acrylate block with precision-drilled models of coronary arteries with diameters of 0.5, 0.8, 1, 2, 3 and 4 mm (corresponding to the vessel diameters expected in this study) filled with 100% of contrast medium and filmed under 10 cm of water with an angiographic catheter that also was filled with contrast medium. The measurement of the diameter of each coronary artery model was performed in 10 successive frames (i.e., 10 times for each model). The measured diameter (mean ± SD) was 0.54 ± 0.04 mm for a 0.5-mm model, 0.8 ± 0.06 mm for a 0.8-mm model, 0.99 ± 0.06 mm for a 1-mm model, 1.97 ± 0.06 mm for a 2-mm model, 3.01 ± 0.08 mm for a 3-mm model and 3.99 ± 0.09 mm for a 4-mm model. The correlation between the measured and true values was excellent ($Y = 0.99X + 0.01$, $r = 0.99$, $p < 0.001$). A slight overestimation was noted for the measurement of a 0.5-mm model, although the standard deviation of the measured values was as small as 0.04 mm. The overall accuracy and precision of this method were 2.18 ± 3.3% and 4.6 ± 2.5%, respectively. Analysis of intraobserver and interobserver variability for the measurement of the coronary artery diameter showed high reproducibility ($r = 0.99$, SEE = 0.05 mm, $p < 0.001$; and $r = 0.99$, SEE = 0.04 mm, $p < 0.001$, respectively).

The minimal lumen diameter and area of the stenotic lesion were defined as those of the stenotic segment. The diameter and area at the site approximately 1 cm proximal to the stenotic lesion and without a stenosis >50% of lumen diameter (proximal segment) were also measured. The measurement was performed before and after acetylcholine injection and after nitroglycerin administration. Special care was taken to take all three measurements at the same site by using anatomic references.

Data analysis. All data are shown as mean values ± 1 SD. The arterial diameters and areas at baseline and after administration of nitroglycerin were compared between the two groups with the unpaired *t* test for the data normally distributed or with the Wilcoxon's unpaired rank sum test for those not normally distributed. The effects of acetylcholine on coronary artery diameter and area were statistically analyzed with a paired *t* test. The response of the coronary artery to acetylcholine was compared between the two groups with an unpaired *t* test and a chi-square test. The degree and morphology of the coronary artery stenoses were compared between groups with a chi-square test. A p value < 0.05 was considered statistically significant.

Table 2. Comparison of Stenotic Lesion Between Two Groups

	Group 1	Group 2
No. of patients	16	16
Age (yr) (mean ± SD)	59 ± 8	58 ± 8
Male/female ratio	14/2	13/3
CAD		
One-vessel	9	4
Two-vessel	6	8
Three-vessel	1	4
Stenotic arteries		
LAD	8	9
LCx	2	5
RCA	6	5
Total	16	19
Type of stenosis		
Concentric	5	8
Eccentric	11	11
(type II*)	(5)	(11)
Length of stenosis		
≤5 mm	10	17
>5 mm	6	2

*Eccentric type of stenosis with a narrow neck or irregular borders, or both, described by Ambrose et al. (22). CAD = coronary artery disease; LAD = left anterior descending coronary artery; LCx = left circumflex coronary artery; RCA = right coronary artery.

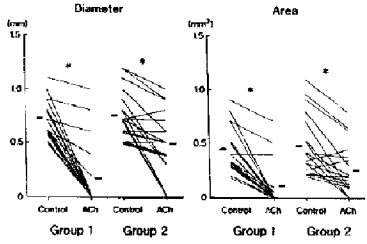

Figure 1. Lumen diameter and area at the *stenotic segment* before (Control) and after intracoronary injection of acetylcholine (ACh) are shown for each study patient. **Horizontal bars** indicate mean values. Group 1 = 16 patients with prior myocardial infarction; Group 2 = 16 patients with stable angina without prior infarction. See text for discussion. *$p < 0.01$.

Results

Coronary Artery Lesions of the Study Patients (Table 2)

Group 1. Of the 16 patients, 9 (56%) had single-vessel disease, 6 (38%) had double-vessel disease and the remaining patient (6%) had triple-vessel disease. Sixteen highly stenotic coronary arteries were considered to be the artery responsible for the previous myocardial infarction (infarct-related artery) and the effect of acetylcholine on these arteries was examined. These 16 arteries included 8 left anterior descending coronary arteries, 2 left circumflex arteries and 6 right coronary arteries. Five of the 16 arteries showed a concentric type of stenosis with the residual lumen on the midline of the artery and the other 11 showed an eccentric type of stenosis. Among these 11 eccentric lesions, 5 manifested the narrow neck or irregular borders, or both, characterized as type II stenosis by Ambrose et al. (22). The length of the stenotic segment was ≤5 mm in 10 arteries and >5 mm in the other 6.

Group 2. Of the 16 patients, 4 (25%) had single-vessel disease, 8 (50%) had double-vessel disease and the remaining 4 (25%) had triple-vessel disease. Twenty-five coronary arteries had an organic stenosis >75% of the lumen diameter. The effect of acetylcholine was analyzed in 19 of these 25 noninfarct-related coronary arteries, which included the 9 left anterior descending arteries, 5 left circumflex arteries and 5 right coronary arteries. Of the remaining six arteries, acetylcholine was not injected into three because the stenosis was present only in the distal segment and in the other three arteries (all left circumflex arteries), acetylcholine was injected but the stenotic segment was not clearly opacified with the arteriograms performed in the right anterior oblique projection and thus the diameter and area changes were not analyzed. Of the 19 coronary arteries studied, the lesion was concentric in 8 and eccentric in the other 11. Among the 11 lesions with eccentric stenosis, only 1 showed type II stenosis (22). The length of the stenotic segment was ≤5 mm in 17 arteries and >5 mm in the other 2. Neither the type nor the length of the stenosis in these noninfarct-related coronary arteries was statistically different from those of the infarct-related arteries of group 1 patients. The incidence of type II stenosis (22) in group 2 was lower than that in group 1, although a statistical difference was not present. In either group, the type of stenosis (concentric or eccentric or eccentric type II stenosis) was not correlated to the constrictor response of the lesion to acetylcholine.

Effect of Acetylcholine on Lumen Area and Diameter

Dose of acetylcholine used in the two groups. The maximal dose of acetylcholine (100 μg for the left and 50 μg for the right coronary artery) was injected into 10 stenotic coronary arteries (63%) in group 1 and in 16 stenotic arteries (84%) in group 2. In the other stenotic arteries in each group, acetylcholine injection was stopped at the dose of 20 or 50 μg since total or subtotal occlusion of the stenotic coronary artery was induced. There was no statistical difference in the dose of acetylcholine injected into the stenotic coronary artery between the two groups.

Effect at the stenotic segment (Fig. 1): The baseline lumen diameter and area at the stenotic segment of the 16 infarct-related arteries (group 1) were 0.72 ± 0.18 mm (range 0.5 to 1.1 mm) and 0.45 ± 0.22 mm^2 (range 0.18 to 0.94 mm^2), respectively; those of the 19 noninfarct-related coronary

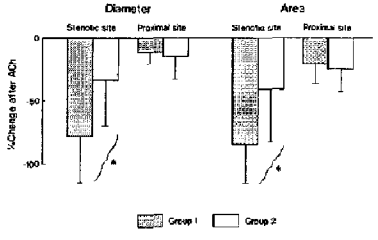

Figure 2. Percent changes in lumen diameter and area at the stenotic and proximal segments after intracoronary injection of acetylcholine (ACh). The reduction in diameter and area at the stenotic segment was greater in group 1 than in group 2, although that at the proximal segment was similar between the two groups. *$p < 0.01$.

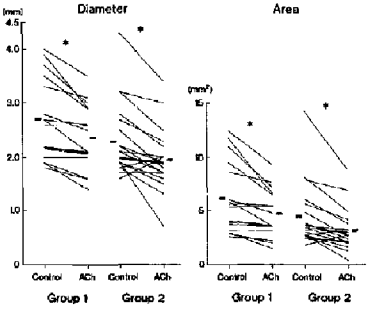

Figure 3. Lumen diameter and area at the *proximal segment* before (Control) and after intracoronary injection of acetylcholine (ACh) in each study patient. **Horizontal bars** indicate mean values. See text for discussion. *$p < 0.01$.

arteries (group 2) were 0.75 ± 0.22 mm (range 0.5 to 1.2) and 0.48 ± 0.29 mm^2 (range 0.17 to 1.11), respectively. There was no statistical difference in diameter or area between the two groups. Intracoronary injection of acetylcholine decreased the diameter and area to 0.18 ± 0.33 mm and 0.10 ± 0.22 mm^2, respectively, in group 1 and to 0.49 ± 0.30 mm and 0.26 ± 0.23 mm^2, respectively, in group 2. All the changes induced by acetylcholine were statistically significant (all $p < 0.01$). Consequently, acetylcholine induced total or subtotal occlusion at the stenotic segment in 11 (69%) of the 16 infarct-related arteries in group 1 and in 4 (21%) of the 19 noninfarct-related arteries in group 2 ($p < 0.01$ group 1 vs. group 2).

The degree of acetylcholine-induced narrowing at the stenotic segment was compared between the two groups (Fig. 2). The percent change in lumen diameter after acetylcholine was −78 ± 37% in group 1 and −34 ± 36% in group 2, and that in lumen area after acetylcholine was −84 ± 31% in group 1 and −41 ± 41% in group 2. The changes in the diameter and area in group 1 were significantly greater than those in group 2 (both $p < 0.01$). There was no significant correlation between the interval since myocardial infarction and the changes in diameter and area in group 1, although the change was relatively small in the two patients whose infarction occurred as long as 19 and 24 months, respectively, before the study (percent change in diameter −11% and −14%, respectively). After administration of nitroglycerin, lumen diameter and area were 0.89 ± 0.24 mm and 0.67 ± 0.39 mm^2, respectively, in group 1 and 0.91 ± 0.24 mm and 0.69 ± 0.44 mm^2, respectively, in group 2. There was no statistical difference in the diameter and area after nitroglycerin between the two groups.

Effect at the proximal segment (Fig. 3). The baseline lumen diameter and area were 2.71 ± 0.75 mm (range 1.8 to 4 mm) and 6.18 ± 3.4 mm^2 (range 2.6 to 12.45), respectively, in group 1 and 2.31 ± 0.67 mm (range 1.7 to 4.3) and 4.5 ± 2.97 mm^2 (range 2.36 to 14.33), respectively, in group 2. There was no statistical difference in baseline diameter and area between the two groups. Intracoronary acetylcholine decreased the diameter and area to 2.38 ± 0.6 mm ($p < 0.01$) and 4.71 ± 2.23 mm^2 ($p < 0.01$), respectively, in group 1 and to 1.95 ± 0.59 mm ($p < 0.01$) and 3.22 ± 1.96 mm^2 ($p < 0.01$), respectively, in group 2. There was no significant difference in the percent changes from the baseline between the two groups (−12 ± 9% for the diameter and −21 ± 16% for the area in group 1 and −15 ± 18% for the diameter and −25 ± 28% for the area in group 2) (Fig. 2).

The dose of acetylcholine was not equal for each of the study patients. Because the vasoconstrictive effect of acetylcholine has been shown to be dose dependent (18), the injection of the maximal dose of acetylcholine (100 μg for the left and 50 μg for the right coronary artery) into all the stenotic coronary arteries would have resulted in the same outcome or more potent vasoconstrictive response. After administration of nitroglycerin, the diameter and area were 3.15 ± 0.86 mm and 8.36 ± 4.31 mm^2, respectively, in group 1 and 2.58 ± 0.72 mm and 5.66 ± 3.74 mm^2, respectively, in group 2, and the diameter of group 1 was significantly greater than that of group 2 ($p < 0.05$).

Effect on the noninfarct-related coronary artery in group 1: In four group 1 patients, a fixed, organic stenosis >75% of the lumen diameter was also present in the artery other than the infarct-related coronary artery. These noninfarct-related stenotic arteries included two left anterior descending arteries and two left circumflex arteries, and the effect of acetylcholine on the stenotic segment of these arteries was examined. The doses of acetylcholine used were 20 μg for one artery, 50 μg for another and 100 μg for the remaining two. The baseline lumen diameter and area of the stenotic seg-

ment were 0.65 ± 0.16 mm and 0.35 ± 0.16 mm², respectively, and those after acetylcholine 0.51 ± 0.04 mm and 0.2 ± 0.03 mm², respectively (p = NS for both changes). Total or subtotal occlusion was not induced in any of these noninfarct-related stenotic arteries.

Discussion

Angiographic studies performed in the early phase of acute myocardial infarction have shown an approximately 90% incidence of total occlusion in the infarct-related coronary artery (1,2). Thrombolytic therapy for acute myocardial infarction is clearly effective in recanalizing the occluded vessel (23,24). Thus, occlusive thrombus in the coronary artery is the common pathway leading to myocardial infarction, but the precise mechanism for the thrombus formation remains to be elucidated. Previous studies (5,6) performed during the acute phase of myocardial infarction or preinfarction angina have revealed that coronary spasm may play an important role in the pathogenesis of acute myocardial infarction. It has been shown that transient coronary artery occlusion due to spasm possibly induces occlusive thrombus formation (25) and consequently acute myocardial infarction (26).

All group 1 patients had myocardial infarction in the territory perfused by the highly stenotic coronary artery. To compare the vasoreactivity of this infarct-related stenotic artery with that of the noninfarct-related artery, we examined the constrictor response of the stenotic lesions to acetylcholine. For the quantitative measurement of lumen diameter and area, we used a computer-assisted coronary angiography analysis system that detects vessel contours automatically with a geometric edge differentiation technique (21). This method was validated in phantom studies in which the diameter of coronary artery models with a known diameter of 0.5 to 4 mm was measured, and the accuracy and precision were found to be excellent.

Effect of acetylcholine on the atherosclerotic coronary arteries. Acetylcholine is an endothelium-dependent vasodilator (17) as well as a potent vasoconstrictor (27). Endothelium-dependent relaxation with acetylcholine has been shown (28) to be present in the nonatherosclerotic human coronary artery but impaired in the atherosclerotic artery. The present study showed that acetylcholine caused a significant reduction in lumen diameter and area of the atherosclerotic coronary arteries not only at the proximal site but at the stenotic site in both groups. The results are consistent with previous clinical observations of the effect of acetylcholine (13–15) and demonstrate that vasoconstriction occurs in response to acetylcholine even at the highly stenotic lesion.

Different response to acetylcholine of infarct-related and noninfarct-related coronary arteries. The analysis of the effect of acetylcholine on lumen diameter and area of the stenotic segment clearly showed that the constrictor response of the infarct-related coronary artery was greater than that of the noninfarct-related coronary artery. This finding was further supported by the greater incidence of acetylcholine-induced total or subtotal occlusion in group 1 than in group 2. Bertrand et al. (16) demonstrated that coronary spasm was induced with intravenous ergometrine in 21% of their patients with recent myocardial infarction. The incidence of coronary spasm in that study is low compared with our finding of a 69% incidence rate of total or subtotal occlusion after intracoronary administration of acetylcholine. This difference may be explained by 1) the difference in the severity of fixed stenosis (the study by Bertrand et al. [16] included patients with insignificant stenosis, whereas all of our patients had a highly stenotic lesion), 2) the difference in study protocol (it was not clarified in the study by Bertrand et al. [16] whether antianginal drugs were withdrawn before the angiographic examination was performed), 3) the difference in the study population (race), and 4) the difference in the vasoconstrictor used (intravenous ergometrine versus intracoronary acetylcholine) between the two studies. Total occlusion of the stenotic lesion after intracoronary infusion of acetylcholine has been documented in five (63%) of the eight patients with stable angina (13), but it was not reported whether the stenotic coronary artery was infarct related.

The present study failed to clarify whether the enhanced constrictor response of the infarct-related as compared with that of the noninfarct-related artery was a cause or a result of myocardial infarction. It has been shown experimentally (29) that reperfusion of an occluded coronary artery induces endothelial injury that results in impairment of endothelium-dependent relaxation with acetylcholine. Because the endothelium-dependent relaxation of the stenotic coronary artery is already impaired by atherosclerosis (29), the effect of reperfusion on the relatively enhanced constrictor response in the infarct-related coronary artery seems to be minimal. To clarify the precise role of this enhanced constrictor response will require a prospective, follow-up study of the patients with coronary artery disease whose atherosclerotic lesion is highly susceptible to the vasoconstrictive effect of acetylcholine, although such a study will be difficult to accomplish.

Mechanism of the different responses. Because the constrictor response at the proximal segment did not differ between the two groups, it is possible that the constrictor response of the stenotic lesion of the infarct-related artery is not necessarily increased. Alternatively, the noninfarct-related artery may have a reduced constrictor response. This possibility is supported by the fact that, in four group 1 patients with a highly stenotic lesion in both the infarct-related and the noninfarct-related artery, acetylcholine induced total or subtotal occlusion only in the infarct-related artery. Our study, however, could not clarify the mechanism for the difference in constrictor response between the infarct-related and the noninfarct-related artery. Type II eccentric stenosis, which was defined angiographically as an eccentric stenosis with a narrow neck or irregular borders,

or both (22), was more common in group 1 (5 of 16) than in group 2 (1 of 19), although this difference was not statistically significant because of the small number of patients. A higher incidence of type II stenosis in patients with unstable angina and acute or recent myocardial infarction than in patients with stable angina was previously reported (22,30). It has been shown that approximately 75% of the stenotic coronary artery has an eccentric residual lumen that is partially circumscribed by an arc of the normal arterial wall segment (9). An eccentric stenotic lesion thus seems to be more pliable than a concentric one that is surrounded with stiff vascular wall.

The highly stenotic coronary artery with the potential for active vasomotion such as seen in the infarct-related artery may have a risk for transient occlusion even with a physiologic change in the vascular tone (geometric theory) (31). On the contrary, the stenotic coronary artery with a reduced vasomotion as seen in the noninfarct-related artery may be at low risk for transient occlusion and thus for the formation of occlusive thrombi. However, many factors affect the tonus of the coronary artery, including the autonomic nervous system (10–12,27), circulating neurohumoral factors (32) and so on; thus, the potential for active vasomotion may be gained even in the noninfarct-related stenotic lesion.

Conclusions. The constrictor response of the stenotic segment of the infarct-related coronary artery is enhanced as compared with that of the noninfarct-related artery. This finding suggests that the relatively enhanced constrictor response of the infarct-related coronary artery is related to the genesis of acute myocardial infarction.

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