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Effect of Angina Pectoris on Myocardial Protection in Patients With Reperfused Anterior Wall Myocardial Infarction: Retrospective Clinical Evidence of "Preconditioning"

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Objectives. **We examined whether angina pectoris occurring shortly before the onset of acute myocardial infarction can actually preserve postischemic left ventricular function in humans.**

Background. **Experimental studies indicate that brief, transient episodes of ischemia render the heart very resistant to infarction from a subsequent sustained ischemic insult, an effect termed ischemic preconditioning. However, no clinical data are available concerning the implications of angina pectoris shortly before the onset of infarction in humans.**

Methods. **We studied 84 patients with an acute anterior myocardial infarction. All patients had total occlusion of the proximal or medial portion of the left anterior descending coronary artery and achieved reflow within 6 h of onset. Patients were classified into three groups on the basis of duration of antecedent angina pectoris: group 1 = no angina (37 patients); group 2 = new angina pectoris occurring ≤7 days of onset of infarction (22 patients); group 3 = angina pectoris beginning >7 days before onset of infarction (25 patients). All patients underwent left ventriculography on the day of, and 28 days after, onset of infarction to determine ejection fraction and regional wall motion in the territory of the left anterior descending coronary artery by the centerline method.**

Results. **Angiographic collateral flow grade was higher in group 3 than in groups 1 and 2 ([mean ± SD] group 1 = 0.8 ± 0.7, group 2 = 0.7 ± 0.7, group 3 = 1.5 ± 0.8). Although there were no differences in baseline ejection fraction and regional wall motion among the three groups, the degree of improvement was significantly greater in groups 2 and 3 than in group 1 (late minus baseline ejection fraction: group 1 = 0 ± 8%, group 2 = 7 ± 10%, group 3 = 6 ± 10% [$p < 0.05$ group 1 vs. groups 2 and 3]; late minus baseline regional wall motion: group 1 = 0.2 ± 0.4, group 2 = 0.6 ± 0.5, group 3 = 0.5 ± 0.6 SD/chord [$p < 0.05$, group 1 vs. group 2]). When the study was limited to those patients with no or poor collateral flow (31 in group 1, 19 in group 2, 10 in group 3), only group 2 patients had a significant improvement in wall motion. Angina pectoris within 24 h before onset of infarction was more frequent in group 2 (82%) than group 3 (28%, $p < 0.05$).**

Conclusions. **Episodes of angina pectoris occurring shortly before the onset of infarction may preserve myocardial contractile function in reperfused myocardial infarction despite less support from collateral flow channels, although these are suggestive results in a limited number of patients.**

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Thrombolysis and coronary angioplasty are widely performed in patients with acute myocardial infarction to restore coronary flow to the jeopardized myocardium (1). Although coronary reflow, if achieved in the early stage of infarction, is useful to limit the progression of myocardial necrosis, its effect on myocardial salvage varies among patients. The variation in the effect of coronary reperfusion can be explained by several factors, such as time from onset of infarction to reperfusion, development of collateral circulation, loading conditions to the left ventricle and medications (e.g., beta-adrenergic blocking agents) (1–3). In addition, recent experimental studies (4,5) have indicated that the occurrence of brief episodes of ischemia may, in itself, limit infarct size and improve functional recovery during a subsequent sustained coronary occlusion and reperfusion, an effect known as "ischemic preconditioning."

In the clinical setting, myocardial infarction is often preceded by an episode or episodes of angina pectoris (6,7). Several clinical studies (8–10) have discussed the significance of this antecedent angina pectoris in relation to its cardioprotective effect. In studies of nonreperfused myocardial infarction (9–11), patients with antecedent angina pectoris occurring >7 days before the infarction showed better collateral circulation and smaller infarct size than those with angina pectoris occurring within only 7 days of the infarction (9–11). However, despite development of less collateral circulation, antecedent angina occurring shortly before the onset of myocardial infarction can also contribute to preservation of myocardial function

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in reperfused myocardial infarction because of cardioprotection due to ischemic preconditioning.

In the present study, we aimed to elucidate whether antecedent angina pectoris can indeed exert a preconditioning effect on the myocardium in patients with a reperfused anterior myocardial infarction. To examine this hypothesis, we classified the patients into three groups on the basis of duration of antecedent angina pectoris (see Methods) and compared global and regional left ventricular function among the three groups in the early and late stages after successful reperfusion.

Methods

Patient selection. This study was designed retrospectively. At our institute, we attach great importance to antecedent angina pectoris and have obtained detailed histories of antecedent angina in patients with myocardial infarction for several years. From October 1986 to November 1993, consecutive patients presenting with an acute anterior myocardial infarction <5 after the onset of symptoms were considered for entry into the study. Inclusion criteria were 1) total occlusion (Thrombolysis in Myocardial Infarction trial [TIMI] grade 0) of the proximal region of the left anterior descending coronary artery revealed by coronary arteriography performed on the day of infarction; 2) no previous myocardial infarction; and 3) successful coronary reflow (TIMI grade 3, residual diameter stenosis ≤75%) achieved within 6 h after onset of infarction. Acute myocardial infarction was diagnosed on the basis of 1) prolonged chest pain >30 min, 2) 2-mm ST segment elevation on the electrocardiogram in two or more contiguous leads; and 3) a greater than threefold increase in serum creatine kinase level. Exclusion criteria were 1) >75% diameter stenosis in another coronary artery; 2) an ischemic event during the follow-up period; 3) high grade residual stenosis after reperfusion (≥90%); 4) >75% diameter stenosis of the infarct-related artery at the time of restudy; 5) in-hospital death; 6) positive bicycle ergometric exercise test result at the convalescent stage; and 7) mechanical complications (free wall, ventricular septal or papillary muscle rupture). Eighty-four patients (68 men, 16 women; mean age 58 years, range 38 to 82) met the inclusion criteria and formed the study group. Coronary reflow was achieved by intracoronary thrombolysis (urokinase, 480,000 to 960,000 U) in 13 patients and by coronary angioplasty in 71. In patients with thrombolysis, coronary reflow was confirmed by coronary angiography repeated every 5 min. Informed written consent was obtained from each patient by one of the investigators. The study protocol was approved by the hospital ethics committee.

Protocol. In all patients, diagnostic coronary angiography followed by contrast left ventriculography (30° right anterior oblique projection) was performed using the femoral approach on the day of onset of infarction. After total occlusion was confirmed, successful coronary reflow was achieved. Coronary angiography and left ventriculography was repeated using the brachial or femoral approach 21 to 36 days (mean 28) after onset of infarction in all patients.

Analysis of antecedent angina. Detailed clinical history, especially of cardiac symptoms before onset of infarction, in all patients was obtained by a staff physician. Cardiac symptoms included chest pain, chest discomfort and left arm and jaw pain. Onset of infarction was defined as the initiation of cardiac symptoms persisting >30 min. Cardiac symptoms that lasted <30 min before onset of infarction and were considered of cardiac origin were defined as antecedent angina pectoris. Duration of antecedent angina pectoris was defined as the time from the first symptom to onset of infarction. The patients were classified into three groups on the basis of the existence and duration of antecedent angina pectoris: *group 1* = no antecedent angina pectoris; *group 2* = angina pectoris occurring for the first time ≤7 days of infarction; *group 3* = angina pectoris beginning >7 days of infarction.

Analysis of catheterization data. Cine films were analyzed in a random sequence by an angiographer who was unaware of clinical findings. Coronary artery segments were identified and categorized according to the reporting system of the American Heart Association. Coronary artery diameter was measured with calipers on adequately magnified 35-mm cine films at end-diastole.

Right anterior oblique views of left ventriculograms obtained before reperfusion and 4 weeks later were used for assessment of global and regional left ventricular function. End-diastolic and end-systolic endocardial borders were hand traced in the frames with maximal and minimal volume, respectively. After left ventricular end-diastolic (LVEDV) and end-systolic (LVESV) volumes were calculated by the area-length method, left ventricular ejection fraction (%) was obtained as follows: (LVEDV − LVESV) × 100/LVEDV. Left ventricular end-diastolic volume was also corrected for body surface area to determine volume index (ml/m^2).

Regional wall motion from the left ventriculogram was assessed with the centerline method, using 100 chords (12). Each shortening fraction was normalized by the end-diastolic perimeter of the left ventricle at end-systole. This normalized wall motion in the territory of the left anterior descending coronary artery (chords 10 to 66) was expressed as the standard deviation from the mean value previously determined in 38 age-matched normal subjects (regional wall motion: SD/chord) (13).

Collateral channels at initial angiography were graded by consensus of two angiographers who had no knowledge of clinical findings: 0 = no collateral vessels; 1 = incomplete slow opacification of the distal vessel; 2 = slow but complete opacification of the distal vessel; 3 = distal vessel well opacified to the same degree as the normal vessel.

Statistical analysis. All data are expressed as mean value ± SD. When data were compared among the three groups, one-way analysis of variance for factor analysis and the Scheffé *F* test were applied. Comparisons between results of baseline and delayed studies were performed by analysis of variance and the Scheffé *F* test for repeated measures. The contribution of factors that may influence ischemic myocardial damage to the improvement in systolic function was evaluated by multi-

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Table 1. Clinical Characteristics of 84 Study Patients

	Antecedent Angina Pectoris		
	Group 1 (none) (n = 37)	Group 2 (≤1 wk) (n = 22)	Group 3 (>1 wk) (n = 25)
Age (yr)	56 ± 11	59 ± 11	58 ± 9
Gender (% male)	81	77	84
Time interval (onset to reperfusion) (h)	3.9 ± 1.3	4.7 ± 0.9	4.2 ± 1.3
Culprit (6/7)	23/14	12/10	17/8
Collateral grade	0.8 ± 0.7*	0.7 ± 0.7*	1.5 ± 0.8
Reperfusion therapy (thrombolysis/angioplasty)	5/23	5/17	3/22
Residual coronary stenosis (%)	26 ± 20	28 ± 19	27 ± 20
Coronary stenosis at F/U (%)	39 ± 25	35 ± 23	41 ± 20
Previous medications (%)			
Beta-blockers	8	9	16
Ca-channel antagonists	11	18	36
Nitrates	8	18	28
Aspirin	3	5	8
Risk factors (%)			
Diabetes mellitus	30	18	36
Hyperlipidemia	30	27	40
Hypertension	30	50	40
Smoking	51	50	40

*p < 0.05 versus group 3. Patients are subgrouped according to duration of preinfarction angina pectoris (see text for details). Data presented are mean value ± SD, unless otherwise indicated. Ca = calcium; Culprit 6/7 = number of lesions proximal and distal to the first septal perforator, respectively; F/U = follow-up.

variate regression analysis, as shown later. For all analyses, $p < 0.05$ was considered significant.

Results

Antecendent angina. Thirty-seven patients (44%) had no antecedent angina pectoris (group 1); 22 (26%) had antecedent angina pectoris occurring for the first time ≤7 days of infarction (group 2); and 25 (30%) had antecedent angina pectoris >7 days of infarction (group 3).

Clinical and angiographic characteristics. Table 1 shows the clinical and angiographic characteristics and medications in the three groups. There were no differences in variables, except angiographic collateral grade, which was higher in group 3 than in groups 1 and 2.

Changes in left ventricular function. Table 2 summarizes changes in left ventricular ejection fraction, end-diastolic volume index and regional wall motion in the three groups. Ejection fraction, end-diastolic volume index and regional wall motion did not differ among the three groups at baseline. There was no change in ejection fraction between the early and late stages in group 1, whereas groups 2 and 3 had a significant increase in ejection fraction at the late stage. End-diastolic volume index increased in group 1, but no left ventricular dilation was observed in groups 2 and 3. Regional wall motion improved in all groups during the late stage, with greater improvement in group 2 than group 1.

Table 2. Changes in Variables Derived From Left Ventriculography (all patients)

	Antecedent Angina Pectoris		
	Group 1 (none)	Group 2 (≤1 wk)	Group 3 (>1 wk)
LVEF (%)			
Early	43 ± 8	43 ± 11	44 ± 10
Late	43 ± 9	50 ± 14	50 ± 12
Late minus early	0 ± 8	7 ± 10*	6 ± 10*
p value	NS	<0.001	<0.01
LVEDVI (ml/m^2)			
Early	90 ± 21	86 ± 20	77 ± 11
Late	100 ± 22	94 ± 23	83 ± 17
p value	<0.01	NS	NS
RWM (SD/chord)			
Early	−3.34 ± 0.40	−3.34 ± 0.66	−3.22 ± 0.69
Late	−3.14 ± 0.45	−2.72 ± 0.75	−2.70 ± 0.89
Late minus early	0.21 ± 0.47	0.62 ± 0.55*	0.52 ± 0.60
p value	<0.01	<0.001	<0.01

*p < 0.05 versus group 1. Data presented are mean value ± SD. LVEDVI = left ventricular end-diastolic volume index; LVEF = left ventricular ejection fraction; p value = early versus late; RWM = regional wall motion.

Although collateral flow grade did not differ between groups 1 and 2 in the early stage (Table 1), group 2 had greater improvement in left ventricular function than group 1. Therefore, the degree of collateral development cannot explain the difference in functional recovery between the two groups. To strengthen this observation, we further assessed changes in left ventricular ejection fraction and regional wall motion in patients with no functionally significant collateral vessels (collateral grade 0 or 1) at initial coronary arteriography (Table 3, Figs. 1 and 2). Among these selected patients (31 patients in group 1, 19 in group 2, 10 in group 3), there was no significant improvement in global or regional function in group 1 and 3 patients. Only group 2 showed a significant improvement in these variables in the late study, with greater improvement in group 2 than group 1. These results suggest that the greater

Table 3. Changes in Variables Derived From Left Ventriculography (patients with no or poor collateral circulation)

	Antecedent Angina Pectoris		
	Group 1 (none)	Group 2 (≤1 wk)	Group 3 (>1 wk)
LVEF (%)			
Early	43 ± 8	43 ± 12	46 ± 10
Late	42 ± 8	50 ± 15	50 ± 14
Late minus early	0 ± 8	7 ± 10*	4 ± 12
p value	NS	<0.05	NS
RWM (SD/chord)			
Early	−3.32 ± 0.40	−3.33 ± 0.71	−2.96 ± 0.83
Late	−3.17 ± 0.44	−2.70 ± 0.80	−2.51 ± 1.11
Late minus early	0.15 ± 0.48	0.64 ± 0.59*	0.45 ± 0.77
p value	NS	<0.001	NS

*p < 0.05 versus group 1. Data presented are mean value ± SD. Abbreviations as in Table 2.

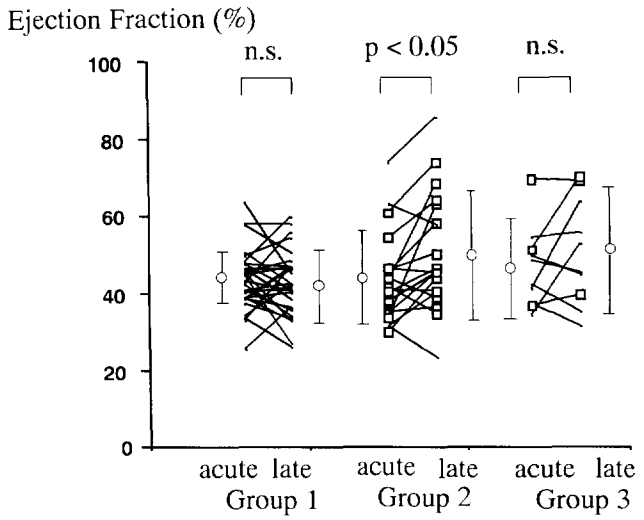

Figure 1. Plots of left ventricular ejection fraction at early and late stages of infarction in patients with no or poor collateral circulation at initial coronary angiography. **Squares** = patients with angina attack within 24 h of onset of infarction; **Circles and vertical bars** = mean value ± SD. Group 1 = no antecedent angina pectoris; Group 2 = angina pectoris occurring within 7 days of infarction; Group 3 = angina pectoris present >7 days before infarction.

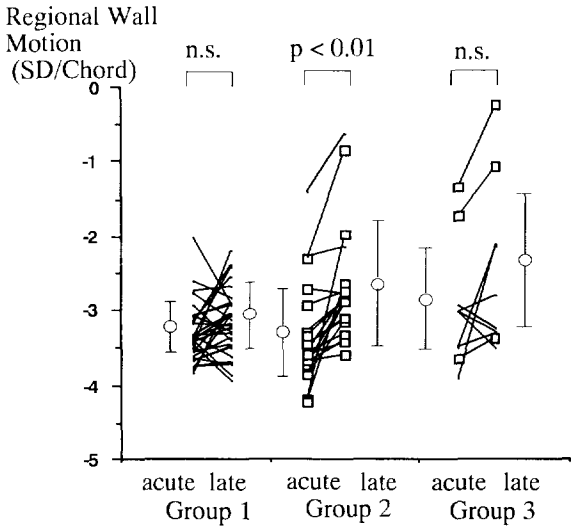

Figure 2. Plots of regional wall motion in the territory of the left anterior descending coronary artery at the early and late stages in patients with no or poor collateral circulation at initial coronary angiography. Symbols and abbreviations as in Figure 1.

functional recovery in group 3 is attributable to the development of collateral vessels, but the comparable extent of functional recovery in group 2 is attributable to a factor other than collateral vessels.

Clinical data for groups 2 and 3. The clinical data for group 2 patients are summarized in Table 4. Data are arranged according to the time interval from the last episode of angina pectoris to onset of infarction. The last episode of angina pectoris was observed within 24 h of onset of infarction in 18 (82%) of 22 patients. Seven patients had multiple episodes of angina pectoris (unstable state) within 24 h before onset of infarction. Improvement in global and regional left ventricular function tended to be greater in patients with antecedent angina within 24 h than in those with angina observed >24 h

Table 4. Clinical Characteristics of Patients in Group 2

Age (yr)/ Gender	Episodes ≤7 days Before AMI	Episodes ≤24 h Before AMI	Last Angina Onset (h)	Onset to Reflow (h)	Collateral Flow Grade	Culprit Lesion	LVEF (%)		RWM (SD/chord)	
							Early	Convalescent	Early	Convalescent
56/F	2	2	2.5	6	1	7	54.5	63.8	−2.95	−2.75
50/M	2	1	3	4.5	0	7	37.4	45.4	−3.73	−2.88
68/M	1	1	3	4.5	1	6	41.5	34.3	−2.73	−2.77
82/M	2	1	4	5.1	1	6	42.9	68.3	−4.2	−1.98
62/M	3	1	5	3.8	0	6	34.5	45.1	−3.87	−3.17
67/M	4	3	5	5	2	6	40.7	48.3	−3.69	−3.04
49/M	3	2	5	5.4	0	6	29.8	43.7	−3.58	−2.79
44/M	1	1	5.5	5.7	1	7	45	57.8	−3.3	−2.87
57/M	2	2	7	5.5	0	7	60.6	73.4	−2.31	−0.86
61/M	1	1	8	5.4	2	7	38.9	49	−3.26	−2.66
52/M	3	3	11.5	4.5	2	6	40.6	49	−3.29	−2.9
42/M	2	1	13	4	0	6	39.7	46.3	−3.46	−3.12
73/F	1	1	15	5.3	1	6	43.3	38.5	−3.69	−3.6
55/M	4	2	17	4.6	1	7	46	45	−3.46	−3.1
65/M	1	1	18.5	3.8	0	7	40.1	40.4	−3.61	−3.44
66/F	2	1	22	5.8	1	7	34.7	36	−3.57	−3.32
66/M	1	1	23.5	3	0	6	45.8	49.9	−3.34	−2.88
46/M	1	1	48	6	1	6	75.1	85.4	−1.42	−0.62
65/M	1	0	48	3.6	0	6	62.8	57.3	−2.29	−2.13
63/M	1	0	120	6	1	6	31.3	39.6	−3.85	−2.91
77/F	1	0	168	4	0	7	31.2	23	−3.72	−3.42

Culprit = preseptal (6), postseptal (7); Episodes = number of episodes of antecedent angina pectoris; F = female; M = male; other abbreviations as in Table 2.

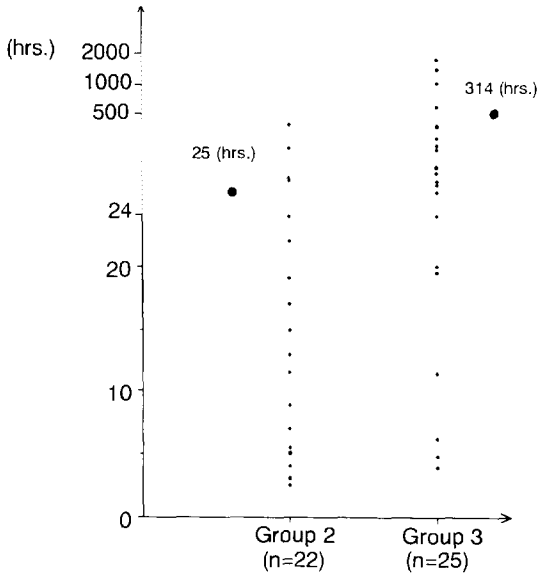

Figure 3. Time interval between the last episode of angina pectoris and onset of infarction in groups 2 and 3. The time interval is shorter in group 2 than group 3. Data are expressed as mean value ± SD. Abbreviations as in Figure 1.

before onset of infarction (late minus baseline ejection fraction 8.2 ± 9.3 vs. 1.6 ± 9.9% SD/chord; late minus baseline regional wall motion 0.64 ± 0.38 vs. 0.55 ± 0.48 SD/chord).

Figure 3 shows the time from the last episode of angina pectoris to onset of infarction in groups 2 and 3. The mean interval in group 2 was markedly shorter than that in group 3 (25 vs. 314 h). Episodes of angina pectoris within 24 h of onset of infarction were observed more frequently in group 2 than group 3 (82% vs. 28%, $p < 0.05$).

Variables contributing to recovery of left ventricular function. Multivariate regression analysis was performed to evaluate the contribution of each variable to the recovery of cardiac function, as shown in Table 5. We hypothesized that the preconditioning effect would decrease with the duration between the last episode of angina pectoris and onset of infarction. Therefore, the reciprocal of the duration between the last episode of angina pectoris and onset of infarction was used as the score of antecedent angina, so no antecedent angina was scored as 0.

Multivariate analysis identified only antecedent angina pectoris score ($p = 0.003$) as the significant predictor of increase in left ventricular ejection fraction from baseline to late studies. Multivariate analysis further identified degree of collateral flow ($p = 0.0405$) and score of antecedent angina pectoris score ($p = 0.008$) as the two significant predictors of increase in regional wall motion. However, these variables together could account for <30% of the total improvement in left ventricular function. Other, still unknown variables need to be identified to explain the variability of the reperfusion effect.

Discussion

Patient selection and study protocol. Preservation of postischemic left ventricular function is determined by several factors other than the presence or absence of antecedent angina pectoris, such as collateral circulation; patency of the infarct-related artery; residual coronary stenosis; time from onset of infarction to reperfusion; and postreperfusion therapy or events, or both. In the present study, we aimed to elucidate whether the presence of episodes of angina pectoris shortly before onset of infarction could itself yield preconditioned myocardium that is more resistant to subsequent ischemia than

Table 5. Multiple Regression Analysis

Variable	DLVEF (p value)	DRWM (p value)
Score of antecedent angina pectoris	0.0030	0.0080
Collateral flow grade	0.0663	0.0405
Interval (onset to reperfusion)	0.0973	0.2941
Gender	0.6429	0.6852
Reperfusion therapy (thrombolysis vs. angioplasty)	0.2087	0.0785
Age	0.6429	0.8122
Percent residual coronary stenosis	0.6441	0.2941
Percent coronary stenosis at time of restudy	0.4260	0.6890
Previous medications		
Nitrates	0.3920	0.5075
Ca-channel antagonists	0.4667	0.1758
Beta-blockers	0.4786	0.7115
Aspirin	0.3743	0.4250
Medications after reperfusion (angiotensin-converting enzyme inhibitions)	0.8638	0.9880
R^2	0.275	0.265

Collateral flow grade = 0 (none) to 3 (good); DLVEF = left ventricular ejection fraction (late minus early); DRWM = regional wall motion (late minus early); Previous medications = 0 (none), 1 (positive); Reperfusion therapy = 0 (thrombolysis), 1 (angioplasty); Score of antecedent angina pectoris (/h) = 1/(time interval between last episode of angina and onset of infarction).

"virgin" myocardium. To normalize factors other than the presence of antecedent angina pectoris, we selected patients who had "total" occlusion of the left anterior descending coronary artery confirmed by initial coronary arteriography and achieved early (≤6 h) and successful (residual stenosis ≤75%) coronary reperfusion. Additionally, we excluded patients with recurrent ischemia, mechanical complications and in-hospital death because these postreperfusion events were considered to affect functional improvement.

In addition, because antecedent angina pectoris possibly contributes to the preservation of myocardial integrity through the development of collateral circulation (8–11), we classified the study patients into three groups on the basis of duration of antecedent angina pectoris to evaluate the role of collateral development in the recovery of left ventricular function. This is based on previous observations (11,14) that development of collateral circulation was greater in patients with antecedent angina pectoris occurring >7 days before infarction (group 3) than in those without antecedent angina pectoris (group 1) or those with angina pectoris occurring within 7 days of the infarction (group 2). In fact, in the present study, group 3 patients exhibited well developed collateral circulation. This observation explains the greater improvement in left ventricular function after reperfusion in group 3 than group 1 patients.

Implications of antecedent angina pectoris. Experimental studies (15) have demonstrated that episodes of brief ischemia before more prolonged ischemia result not only in reduced infarct size, but also in significantly better recovery of systolic function (15). However, there have been limited clinical data as to whether preconditioning can actually preserve wall motion in reperfused hearts, the ultimate goal of any salvage intervention. In patients with reperfusion, our data demonstrated that groups 2 and 3 had greater improvement in global and regional left ventricular function than group 1. Collateral circulation played an important role in the preservation of contractile function in group 3. The greater improvement in left ventricular function in group 2 than group 1 cannot be explained by collateral circulation, time from onset infarction to reperfusion or preinfarction medication. Therefore, our data suggest that antecedent angina pectoris, in itself, may exert a beneficial effect on the preservation of postischemic myocardial function aside from collateral circulation.

To strengthen these observations, we compared the improvement in left ventricular function after reperfusion among selected patients who had grade 0 or 1 collateral circulation. As a result, only group 2 patients showed significant improvement in left ventricular function, in contrast to group 1 and 3 patients with little or no improvement. Therefore, antecedent angina pectoris shortly before infarction indeed exerted a cardioprotective effect in group 2 in addition to collateral circulation, which also played an important role in preservation of myocardial function in group 3. Although these are suggestive results in a limited number of patients, to our knowledge this is the first report to document the presence of preconditioning in humans.

The mechanism of preconditioning is not fully understood. Preconditioning does not simply accrue from the energy savings associated with turning off the contractile machinery, which is depressed shortly after the onset of occlusion (16). Several studies (17–20) indicate that adenosine release from the ischemic myocardium plays a significant role in preserving the integrity of the myocardium and microcirculation. A recent experimental study (21) indicated that augmentation of the synthesis of proteins, such as manganese superoxide dismutase, may contribute to the preconditioning effect observed 24 h after a brief episode of ischemia (21).

Type of angina pectoris and preconditioning. In a canine experiment, Murry et al. (4) demonstrated that much of the protective effect was lost if the time between the preconditioning episode(s) of brief ischemia and the later sustained ischemia was extended for several hours. This observation indicates the possibility that the preconditioning effect of angina pectoris is lost if the time interval from the last episode of angina pectoris and onset of infarction exceeds a certain time limit. In contrast, Kuzuya et al. (21) recently demonstrated that after the initial preconditioning effect was lost, the delayed preconditioning effect appeared 24 h after a brief episode of ischemia, and, at that time, the synthesis of manganese superoxide dismutase was augmented. Therefore, it is important to determine how angina pectoris exerts a preconditioning effect on the ischemic myocardium in humans.

We first investigated the time interval from the last episode of angina pectoris to the onset of infarction in group 2 and compared the results with those in group 3, in whom collateral circulation played a significant role in myocardial protection. This time interval was markedly shorter in group 2 than group 3. Moreover, the majority (82%) of group 2 patients had episodes of angina pectoris within 24 h of infarction, in contrast to only 28% of group 3 patients. Among group 2 patients, the improvement in left ventricular function tended to be greater in those with than without an anginal episode within 24 h before onset. In addition, group 3 patients with antecedent angina within 24 h of onset of infarction had somewhat greater improvement in left ventricular function than those without angina within 24 h before onset (data not shown). Therefore, the interval between the episode of last angina pectoris and onset of infarction seems to determine whether angina pectoris can exert a preconditioning effect. Our data also imply that antecedent angina pectoris within 24 h can indeed preserve myocardial contractile function in the clinical setting.

We examined whether a shorter interval between the last episode of angina pectoris and onset of infarction results in greater improvement in left ventricular function. We determined the antecedent angina score, defined as the reciprocal of the interval, and compared several variables, including this score, with the degree of increase in ejection fraction or regional wall motion by multivariate analysis. Our data indicated that antecedent angina pectoris and grade of collateral flow contribute to improvement in ventricular function after reperfusion and, in particular, that the cardioprotective effect

of angina pectoris becomes weaker as the time interval between the last angina attack and onset of infarction increases.

Medical treatment. Medical treatment before acute myocardial infarction may also contribute to the reduction in infarct size. In particular, administration of a beta-adrenergic blocking agent as pretreatment before a coronary occlusion is reported to be beneficial in limiting the size of myocardial infarction (3). Functional improvement in left ventricular function after reperfusion in group 2 was equal to that in group 3 in the present study, but beta-blocker use in group 2 (7%) was not as frequent as that in group 3 (30%). In contrast, angiotensin-converting enzyme inhibitors may improve left ventricular function after reperfusion (22). However, there was no difference in angiotensin-converting enzyme inhibitor use after infarction among the three groups (8%, 9% and 0%, respectively, for groups 1, 2 and 3).

Study limitations. It is sometimes difficult to determine the exact time of onset of infarction in patients with unstable angina with frequent angina pectoris at rest. In such patients, it may not be possible to differentiate preinfarction and postinfarction angina simply from symptoms. In the present study we arbitrarily defined the onset of symptoms with duration >30 min as the onset of infarction. In addition, we utilized the release pattern of creatine kinase and temporal changes in ECGs, if available, for the confirmation of onset of infarction.

Objective markers of antecedent angina pectoris were not obtained in all study patients because most patients were admitted to our hospital only after onset of myocardial infarction. However, in two patients (11%) in group 2, ECGs were recorded during an anginal attack during the previous hospital admission. The ST segments were elevated in the precordial leads during the attack and returned to baseline after remission of chest pain.

It is well known that myocardial ischemia is not always symptomatic. Ambulatory ECG monitoring has demonstrated that myocardial ischemia is asymptomatic in 10% to 40% of events (23,24). Moreover, myocardial infarction, in itself, is reported to be asymptomatic in 30% of patients (25). Because our study was based on a detailed history of symptoms of cardiac origin from each patient, the significance of this silent ischemia could not be evaluated.

It is difficult to quantitate myocardial infarction size as performed in earlier experimental studies because infarct size reflects ventricular function in the late stage, but residual left ventricular function is a major determinant of prognosis (26). We therefore compared the improvement in postischemic left ventricular global and regional function among the three categories of antecedent angina pectoris to evaluate the cardioprotective effect of antecedent angina pectoris.

Visualization of collateral vessels by coronary angiography is affected by several factors, and there may be some collateral channels that cannot be detected. However, angiographic assessment of collateral flow grade is still the reference standard in the clinical setting.

Clinical implications. In the clinical setting, acute myocardial infarction is often preceded by episodes of angina pectoris. As shown in the present study, antecedent angina pectoris could be a favorable sign in terms of preservation of left ventricular function, regardless of the duration of antecedent angina. Long-standing angina pectoris plays an important role in allowing greater development of collateral circulation, thereby improving left ventricular function after coronary reperfusion. By contrast, episodes of angina pectoris that occur shortly before onset of infarction may precondition the myocardium without the development of collateral circulation, and, in so doing, may decrease the extent of cell death after onset of infarction and slow the early progression of cell death (4,16). A slower progression of cell death implies a longer window of time during which it may be possible to salvage the myocardium through reperfusion, such as thrombolysis or coronary angioplasty. Such patients may also have an increased time frame for successful emergency coronary artery bypass graft surgery and revascularization.

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