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Angina-Induced Protection Against Myocardial Infarction in Adult and Elderly Patients: A Loss of Preconditioning Mechanism in the Aging Heart?

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Objectives. **The present study examined whether angina 48 h before myocardial infarction provides protection in adult and elderly patients.**

Background. **The mortality rate for coronary artery disease is greater in elderly than in young patients. In experimental studies, ischemic preconditioning affords an endogenous form of protection against ischemia–reperfusion injury in adult but not in senescent hearts. Angina before myocardial infarction, a clinical equivalent of experimental ischemic preconditioning, has a protective effect in adult patients. It is not known whether angina before myocardial infarction is also protective in aged patients.**

Methods. **We retrospectively verified whether antecedent angina within 48 h of myocardial infarction exerts a beneficial effect on in-hospital outcomes in adult (<65 years old, n = 293) and elderly (≥65 years old, n = 210) patients.**

Results. **In-hospital death was more frequent in adult patients without than in those with previous angina (10% vs. 2.6%, p < 0.01), as were congestive heart failure or shock (10.7% vs. 3.3%, p < 0.02) and the combined end points (in-hospital death and congestive heart failure or shock) (20.7% vs. 5.9%, p < 0.0003). In contrast, the presence or absence of previous angina before acute myocardial infarction in elderly patients seems not to influence the incidence of in-hospital death (14.4% vs. 15.2%, p = 0.97), congestive heart failure or shock (11.0% vs. 11.9%, p = 0.99) and the combined end points (25.4% vs. 27.1%, p = 0.89). Logistic regression analysis models for in-hospital end points show that previous angina is a positive predictor in adult but not in elderly patients.**

Conclusions. **The presence of angina before acute myocardial infarction seems to confer protection against in-hospital outcomes in adults; this effect seemed to be less obvious in elderly patients. This study suggests that the protection afforded by angina in adult patients may involve the occurrence of ischemic preconditioning, which seems to be lost in senescent patients.**

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Death due to coronary artery disease increases progressively with age (1–6). In the United States, 80% of deaths from coronary artery disease occur among patients >65 years (6). Tofler et al. (7) showed that 7 adverse baseline and 12 additional in-hospital characteristics did not account for the increased mortality rate of elderly patients in either in-hospital or 1- or 4-year hospital survivors. The increased incidence of death in elderly patients may be the result of the reduction of thrombolytic therapy because of a higher incidence of complicating illness, absence of chest pain on admission and nonspecific electrocardiographic (ECG) abnormalities (8). Maggioni et al. (9) demonstrated that age is a powerful independent predictor of both in-hospital and postdischarge mortality rates in patients with a first myocardial infarction who received thrombolytic therapy, and they excluded a correlation between age-related higher mortality for myocardial infarction and more extensive coronary artery disease. They found that the number and degree of critical coronary stenoses did not differ according to age group in 20% of patients who died during the hospital period and underwent autopsy.

Experimental studies demonstrated that preconditioning myocardium through brief ischemic episodes before a prolonged coronary occlusion protects the heart by delaying lethal injury, including postischemic electrical and mechanical dysfunction (10). Patients with myocardial infarction presenting with prodromal angina have a significantly smaller infarct size (11) and a better in-hospital outcome (12) than patients without prodromal symptoms. Although the presence of an-

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Abbreviations and Acronyms

CK = creatine kinase
CK-MB = creatine kinase, MB fraction
ECG = electrocardiographic

gina before myocardial infarction may be a marker of a more extensive coronary collateral circulation, these reports suggest that ischemic preconditioning plays a role in the better prognosis of patients with a myocardial infarction. We recently demonstrated (13) that ischemic preconditioning significantly reduces electromechanical postischemic dysfunction in adult but not in senescent rat hearts, suggesting that age-related reduction of this endogenous mechanism may be responsible for the higher mortality observed in aging patients with myocardial infarction.

We performed a retrospective analysis of the effect of previous angina 48 h before acute myocardial infarction on several in-hospital end points, including mortality, congestive heart failure and cardiogenic shock, in patients ≥65 years old compared with those <65 years old.

Methods

Patients. Between January 1993 and December 1995, 530 patients with an acute myocardial infarction were admitted to our coronary care unit; 298 were <65 years old, and 232 were ≥65 years old. Patients were included in this retrospective study if they had at least two of the following criteria: 1) typical chest pain; 2) ECG changes with evolution of Q waves (transmural infarction); and 3) elevation of creatine kinase (CK) levels. Nontransmural infarction was diagnosed by typical changes in ST segments and T waves accompanied by increased CK levels. We recorded data from the history, physical examination, laboratory studies, echocardiographic variables and the ECG. Family history was considered positive when symptomatic coronary artery disease occurred before age 60 in siblings, parents, parents' siblings or grandparents. Patients with documented systolic blood pressure ≥160 mm Hg or diastolic blood pressure ≥100 mm Hg and those taking antihypertensive drugs were considered hypertensive. A previous myocardial infarction was documented by ECG or hospital records. Other historical variables were history of congestive heart failure (shortness of breath on exertion associated with either orthopnea or paroxysmal nocturnal dyspnea), history of diabetes, hypercholesterolemia (>200 mg/dl), smoking and low educational level (<8 years). Information on the administration of digitalis, diuretic drugs, nitrates, calcium antagonists, beta-adrenergic blocking agents, angiotensin-converting enzyme inhibitors and aspirin was recorded at admission. Thrombolytic therapy was given to all patients except those presenting with complicating illness, absence of chest pain on admission or nonspecific ECG abnormalities, including ST segment depression. Age ≥65 years was not considered a contraindication for thrombolytic therapy. All patients ≥65 years old with an acute myocardial infarction were admitted to our coronary care unit regardless of functional status. Patients with advanced or terminal illness, cerebrovascular disease and such neuropsychiatric disorders as dementia and delirium were not included in the study. In particular, among patients <65 years old, two (0.7%) with terminal illness and three (1.0%) with cerebrovascular disease were excluded. Among patients ≥65 years old, 6 (2.5%) with terminal illness, 6 (2.6%) with cerebrovascular disease and 10 (4.3%) with dementia were excluded. In our coronary care unit, patients with suspected cerebrovascular disease or dementia are immediately examined by a consultant neurologist (available 24 h/day for all clinical departments) to confirm or exclude these conditions. The criteria for the diagnosis of dementia are memory impairment and one or more neurologic disturbances (aphasia, apraxia, agnosia, disturbance in executive functioning), as described in Diagnostic and Statistical Manual of Mental Disorders (DSM-IV, American Psychiatric Association).

The following ECG variables were determined: presence or absence of ventricular tachycardia and fibrillation; atrial fibrillation and flutter; atrial and junctional tachycardia; bundle branch block; intraventricular conduction delay; and first, second or complete heart block. We also used continuous ECG monitoring to analyze complex ventricular arrhythmias when present and defined them as frequent ventricular beats (>1 beat/min or 30 beats/h), multiform ventricular premature beats, couplets and ventricular tachycardia (>3 premature ventricular beats). These ECG variables were monitored during the entire clinical course.

Blood samples for assay of CK and CK-MB plasma levels were taken on admission and 8, 16 and 24 h after enrollment. The upper limits of normal range in our laboratory are 160 and 12.8 IU/liter for plasma CK and CK-MB, respectively. The time to CK-MB peak levels was measured from the onset of myocardial infarction symptoms.

Major in-hospital end points in the coronary care unit were death, congestive heart failure (presence of rales that do not clear with coughing over >50% of the lung field and radiographic confirmation of pulmonary congestion) and cardiogenic shock; minor end points were infarct extension, persistent chest pain (>30 min), CK-MB peak level, CK-MB time to peak level, ventricular fibrillation and tachycardia (≥3 consecutive premature ventricular complexes), high grade atrioventricular block, left ventricular dysfunction (after the fourth hospital day, indicated by the presence of an S_3 gallop, rales or radiographic evidence of pulmonary congestion or as extensive left ventricular injury in the absence of clinical heart failure [indicated by left ventricular ejection fraction ≤35% on echocardiography] or as injury to ≥45% of myocardial segments [akinetic–dyskinetic scores]) (14). Left ventricular ejection fraction was available only in 83 adult and 52 elderly patients (28.3% and 24.7%, respectively).

Analysis of previous angina. A staff physician collected a detailed clinical history for all patients. Patients who had not experienced chest pain, chest discomfort or left arm and jaw

Table 1. Baseline Characteristics of Adult (<65 years old) and Elderly (≥65 years old) Patients With Acute Myocardial Infarction

	Adult Patients (n = 293)	Elderly Patients (n = 210)	p Value
Age	52.7 ± 9.2	74.1 ± 7.1	0.01
Male	256 (87.4)	138 (63.2)	0.0000
Family history	83 (28.3)	56 (26.9)	0.75 (NS)
Low educational level	198 (67.5)	174 (82.7)	0.0001
Chronic angina	101 (34.5)	69 (33.0)	0.77 (NS)
Previous MI	74 (25.2)	47 (22.5)	0.52 (NS)
Smoking	241 (82.3)	129 (61.5)	0.0000
Hypertension	106 (36.3)	92 (43.9)	0.10 (NS)
CHF	36 (12.2)	27 (13.0)	0.95 (NS)
Diabetes	80 (27.3)	64 (30.5)	0.49 (NS)
Hypercholesterolemia	98 (33.6)	28 (13.1)	0.0000
Nitrates	47 (16.0)	46 (22.0)	0.12 (NS)
Beta-blockers	16 (5.4)	7 (3.3)	0.36 (NS)
Calcium blockers	62 (21.0)	56 (26.5)	0.18 (NS)
Aspirin	37 (12.6)	35 (16.5)	0.25 (NS)
S_3 sounds	33 (11.4)	19 (9.1)	0.51 (NS)
Rales >⅓ lung fields	23 (7.8)	17 (8.0)	0.94 (NS)

Data presented are mean value ± SD or number (%) of patients. CHF = congestive heart failure; MI = myocardial infarction.

Table 2. In-Hospital Outcomes of Adult Patients (<65 years old) With or Without Previous Angina 48 Hours Before Acute Myocardial Infarction

	Previous Angina		
In-Hospital End Points	Yes (n = 153)	No (n = 140)	p Value
In-hospital death	4 (2.6)	14 (10.0)	0.01
CHF	5 (3.3)	15 (10.7)	0.02
Death or CHF	9 (5.9)	29 (20.7)	0.0003
Lytic therapy	72 (46.8)	58 (41.2)	0.39 (NS)
Time to lytic therapy			
≥4 h	63 (41.0)	55 (39.5)	0.83 (NS)
>4 h	10 (6.8)	6 (4.1)	0.55 (NS)
t-PA	53 (34.7)	36 (25.6)	0.12 (NS)
Urokinase	23 (15.0)	24 (16.9)	0.73 (NS)
In-hospital reinfarction	14 (9.1)	9 (6.5)	0.51 (NS)
Recurrent ischemic pain	21 (13.5)	13 (9.5)	0.31 (NS)
Q wave MI	95 (62.1)	103 (73.5)	0.04
CK-MB peak (IU/liter)	117 ± 79	219 ± 95	0.01
Time to peak CK (min)	10.5 ± 3.4	9.8 ± 3.1	0.42 (NS)
Ventricular fibrillation	5 (3.0)	13 (9.2)	0.05
Ventricular tachycardia	44 (29.0)	52 (37.0)	0.16 (NS)
High grade AV block	9 (6.0)	13 (9.2)	0.37 (NS)
LV dysfunction	20 (13.0)	32 (22.8)	0.04

Data presented are mean value ± SD or number (%) of patients. AV = atrioventricular; CK = creatine kinase; CK-MB = creatine kinase, MB fraction; LV = left ventricular; t-PA = tissue-type plasminogen activator; other abbreviations as in Table 1.

pain 48 h before the episode leading to admission were defined as having "no previous angina." Patients showing angina lasting <30 min 48 h before the acute myocardial infarction were defined having "previous angina." Patients with a history of angina at any time independently by the presence or absence of angina 48 h before the acute myocardial infarction were defined having "chronic angina."

Statistical analysis. Categoric data were compared with chi-square analyses. The Student *t* test was used to compare continuous variables such as age. Logistic regression models were used to assess the role of previous angina in death, congestive heart failure and cardiogenic shock and the combined end points unadjusted and simultaneously adjusted for thrombolytic therapy, antianginal treatment and demographic variables (age, gender, family history, low educational level, smoking, chronic angina, previous myocardial infarction, congestive heart failure, hypertension, diabetes and cholesterolemia). A p value of 0.05 was considered significant.

Results

Baseline characteristics. Adult (<65 years old) and elderly patients (≥65 years old) differed with regard to age, gender, educational level, smoking and hypercholesterolemia (Table 1). However, there was no difference in family history, chronic angina, previous myocardial infarction, hypertension, history of heart failure, diabetes, antianginal therapy and clinical symptoms of heart failure.

Age, gender, family history, sedentary lifestyle and low educational level did not differ between adult patients with versus without angina before acute myocardial infarction. More adult patients with angina had an antecedent myocardial infarction ($p < 0.0001$), and more took antianginal medicines (nitrates: $p < 0.0001$; calcium channel blocking agents: $p = 0.001$) and aspirin ($p < 0.00001$). There was no difference in history of smoking, hypertension, heart failure, diabetes and hypercholesterolemia. More elderly patients with previous angina had an antecedent myocardial infarction ($p < 0.001$), and more took antianginal drugs (nitrates: $p < 0.0001$; calcium blockers: $p < 0.003$) and aspirin ($p < 0.004$) than those without previous angina.

In-hospital outcome. As shown in Table 2, in-hospital death was more frequent in adult patients without than in those with a previous history of angina (10% vs. 2.6%, $p < 0.01$). Congestive heart failure or shock (10.7% vs. 3.3%, $p < 0.05$) and the combined end points (in-hospital death and congestive heart failure or shock: 20.7% vs. 5.9%, $p < 0.0003$) were more frequent in adult patients without than in those with previous angina before acute myocardial infarction (Fig. 1). However, in elderly patients the presence or absence of previous angina before an acute myocardial infarction seems not to influence the occurrence of in-hospital death ($p = 0.97$), congestive heart failure or shock ($p = 0.99$) and the combined end points ($p = 0.89$) (Table 3, Fig. 1).

Similarly, adult patients with angina were less likely to have a Q wave myocardial infarction and ventricular fibrillation and had a lower CK-MB release and a lower incidence of left ventricular dysfunction than those without angina (Table 2). These in-hospital end points were similar in elderly patients with and without angina (Table 3). Time to lytic therapy (≥4 h)

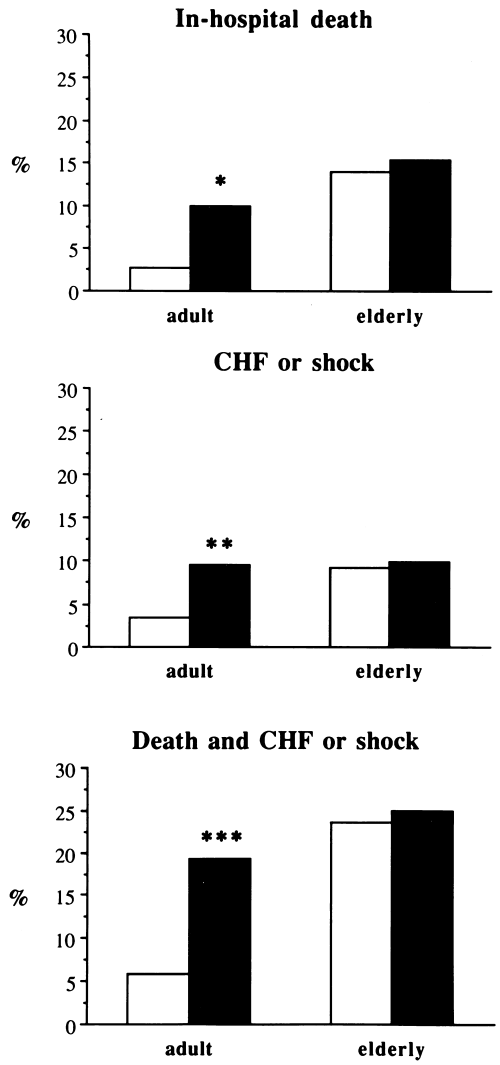

Figure 1. Percentage of in-hospital death; congestive heart failure (CHF) or shock; and in-hospital death and congestive heart failure or shock in adult (<65 years old) and elderly patients (≥65 years old) with **(open bars)** or without **(solid bars)** previous angina 48 h before acute myocardial infarction. *p < 0.01, **p < 0.02, ***p < 0.0003 versus angina.

and lytic therapy (recombinant tissue-type plasminogen activator or urokinase) was similar in adult patients with and without angina (Table 2). Thrombolytic therapy was given in fewer elderly than adult patients (25.7% vs. 44.3%, $p < 0.005$) and in fewer elderly patients without than with angina (15.2% vs. 34.1%, $p < 0.003$) (Table 3).

Table 3. In-Hospital Outcomes of Elderly Patients (≥65 years old) With or Without Previous Angina 48 Hours Before Acute Myocardial Infarction

In-Hospital End Points	Previous Angina: Yes (n = 118)	Previous Angina: No (n = 92)	p Value
In-hospital death	17 (14.4)	14 (15.2)	0.97 (NS)
CHF	13 (11.0)	11 (11.9)	0.99 (NS)
Death or CHF	30 (25.4)	25 (27.1)	0.89 (NS)
Lytic therapy	40 (34.1)	14 (15.2)	0.003
Time to lytic therapy			
≤4 h	30 (25.6)	13 (14.1)	0.04
>4 h	11 (9.4)	1 (0.9)	0.01
t-PA	25 (21.6)	9 (10.2)	0.02
Urokinase	16 (13.2)	7 (7.9)	0.25 (NS)
In-hospital reinfarction	6 (5.4)	6 (7.1)	0.88 (NS)
Recurrent ischemic pain	14 (12.0)	11 (11.7)	0.84 (NS)
Q wave MI	78 (66.5)	65 (70.5)	0.58 (NS)
CK-MB peak (IU/liter)	221 ± 95	236 ± 141	0.82 (NS)
Time to peak CK (min)	12.1 ± 3.6	11.9 ± 4.6	0.73 (NS)
Ventricular fibrillation	8 (7.1)	8 (8.5)	0.79 (NS)
Ventricular tachycardia	30 (25.6)	28 (30.2)	0.51 (NS)
High grade AV block	15 (12.7)	13 (13.8)	0.92 (NS)
LV dysfunction	20 (17.0)	15 (16.8)	0.95 (NS)

Data presented are mean value ± SD or number (%) of patients. Abbreviations as in Table 2.

The percentage of patients with chronic angina presenting with symptoms 48 h before the acute myocardial infarction was 51.4% in patients <65 years old and 55.8% in patients ≥65 years old ($p = 0.87$). There was no significant difference in end points between patients with or without a history of chronic angina in either the elderly or the younger group.

Logistic regression models for death and congestive heart failure or shock. To assess the role of previous angina we performed logistic regression analysis with death, congestive heart failure or shock and the combined end points (in-hospital death and congestive heart failure or shock) as dependent variables. The unadjusted model (Table 4) shows the protective role of previous angina in adult but not in elderly patients. However, thrombolytic therapy was performed less frequently

Table 4. Protective Role of Angina 48 Hours Before Acute Myocardial Infarction in Adult and Elderly Patients: Unadjusted Regression Model for In-Hospital Death and Congestive Heart Failure or Shock and Combined End Points (in-hospital death, congestive heart failure or shock)

	Adult			Elderly		
	Chi-Square	OR (95% CI)	p Value	Chi-Square	OR (95% CI)	p Value*
In-hospital death	5.69	0.24 (0.07–0.81)	0.01	0.00	0.94 (0.41–2.16)	0.97
CHF or shock	5.26	0.28 (0.09–0.86)	0.02	0.00	0.91 (0.36–2.32)	0.99
Death and CHF or shock	12.96	0.24 (0.10–0.55)	0.0003	0.02	0.91 (0.47–1.78)	0.90

*p = NS for all comparisons. CHF = congestive heart failure; CI = confidence interval; OR = odds ratio.

Table 5. Protective Role of Angina 48 Hours Before Acute Myocardial Infarction in Adult and Elderly Patients: Adjusted Regression Model for In-Hospital Death and Congestive Heart Failure or Shock and Combined End Points (in-hospital death, congestive heart failure or shock)*

	Adult			Elderly		
	Chi-Square	OR (95% CI)	p Value	Chi-Square	OR (95% CI)	p Value†
In-hospital death	9.27	0.04 (0.005–0.32)	0.002	1.48	0.49 (0.15–1.90)	0.22
CHF or shock	4.95	0.20 (0.04–0.82)	0.02	1.82	0.42 (0.11–1.48)	0.18
Death and CHF or shock	10.84	0.13 (0.03–0.43)	0.001	0.57	0.63 (0.19–2.08)	0.45

*The models were simultaneously adjusted for thrombolytic therapy, antianginal therapy and several variables, including age, gender, family history, low education level, smoking, chronic angina, previous myocardial infarction, congestive heart failure (CHF), hypertension, diabetes and cholesterolemia. †p = NS for all comparisons. Other abbreviations as in Table 4.

in elderly than in adult patients, and among elderly patients less frequently in those without than in those with previous angina. Antianginal therapy in patients with previous angina should improve in-hospital end points. In addition, demographic variables such as previous myocardial infarction, which was more frequent in both age groups with previous angina, can also affect the results. Therefore, we performed a logistic regression analysis with simultaneous adjustment for lytic therapy, antianginal drugs and demographic variables to evaluate the protective role of angina regardless of these possible confounding variables (Table 5). This analysis also confirmed the protective role of previous angina in adult but not elderly patients. In particular, as shown in Table 6, the only predictive variable for "in-hospital mortality" is the previous angina in adult patients, whereas only age is predictive in elderly patients. However, our logistic regression model is influenced by the presence of variables such as history of previous myocardial infarction, hypertension or congestive heart failure. In the absence of these variables, the odds ratio for previous angina is 0.11 (95% confidence interval 0.02 to 0.58, chi-square 6.72, $p < 0.01$), which is a value close to that observed in the unadjusted model. A possible interpretation is that the history of previous myocardial infarction, hypertension and congestive heart failure makes the previous angina even more protective than in their absence.

Discussion

The present study suggests that in adult patients (<65 years old), previous angina 48 h before acute myocardial infarction is responsible for the lower occurrence of in-hospital death, congestive heart failure or shock and combined end points when compared with patients without previous angina. The protective effect of previous angina was unrelated to the use of thrombolytic therapy and antianginal drugs and demographic variables such as a previous myocardial infarction. Surprisingly, previous angina seems to lose its protective effect in elderly patients (≥65 years old). The presence of previous

Table 6. Multivariate Analysis Including All Variables for In-Hospital Mortality in Adult (<65 years old) and Elderly Patients (≥65 years old)

	Adult			Elderly		
	Chi-Square	OR (95% CI)	p Value	Chi-Square	OR (95% CI)	p Value
Previous angina	9.27	0.04 (0.005–0.32)	0.002	1.47	0.49 (0.15–1.56)	0.225 (NS)
Age	0.04	0.97 (0.90–1.06)	0.620 (NS)	16.02	1.17 (1.08–1.27)	0.001
Chronic angina	0.07	0.80 (0.15–4.12)	0.789 (NS)	0.02	1.08 (0.39–2.95)	0.882 (NS)
Gender	1.48	0.33 (0.05–1.93)	0.223 (NS)	0.24	1.28 (0.48–3.39)	0.622 (NS)
Previous MI	2.19	3.71 (0.65–21.07)	0.138 (NS)	0.44	0.60 (0.13–2.67)	0.505 (NS)
Thrombolytic therapy	0.10	0.77 (0.16–3.53)	0.741 (NS)	0.56	0.57 (0.13–2.42)	0.452 (NS)
CHF	2.98	5.28 (0.79–35.03)	0.084 (NS)	0.00	0.98 (0.20–4.74)	0.982 (NS)
Hypertension	2.59	5.18 (0.28–11.44)	0.107 (NS)	0.01	1.07 (0.35–3.27)	0.899 (NS)
Diabetes	0.39	1.80 (0.28–5.78)	0.531 (NS)	1.05	1.75 (0.60–5.10)	0.304 (NS)
Family history	0.10	1.28 (0.30–6.33)	0.745 (NS)	0.05	0.87 (0.28–2.72)	0.819 (NS)
Low educational level (<8 yr)	0.74	2.75 (0.27–27.26)	0.386 (NS)	0.00	0.95 (0.24–3.81)	0.948 (NS)
Smoking	0.00	1.00 (0.48–2.11)	0.986 (NS)	0.97	1.42 (0.71–2.85)	0.325 (NS)
Nitrate	0.14	0.62 (0.05–6.94)	0.704 (NS)	0.12	0.79 (0.21–2.91)	0.718 (NS)
Beta-blocker	0.06	1.47 (0.07–28.11)	0.796 (NS)	0.07	0.70 (0.06–7.99)	0.777 (NS)
Calcium antagonist	1.35	2.81 (0.49–16.12)	0.245 (NS)	0.87	1.85 (0.51–6.73)	0.350 (NS)
Aspirin	0.00	1.08 (0.09–12.90)	0.949 (NS)	0.01	0.92 (0.27–3.22)	0.899 (NS)
Cholesterol (10-mg increase)	0.70	0.95 (0.30–2.95)	0.402 (NS)	0.02	0.99 (0.99–1.01)	0.882 (NS)

Abbreviations as in Tables 1 and 4.

angina, in fact, represents a protective variable against these in-hospital outcomes in the adult; this effect seems to be less marked in elderly patients. CK-MB peak, number of Q wave myocardial infarctions, ventricular fibrillation and left ventricular dysfunction were significantly higher in adult patients without than in those with angina before acute myocardial infarction. These findings demonstrate that in adult patients the absence of angina before acute myocardial infarction represents a risk factor for myocardial infarction-induced electromechanical modifications. In elderly patients previous angina loses to some extent its protective role: The occurrence of in-hospital death, congestive heart failure or shock and combined end points were similar in elderly patients with and without previous angina. CK-MB peak, number of Q wave myocardial infarctions, ventricular fibrillation and left ventricular dysfunction were also similar in elderly patients with and without previous angina.

Protective effects of previous angina. Results obtained from adult patients confirm published reports that previous angina plays a protective role in patients with acute myocardial infarction. Hirai et al. (15) demonstrated that left ventricular ejection fraction was higher and wall motion abnormalities rarer in patients with angina >1 week before acute myocardial infarction than in those without angina. In addition, left ventricular performance is better in patients with a history of angina before acute myocardial infarction (16–18). A history of angina was correlated with fewer episodes of reocclusion after thrombolytic therapy and a reduced incidence of in-hospital mortality (19). In another study (11), patients with prodromal angina had a significantly smaller infarct size than those without prodromal symptoms. More recently, Kloner et al. (12) reported that previous angina has a beneficial effect on in-hospital outcome after acute myocardial infarction. Finally, Nakagawa et al. (20) demonstrated the protective effect of angina pectoris in patients with reperfused anterior wall myocardial infarction. To our knowledge, there are no reports on the relation between effect of previous angina and myocardial infarction in elderly patients.

Speculations on the protective mechanism of previous angina. It is not known how previous angina exerts its protective role. Experimental studies have demonstrated that brief episodes of ischemia trigger adaptive changes that protect the myocardium from the effects of a subsequent, prolonged ischemic insult. This phenomenon, now known as "ischemic preconditioning" (10,21), has been extended to humans. Ischemic preconditioning in humans is defined as unstable angina before acute myocardial infarction, percutaneous transluminal coronary angioplasty and coronary artery bypass surgery with intermittent cross-clamp fibrillation episodes (22). Induction of stress protein (23,24), prostacyclin (25), adenosine release (26), activation of adenose triphosphate–regulated K^+ channels (27) and, more recently, norepinephrine (28) have been involved as mediators of ischemic preconditioning. We recently demonstrated (13) that ischemic preconditioning does not occur in isolated hearts from senescent animals, whereas exogenous norepinephrine produces preconditioning in both adult and senescent hearts. Therefore, in the senescent heart the absence of ischemic preconditioning may be due to the absence of a mediator that triggers this protective endogenous mechanism (13). This hypothesis is in agreement with studies showing a reduction of norepinephrine release from cardiac adrenergic terminals after ischemia and reperfusion in older animals (29,30). In addition, Nitta et al. (31) suggested that the greater vulnerability of aged hearts to ischemia may be due to impaired protective mechanisms provided by heat shock proteins. Ischemic preconditioning has been related to the induction of stress proteins (23,24); therefore, the age-related absence of ischemic preconditioning could be due to the reduction of heat shock protein synthesis observed in old hearts during myocardial ischemia. The absence of this endogenous mechanism may explain why the aging heart is more sensitive to electromechanical dysfunction induced by myocardial ischemia (13).

Reperfusion-induced protective effect of previous angina. One possibility why elderly patients did not benefit from preinfarction angina is that they were less likely to have reperfusion. Kloner et al. (32) reported that a history of angina before a nonthrombolyzed acute myocardial infarction is a marker of increased risk of infarct extension, recurrent ischemic pain and mitral regurgitation. However, a history of previous angina was associated with a trend toward smaller infarct size in patients who had spontaneous thrombolysis. Spontaneous thrombolysis was equated with a CK-MB peak at or within 15 h. In our study CK-MB was lower in adult (10.5 ± 3.4) than in elderly (12.1 ± 3.6) patients with previous angina. However, both values were obtained within 15 h, suggesting that both adult and senescent patients had similar reperfusion. Thrombolytic therapy resulted in more rapid reperfusion and smaller infarct size in patients with an acute myocardial infarction preceded by unstable angina than in those without preinfarction angina (33). The protective effect of previous angina found in the group of elderly patients could have been lost because fewer of these patients received thrombolytic therapy than did adult patients. In other words, if the protective effect of preinfarction angina is related to the speed of coronary reperfusion in patients receiving thrombolytic therapy, the age-related absence of angina-induced protection must be due to the reduction of the number of elderly patients receiving thrombolytic therapy. In our logistic regression analysis, previous angina was protective in adult but not in elderly patients, independent of thrombolytic therapy.

Limitations of the study. In general, data from retrospective studies should be viewed with caution (34). We established criteria for patient inclusion before studying the patient record. In addition to biased recall of events, data obtained from hospital records may be incomplete. However, the major limitation of this study is the number of patients. The statistical power of detecting clinically significant differences in patients with a myocardial infarction was 87%, under a type 1 error of 0.05 and an odds ratio as large as 2.60 (corresponding to a mortality rate of 12% in patients without angina before myocardial infarction). The power declined progressively to

60%, 24% and 9%, with declining odds ratios of 2.00, 1.50, and 1.25. Moreover, if elderly patients are considered separately (mortality rate 17%), the power further decreases with progressively declining odds ratios (i.e., from 57% to 33%, 13% and 6%, respectively). The significance of our results should be considered in the view of these findings. In addition, in the adjusted model, the odds ratio of death in elderly patients becomes 0.49, suggesting that there is a 50% improvement in outcome in elderly patients who have preinfarction angina. This finding means that the potential for ischemic preconditioning remains in the elderly and that the age difference in preconditioning is relative rather than absolute. Because most physiologic modifications that occur during aging are progressive and are therefore not "on–off," the reduction of this mechanism could have a progressive decline. Further prospective studies should be conducted to confirm the nonsignificant difference in hospital outcomes between elderly patients with or without previous angina before acute myocardial infarction.

Coronary angiography had not been performed in most of the patients, and therefore the hypothetic difference in epicardial collateral arteries between patients with and without angina was not investigated. Ottani et al. (11) demonstrated that prodromal angina limits infarct size in patients with a complete absence of collateral circulation to the infarct-related artery. Also Kloner et al. (12) demonstrated that the beneficial effect on in-hospital outcomes of a history of previous angina before acute myocardial infarction is independent of an increase in collateral flow. However, experimental studies have shown (35) that ischemic preconditioning is not a consequence of increased collateral perfusion. According to experimental studies (36), the clinical equivalent of ischemic preconditioning is an episode of myocardial ischemia very near to subsequent sustained myocardial ischemia. We defined previous angina as an episode of chest pain that occurred at most 48 h before myocardial infarction, independent of a history of chronic angina. Nakagawa et al. (20) demonstrated that patients with angina beginning >7 days before the onset of infarction had better collateral coronary circulation than those with new angina occurring ≤7 days of onset of infarction. However, myocardial contractility was preserved after myocardial infarction in both groups of patients (20).

Another limitation of this study is the quantification of ischemic episodes. Ambulatory ECG monitoring was not performed in our study cohort before acute myocardial infarction, and therefore episodes of silent ischemia, which are particularly frequent in elderly patients, were not taken into account in patient stratification (37,38). However, undetected episodes of myocardial ischemia in elderly patients corroborate the hypothesis of the absence of preconditioning in the aging heart. In other words, if elderly patients had more silent ischemic episodes than adults and preconditioning occurred, they would have a lower mortality than adult patients. Alternatively, a high frequency of underestimated episodes of myocardial ischemia in elderly patients could deplete the mechanism responsible for the protection induced by preconditioning. In the latter case, the absence of a protective effect of angina in elderly patients is only apparent.

Conclusions and clinical implications. Previous angina before acute myocardial infarction seems to confer protection against in-hospital outcomes, such as death, congestive heart failure or shock in adult patients, regardless of thrombolytic therapy, antianginal drug use and demographic variables, such as previous myocardial infarction; this effect seemed to be less evident in elderly patients. It is feasible that these results are related to the presence or absence of preconditioning. Prospective studies are needed to verify the protective role of previous angina before acute myocardial infarction and the hypothetic loss of preconditioning in elderly patients. The possible absence of preconditioning in the aging heart might account in part for the higher mortality rate from acute myocardial infarction observed in elderly patients.

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References

1. Harris R, Piracha AR. Acute myocardial infarction in the aged: prognosis and management. J Am Geriatr Soc 1970;18:893–904.
2. Latting CA, Silverman ME. Acute myocardial infarction in hospitalized patients over age 70. Am Heart J 1980;100:311–8.
3. Coodley EL, Zebari D. Characteristics of myocardial infarction in the elderly. In: Coodley EL, editor. Geriatric Heart Disease. Littleton (MA): PSG Publishing, 1985:334–45.
4. Gersh BJ. Clinical manifestations of coronary heart disease in the elderly. In: Wenger NK, Furberg CK, Pitt E, editors. Coronary Heart Disease in the Elderly. New York: Elsevier, 1986:276–97.
5. Yang XS, Willems JL, Pardaens J, DeGeest H. Acute myocardial infarction in the very elderly. Acta Cardiol 1987;42:59–68.
6. Gurwitz JH, Goldberg RJ, Gore JM. Coronary thrombolysis for the elderly? JAMA 1991;265:1720–3.
7. Tofler GH, Muller JE, Stone PH, Willich SN, Davis VG, Poole WK, Braunwald E, and the MILIS Study Group. Factors leading to shorter survival after acute myocardial infarction in patients ages 65 to 75 years compared with younger patients. Am J Cardiol 1988;62:860–7.
8. Weaver WD, Litwin PE, Martin JS, et al. Effect of age on use of thrombolytic therapy and mortality in acute myocardial infarction. J Am Coll Cardiol 1991;18:657–62.
9. Maggioni AP, Maseri A, Fresco C, et al. Age-related increase in mortality among patients with first myocardial infarctions treated with thrombolysis. N Engl J Med 1993;329:1442–8.
10. Murry CE, Sennings RB, Reimer KA. Preconditioning with ischemia: a delay of lethal cell injury in ischemic myocardium. Circulation 1986;74:1124–36.
11. Ottani F, Galvani M, Ferrini D, et al. Prodromal angina limits infarct size: a role of ischemic preconditioning. Circulation 1995;91:291–7.
12. Kloner RA, Shook T, Przyklenk K, et al. Previous angina alters in-hospital outcome in TIMI 4: a clinical correlate to preconditioning? Circulation 1995;91:37–47.
13. Abete P, Ferrara N, Cioppa A, et al. Preconditioning does not prevent post-ischemic dysfunction in aging heart. J Am Coll Cardiol 1996;27:1777–86.
14. Folland ED, Parisi AF, Moynihan PF, Jones DR, Feldman CL, Tow DE. Assessment of left ventricular ejection fraction and volumes by real-time two dimensional echocardiography: a comparison of cineangiographic and radionuclide techniques. Circulation 1979;60:760–6.
15. Hirai T, Fujita M, Yamanishi K, Ohno A, Mika K, Sasayama S. Significance of preinfarction angina for preservation of left ventricular function in acute myocardial infarction. Am Heart J 1992;124:19–23.
16. Matsuda Y, Ogawa H, Moritani K, et al. Effects of the presence or absence of preceding angina pectoris on left ventricular function after acute myocardial infarction. Am Heart J 1984;108:955–8.

17. Cortina A, Ambrose JA, Prieto-Granada J, et al. Left ventricular function after myocardial infarction: clinical and angiographic correlations. J Am Coll Cardiol 1985;5:619–24.
18. Iwasaka T, Nakamuara S, Karakawa M, Sugiura T, Inada M. Cardioprotective effect of unstable angina prior to acute anterior myocardial infarction. Chest 1994;105:57–61.
19. Muller DW, Topol EJ, Califf RM, et al. and the TAMI Study Group. Relationship between antecedent angina pectoris and short-term prognosis after therapy for acute myocardial infarction. Am Heart J 1990;2:119–24.
20. Nakagawa Y, Ito H, Kitakaze M, et al. Effect of angina pectoris on myocardial protection in patients with reperfused anterior wall myocardial infarction: retrospective clinical evidence of "preconditioning." J Am Coll Cardiol 1995;25:1076–83.
21. Murry CE, Richard VJ, Reimer KA, Jennings RB. Ischemic preconditioning slows energy metabolism and delays ultrastructural damage during a sustained ischemic episode. Circ Res 1990;66:913–31.
22. Kloner RA, Yellon D. Does ischemic preconditioning occur in patients? J Am Coll Cardiol 1994;24:1133–42.
23. Yellon DM, Latchmann DS. Stress proteins and myocardial protection. J Mol Cell Cardiol 1992;24:113–24.
24. Walker DM, Yellon DM. Ischaemic preconditioning: from mechanism to exploitation. Cardiovasc Res 1992;26:734–9.
25. Vegh A, Szekeres L, Parrat JR. Protective effects of preconditioning of the ischemic myocardium involve cyclooxygenase products. Cardiovasc Res 1990;24:1020–3.
26. Liu GS, Thornton J, Winkle DM, Stanley AWH, Olsson RA, Downey JM. Protection against infarction afforded by preconditioning is mediated by A_1 adenosine receptors in rabbit heart. Circulation 1991;84:350–6.
27. Grass GJ, Auchampach JA. Blockade of ATP-sensitive K_+ channels prevents myocardial preconditioning in dogs. Circ Res 1992;70:223–33.
28. Banerrjee A, Locke-Winter C, Rogers KB, Mitchell MB. Preconditioning against myocardial dysfunction after ischemia and reperfusion by an α_1-adrenergic mechanism. Circ Res 1993;73:656–70.
29. Mortimer ML, Tumer N, Johnson MD, Roberts J. Effect of age on presynaptic $beta_2$ receptor mediated response in the rat heart. Mech Ageing Dev 1991;59:17–25.
30. Snyder DL, Gao E, Johnson MD, Roberts J. Decrease in norepinephrine release from cardiac adrenergic nerve terminal after ischemia and reperfusion. Ann N Y Acad Sci 1994;723:389–91.
31. Nitta Y, Abe K, Aoki M, Ohno I, Isoyama S. Diminished heat shock protein 70 mRNA induction in aged rat hearts after ischemia. Am J Physiol 1994;267:H1795–803.
32. Kloner RA, Muller J, Davis V, for the MILIS Study Group. Effects of previous angina pectoris in patients with first acute myocardial infarction not receiving thrombolytics. Am J Cardiol 1995;75:615–7.
33. Andreotti F, Pasceri V, Hackett DR, Davies GJ, Haider AW, Maseri A. Preinfarction angina as a predictor of more rapid coronary thrombolysis in patients with acute myocardial infarction. N Engl J Med 1996;334:7–12.
34. Altman DG. Designing research. In: Altman DG, editor. Practical Statistics for Medical Research. London: Chapman and Hall, 1993:74–106.
35. Hale SL, Kloner RA. Effect of preconditioning on regional myocardial blood flow in the rabbit heart. Coronary Artery Dis 1992;3:133–40.
36. Li Y, Whittaker P, Kloner RA. The transient nature of the effect of ischemic preconditioning on myocardial infarct size and ventricular arrhythmia. Am Heart J 1992;123:346–53.
37. Aronow WS, Epstein S. Usefulness of silent myocardial ischemia detected by ambulatory electrocardiographic monitoring in predicting new coronary events in elderly patients. Am J Cardiol 1988;62:1295–6.
38. Miller PF, Sheps DS, Bragdon EE, et al. Aging and pain perception in ischemic heart disease. Am Heart J 1990;120:22–30.