

## ASSOCIATION BETWEEN PREINFARCTION ANGINA AND A LOWER RISK OF RIGHT VENTRICULAR INFARCTION

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**ABSTRACT**

**Background** Right ventricular infarction occurs in conjunction with inferior myocardial infarction caused by proximal occlusion of the right coronary artery. However, right ventricular infarction occurs infrequently, and the reasons for this are uncertain.

**Methods** We retrospectively assessed the association between preinfarction angina and right ventricular infarction, as well as the short-term outcome, in 113 patients with a first acute inferior myocardial infarction caused by right-coronary-artery occlusion. The association between the timing of angina during the week before infarction and the clinical outcome was also assessed.

**Results** The absence of preinfarction angina predicted the development of right ventricular infarction (odds ratio, 6.3; 95 percent confidence interval, 2.7 to 15.1;  $P < 0.001$ ), complete atrioventricular block (odds ratio, 3.6; 95 percent confidence interval, 1.4 to 10.3;  $P = 0.01$ ), and combined hypotension and shock (odds ratio, 12.4; 95 percent confidence interval, 4.5 to 40.6;  $P < 0.001$ ). Angina 24 to 72 hours before infarction was most strongly associated with reductions in the rates of right ventricular infarction (adjusted odds ratio, 0.2; 95 percent confidence interval, 0 to 0.8;  $P = 0.02$ ) and combined hypotension and shock (adjusted odds ratio, 0.1; 95 percent confidence interval, 0 to 0.5;  $P = 0.02$ ).

**Conclusions** Preinfarction angina was an independent predictor of the absence of right ventricular infarction in patients with acute inferior myocardial infarction. The patients with preinfarction angina also had better short-term outcomes than those without preinfarction angina. (N Engl J Med 1998;338:941-7.)

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**R**IGHT ventricular infarction results from occlusion of the right coronary artery proximal to the marginal branches that perfuse the anterior wall of the right ventricle.<sup>1,2</sup> However, the anterior free wall of the right ventricle is involved less frequently than the posterior wall in patients with inferior myocardial infarction.<sup>1,3,4</sup> Furthermore, right ventricular infarction occurs less often than would be expected on the basis of the frequency of proximal occlusion of the right coronary artery.<sup>5,6</sup> The explanations for the pathological findings and for the relative infrequency of right ventricular infarction are uncertain.

Recent studies suggest that patients with prein-

farction angina have smaller infarcts<sup>7,8</sup> and better prognoses<sup>9-16</sup> than those without angina. Several mechanisms have been proposed to explain these benefits in patients with anterior infarction. However, it is unclear whether preinfarction angina in patients with inferior infarction has the same benefits.<sup>8,12,17-20</sup> We hypothesized that preinfarction angina may reduce the incidence of right ventricular infarction and improve the clinical outcome in patients with acute inferior myocardial infarction.

**METHODS****Study Design**

We retrospectively reviewed the medical records of more than 527 consecutive patients admitted to our coronary care units between January 1992 and March 1996 with a suspected first acute myocardial infarction. Patients were eligible for inclusion in the study if they had acute inferior myocardial infarction caused by right-coronary-artery occlusion, diagnosed on the basis of electrocardiography, including the use of right precordial leads, performed within 10 hours after the onset of infarction. A total of 113 patients met these criteria.

Acute inferior myocardial infarction was defined as the presence of typical chest pain lasting for more than 30 minutes; ST-segment elevation of more than 0.1 mV in two or more of leads II, III, and aVF; and a serum creatine kinase concentration that was more than twice the upper limit of the normal range. Standard 12-lead and right precordial electrocardiograms were obtained immediately after admission. Right ventricular infarction was defined as ST-segment elevation of more than 0.1 mV in lead V<sub>4R</sub>. The infarct-related artery was identified by coronary angiography during hospitalization.

Patients who met the inclusion criteria were divided into two groups according to the presence or absence of angina during the week before infarction. Preinfarction angina was defined as one or more episodes of typical chest pain lasting less than 30 minutes during the week before infarction. The preinfarction interval was further divided into three categories: within 24 hours, within 24 to 72 hours, or within 72 hours to 1 week before infarction. The presence or absence of angina during these three periods was determined by the attending physicians who had interviewed the patients or their families at least twice: at the time of admission and within the following seven days.

The size of the infarct was estimated on the basis of peak and total serum creatine kinase values. These two values were normalized by dividing them by the upper limit of normal serum creatine

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kinase activity at each institution.<sup>14</sup> The results are expressed as normalized units. Serum creatine kinase activity was monitored every 6 hours during the first 24 hours after admission. Total serum creatine kinase activity was defined as the area under the curve for the creatine kinase concentration over a period of 24 hours, divided into four 6-hour blocks, as shown by the following formula:

$$\frac{1}{U_{pCK}} \sum_{i=0}^3 \frac{1}{2} (CK_i + CK_{i+1}) \times 6,$$

where  $CK_0$  and  $CK_i$  are the creatine kinase values at admission and at six-hour intervals after admission, respectively, and  $U_{pCK}$  is the upper limit of the normal range of creatine kinase activity at each institution.<sup>14</sup>

The cardiac index, right ventricular end-diastolic pressure, and pulmonary-capillary wedge pressure were determined in the absence of catecholamine therapy. The cardiac index was measured five times by the thermodilution method and was calculated as the average of three values, with the maximal and minimal values excluded.

Coronary angiography was performed during hospitalization to visualize the culprit lesion, the degree of stenosis, and the extent of coronary artery disease. Coronary collaterals were graded on the basis of coronary angiographic findings in the acute phase with the use of a scoring system described by Rentrop et al.<sup>21</sup> The site of occlusion of the right coronary artery was defined as proximal or distal on the basis of the origin of the marginal branch.

**Statistical Analysis**

We compared the infarct size, hemodynamic measurements, rate of in-hospital mortality, and incidence of major complications (right ventricular infarction, complete atrioventricular block, and combined hypotension and shock) in the group of patients with preinfarction angina and the group without angina. Fisher's exact test or the chi-square test was used to examine the associations between preinfarction angina and the categorical variables. The mean values for continuous variables were compared with use of Student's t-test. Descriptive results are expressed as means ±SD.

We performed multiple logistic-regression analyses with preinfarction angina, triple-vessel disease, and the site of occlusion of the right coronary artery included as independent variables and with the occurrence of right ventricular infarction, complete atrioventricular block, combined hypotension and shock, and in-hospital death included as dependent variables. The association between the timing of preinfarction angina and the clinical outcome was further assessed with unconditional logistic-regression analyses after adjustment for potential confounders. Odds ratios were calculated with corresponding 95 percent confidence intervals. All P values were determined with two-tailed tests.

**RESULTS**

**Characteristics of the Patients**

Of the 527 consecutive patients who were admitted to our institutions with a first acute myocardial infarction, 158 were confirmed to have inferior myocardial infarction caused by occlusion of the right coronary artery. Forty-five patients were excluded because right precordial electrocardiograms were not obtained within 10 hours after the onset of infarction. Of the 113 patients who met the inclusion criteria, 62 had preinfarction angina, and 51 did not. The frequency of angina (55 percent) was slightly lower than that in the entire study population (56 percent).

There were no significant differences in age, sex,

**TABLE 1. CHARACTERISTICS OF 113 PATIENTS WITH ACUTE MYOCARDIAL INFARCTION, ACCORDING TO THE PRESENCE OR ABSENCE OF PREINFARCTION ANGINA.\***

CHARACTERISTIC	PATIENTS WITH ANGINA (N=62)	PATIENTS WITHOUT ANGINA (N=51)
Age — yr	63±10	61±12
Sex — M/F	49/13	41/10
Coronary risk factors — no. (%)		
Diabetes mellitus	22 (35)	21 (41)
Smoking	41 (66)	30 (59)
Hypertension	30 (48)	26 (51)
Hypercholesterolemia	21 (34)	22 (43)
Preadmission medications — no. (%)		
Aspirin	4 (6)	5 (10)
Nitrates	3 (5)	2 (4)
Beta-blockers	9 (15)	5 (10)
Calcium-channel blockers	13 (21)	14 (27)
No. of vessels with marked stenosis — no. (%)†		
1	17 (27)	20 (39)
2	26 (42)	20 (39)
3	19 (31)	11 (22)
Site of occlusion of RCA — no. (%)		
Proximal	40 (65)	38 (75)
Distal	22 (35)	13 (25)
Score for coronary collaterals — no. (%)‡		
0	10 (34)	16 (52)
1	6 (21)	8 (26)
2	12 (41)	7 (23)
3	1 (3)	0
Acute-phase reperfusion therapy — no. (%)§		
PTCA	16 (44)	24 (62)
Thrombolysis	22 (61)	20 (51)
CABG	2 (6)	0

\*None of the characteristics differed significantly between the patients with and those without preinfarction angina. Plus-minus values are means ±SD. Some patients may have had more than one coronary risk factor, may have received more than one medication before admission, or may have received more than one type of reperfusion therapy in the acute phase. RCA denotes right coronary artery, PTCA percutaneous transluminal coronary angioplasty, and CABG coronary-artery bypass grafting.

†The degree of coronary-artery stenosis was determined according to the criteria proposed by the American Heart Association. Marked stenosis was defined as more than a 75 percent reduction in the diameter of the vessel.

‡The acute-phase coronary angiogram was used to score collaterals on a scale of 0 to 3 (0, distal filling; 1, filling of side branches only; 2, partial filling of the distal epicardial segment; and 3, complete filling of the distal epicardial segment). Data on collaterals were available for 29 patients with angina and 31 without angina.

§Data on reperfusion therapy were available for 36 patients with angina and 39 without angina.

coronary risk factors, preadmission medications, elapsed time from the onset of infarction to the initial electrocardiogram, reperfusion therapy, and the extent of coronary artery disease between the patients with preinfarction angina and those without it. There was a trend toward more abundant collaterals in the patients with angina, but the difference was not statistically significant. The distribution of culprit lesions was similar in the two groups (Table 1).

### Clinical Outcomes

Right ventricular infarction, diagnosed on the basis of the presence of ST-segment elevation in lead  $V_{4R}$  of the electrocardiogram, was found in only 43 of 78 patients with proximal occlusion of the right coronary artery (55 percent). Of these 43 patients, 22 (51 percent) had ST-segment elevation in lead  $V_1$ .

ST-segment elevation in lead  $V_{4R}$  was noted less frequently in patients with preinfarction angina than in those without angina (27 percent vs. 71 percent,  $P < 0.001$ ) (Table 2). The frequency of ST-segment elevation in leads  $V_1$  and  $V_{4R}$  was also significantly lower in patients with angina than in those without angina (6 percent vs. 39 percent,  $P < 0.001$ ). In addition, the patients with angina were less likely than those without angina to have complete atrioventricular block (11 percent vs. 33 percent,  $P = 0.004$ ) or combined hypotension and shock (8 percent vs. 53 percent,  $P < 0.001$ ). However, the rates of in-hospital mortality did not differ significantly between the two groups (Table 2).

The patients with preinfarction angina had a significantly higher cardiac index than those without angina ( $3.5 \pm 1.2$  vs.  $2.7 \pm 0.8$  liters per minute per square meter of body-surface area,  $P = 0.03$ ) and significantly lower right ventricular end-diastolic pressure ( $5 \pm 4$  vs.  $8 \pm 4$  mm Hg,  $P = 0.03$ ). The pulmonary-capillary wedge pressure did not differ significantly between the two groups. The infarct size, estimated on the basis of enzyme studies, was significantly smaller in the patients with angina than in those without angina (peak serum creatine kinase activity,  $14 \pm 15$  vs.  $22 \pm 19$  normalized units;  $P = 0.02$ ; total serum creatine kinase activity,  $226 \pm 184$  vs.  $335 \pm 285$  normalized units;  $P = 0.02$ ) (Table 3).

There was no significant difference in the elapsed time from the onset of chest pain to the first electrocardiogram between patients with and those without ST-segment elevation in lead  $V_{4R}$ . The patients with ST-segment elevation in lead  $V_{4R}$  had a lower cardiac index than those without ST-segment elevation ( $2.8 \pm 0.9$  vs.  $3.8 \pm 1.1$  liters per minute per square meter,  $P = 0.004$ ) and higher right ventricular end-diastolic pressure ( $8 \pm 4$  vs.  $4 \pm 3$  mm Hg,  $P = 0.003$ ). However, the pulmonary-capillary wedge pressure was similar in the two groups. The patients with ST-segment elevation in lead  $V_{4R}$  had higher peak creatine kinase activity than those without ST-segment elevation ( $22 \pm 19$  vs.  $14 \pm 14$  normalized units,  $P = 0.01$ ), as well as higher total serum creatine kinase activity ( $347 \pm 274$  vs.  $213 \pm 195$  normalized units,  $P = 0.004$ ) (Table 4).

Multiple logistic-regression analysis indicated that the absence of preinfarction angina was a stronger predictor of the development of right ventricular infarction (odds ratio, 6.3; 95 percent confidence interval, 2.7 to 15.1;  $P < 0.001$ ) than the presence of proximal occlusion of the right coronary artery

**TABLE 2.** ELECTROCARDIOGRAPHIC FINDINGS AND CLINICAL OUTCOME, ACCORDING TO THE PRESENCE OR ABSENCE OF PREINFARCTION ANGINA.

OUTCOME	PATIENTS WITH ANGINA (N=62)	PATIENTS WITHOUT ANGINA (N=51)	P VALUE*
	no. of patients (%)		
ST-segment elevation†			
Lead $V_{4R}$	17 (27)	36 (71)	<0.001
Leads $V_1$ and $V_{4R}$	4 (6)	20 (39)	<0.001
Complete atrioventricular block	7 (11)	17 (33)	0.004
Combined hypotension and shock‡	5 (8)	27 (53)	<0.001
In-hospital death	3 (5)	5 (10)	0.26

\*The chi-square test or Fisher's exact test was used to compare the two groups.

†ST-segment elevation was defined as an elevation of more than 0.1 mV, as measured 0.08 second after the J point.

‡Combined hypotension and shock was defined as a systolic pressure of less than 80 mm Hg at the time of admission to the hospital.

**TABLE 3.** TIME TO ELECTROCARDIOGRAPHY, CREATINE KINASE ACTIVITY, AND HEMODYNAMIC VARIABLES, ACCORDING TO THE PRESENCE OR ABSENCE OF PREINFARCTION ANGINA.\*

VARIABLE	PATIENTS WITH ANGINA (N=62)	PATIENTS WITHOUT ANGINA (N=51)	P VALUE
Time to electrocardiography (hr)†	$2.1 \pm 2.4$	$1.9 \pm 1.8$	0.62
Serum creatine kinase (normalized units)‡			
Peak	$14 \pm 15$	$22 \pm 19$	0.02
Total	$226 \pm 184$	$335 \pm 285$	0.02
Hemodynamic variables§			
Cardiac index (liters/min/m <sup>2</sup> )	$3.5 \pm 1.2$	$2.7 \pm 0.8$	0.03
Pulmonary-capillary wedge pressure (mm Hg)	$11 \pm 8$	$13 \pm 6$	0.34
Right ventricular end-diastolic pressure (mm Hg)	$5 \pm 4$	$8 \pm 4$	0.03

\*Plus-minus values are means  $\pm$ SD. P values were calculated with Student's t-test.

†Time to electrocardiography denotes elapsed time from the onset of acute myocardial infarction to the initial electrocardiogram obtained on admission.

‡Serum creatine kinase values were normalized by dividing them by the upper limit of normal serum creatine kinase activity at each institution.

§Hemodynamic data were available for 24 patients with angina and 16 without angina.

**TABLE 4.** TIME TO ELECTROCARDIOGRAPHY, CREATINE KINASE ACTIVITY, AND HEMODYNAMIC VARIABLES, ACCORDING TO THE PRESENCE OR ABSENCE OF RIGHT VENTRICULAR INFARCTION.\*

VARIABLE	PATIENTS WITH RIGHT VENTRICULAR INFARCTION (N=53)	PATIENTS WITHOUT RIGHT VENTRICULAR INFARCTION (N=60)	P VALUE†
Time to electrocardiography (hr)	2.1±2.1	2.0±2.2	0.79
Serum creatine kinase (normalized units)‡			
Peak	22±19	14±14	0.01
Total	347±274	213±195	0.004
Hemodynamic variables§			
Cardiac index (liters/min/m <sup>2</sup> )	2.8±0.9	3.8±1.1	0.004
Pulmonary-capillary wedge pressure (mm Hg)	13±7	9±7	0.08
Right ventricular end-diastolic pressure (mm Hg)	8±4	4±3	0.003

\*Right ventricular infarction was defined as ST-segment elevation of more than 0.1 mV in lead V<sub>4R</sub>. Plus-minus values are means ±SD.

†P values were calculated with Student's t-test.

‡Serum creatine kinase values were normalized by dividing them by the upper limit of normal serum creatine kinase activity at each institution.

§Hemodynamic data were available for 23 patients with right ventricular infarction and 17 without right ventricular infarction.

(odds ratio, 3.0; 95 percent confidence interval, 1.2 to 8.1; P=0.02). Furthermore, the absence of preinfarction angina was an independent risk factor for complete atrioventricular block (odds ratio, 3.6; 95 percent confidence interval, 1.4 to 10.3; P=0.01) and combined hypotension and shock (odds ratio, 12.4; 95 percent confidence interval, 4.5 to 40.6; P<0.001). No independent clinical factor was found to predict in-hospital death (Table 5).

Adjusted analysis of the association between the timing of angina and the clinical outcome indicated that the presence of angina 24 to 72 hours before infarction was most strongly associated with decreased rates of right ventricular infarction (odds ratio, 0.2; 95 percent confidence interval, 0 to 0.8; P=0.02) and combined hypotension and shock (odds ratio, 0.1; 95 percent confidence interval, 0 to 0.5; P=0.02). However, there was no significant association between the timing of angina and the development of complete atrioventricular block (Table 6).

## DISCUSSION

In our study, the absence of preinfarction angina was an important predictor of the occurrence of right ventricular infarction in patients with acute inferior myocardial infarction. In general, the incidence of right ventricular infarction is lower than would be expected on the basis of the frequency of proximal occlusion of the right coronary artery.<sup>5,6</sup> Furthermore, the anterior wall of the right ventricle, which is primarily perfused by right ventricular branches arising from the proximal portion of the

right coronary artery, is involved less frequently than the posterior wall.<sup>1,3,4</sup> As compared with the left ventricle, the right ventricle has several characteristics that may protect it from ischemia: a lower oxygen requirement due to its smaller muscle mass and workload and a greater oxygen supply due to more extensive collaterals, in addition to direct diffusion of oxygen from the right ventricular cavity.<sup>6,22,23</sup> These factors may limit the size of right ventricular infarcts but do not fully explain the distinct differences in clinical characteristics between patients with and those without right ventricular infarction.

ST-segment elevation in lead V<sub>4R</sub> has been considered the most sensitive and specific diagnostic marker of right ventricular infarction.<sup>24-27</sup> In our study, ST-segment elevation in lead V<sub>4R</sub> was less frequent in patients with preinfarction angina than in those without angina. ST-segment elevation in lead V<sub>1</sub> was also less frequent in patients with angina than in those without angina. Although this abnormality is dependent on the magnitude of concomitant, opposing inferoposterior forces causing injury,<sup>28,29</sup> its presence indicates at least the involvement of the anterior wall of the right ventricle in patients with inferior myocardial infarction. Furthermore, multivariate analysis indicated that the absence of preinfarction angina was a stronger determinant of the development of right ventricular infarction than the site of occlusion. Thus, preinfarction angina may help explain the relative infrequency of right ventricular infarction and may also be associated with a diminished tendency for the infarction to extend to the anterior wall.

In our study, the patients without preinfarction angina were three times as likely to have complete atrioventricular block as those with angina. Many investigators have shown an association between complete heart block and overall infarct size.<sup>30,31</sup> Therefore, the lower incidence of complete atrioventricular block in our patients with angina may reflect the smaller infarcts in these patients. Furthermore, preinfarction angina may have provided some protection against the subsequent ischemic burden on the atrioventricular node.

The incidence of combined hypotension and shock was also substantially lower in the patients with preinfarction angina than in those without angina. Despite the similar pulmonary-capillary wedge pressure in the two groups, the patients with angina had a lower right ventricular end-diastolic pressure and a higher cardiac output than those without angina. These hemodynamic results may indicate that cardiac output was influenced more by the magnitude of right ventricular dysfunction than by that of left ventricular dysfunction. Therefore, the lower incidence of right ventricular infarction in patients with preinfarction angina seems to be associated with a lower incidence of hypotension and shock in

**TABLE 5.** ODDS RATIOS FOR RIGHT VENTRICULAR INFARCTION, COMPLETE ATRIOVENTRICULAR BLOCK, COMBINED HYPOTENSION AND SHOCK, AND IN-HOSPITAL DEATH.\*

RISK FACTOR	RIGHT VENTRICULAR INFARCTION (N=53)		COMPLETE ATRIOVENTRICULAR BLOCK (N=24)		HYPOTENSION AND SHOCK (N=32)		IN-HOSPITAL DEATH (N=8)	
	ODDS RATIO (95% CI)	P VALUE	ODDS RATIO (95% CI)	P VALUE	ODDS RATIO (95% CI)	P VALUE	ODDS RATIO (95% CI)	P VALUE
Triple-vessel disease	0.9 (0.3–2.2)	0.74	0.4 (0.1–1.2)	0.14	0.5 (0.1–1.5)	0.2	0.4 (0–2.6)	0.43
Proximal occlusion of RCA	3.0 (1.2–8.1)	0.02	2.4 (0.8–9.0)	0.16	2.2 (0.7–7.3)	0.17	3.0 (0.5–58.0)	0.31
Absence of angina	6.3 (2.7–15.1)	<0.001	3.6 (1.4–10.3)	0.01	12.4 (4.5–40.6)	<0.001	1.9 (0.4–9.7)	0.41

\*P values and odds ratios were determined by multivariate logistic-regression analysis. The odds ratios are for patients with the risk factor in question as compared with those without it. CI denotes confidence interval, and RCA right coronary artery.

**TABLE 6.** ASSOCIATION BETWEEN THE TIMING OF PREINFARCTION ANGINA AND THE SHORT-TERM OUTCOME.\*

INTERVAL BETWEEN ANGINA AND ONSET OF INFARCTION	RIGHT VENTRICULAR INFARCTION (N=53)		COMPLETE ATRIOVENTRICULAR BLOCK (N=24)		HYPOTENSION AND SHOCK (N=32)	
	ODDS RATIO (95% CI)	P VALUE	ODDS RATIO (95% CI)	P VALUE	ODDS RATIO (95% CI)	P VALUE
24 Hr						
Univariate analysis	—	0.003	—	0.12	—	0.002
Multivariate analysis	0.7 (0.2–2.1)	0.47	0.5 (0.1–1.8)	0.30	0.4 (0.1–1.5)	0.18
24–72 Hr						
Univariate analysis	—	<0.001	—	0.20	—	0.001
Multivariate analysis	0.2 (0–0.8)	0.02	0.4 (0.1–2.0)	0.32	0.1 (0–0.5)	0.02
72 Hr–1 wk						
Univariate analysis	—	0.002	—	0.54	—	0.02
Multivariate analysis	0.8 (0.2–3.8)	0.74	2.3 (0.4–18.3)	0.38	2.1 (0.2–26.2)	0.52

\*P values were determined by logistic-regression analysis. Some patients had angina in more than one preinfarction interval. The odds ratios are for patients with angina during the interval in question, as compared with those without angina. Values are adjusted for age and sex and for the presence or absence of triple-vessel disease, proximal occlusion of the right coronary artery, hypertension, hypercholesterolemia, diabetes, and smoking. CI denotes confidence interval.

such patients. Complete atrioventricular block leading to bradycardia and loss of atrioventricular synchrony accounts in part for the development of hypotension and shock.<sup>32</sup> Furthermore, contraction of the posterior interventricular septum is believed to be important to compensate for the loss of contractility of the right ventricular free wall and maintain cardiac output.<sup>33</sup>

Many authors have suggested that preinfarction angina has a favorable rather than a harmful effect on the clinical outcome. A smaller infarct,<sup>7,8</sup> better preservation of left ventricular function,<sup>9,10,12</sup> a lower incidence of shock,<sup>14</sup> less frequent reocclusion after thrombolysis,<sup>11</sup> and more rapid reperfusion<sup>34</sup> have been reported in patients with preinfarction angina as compared with those without angina. Several mechanisms have been proposed to account for these favorable outcomes.<sup>8,12,17–20</sup> The use of antianginal drugs and a shorter interval between the onset of infarction and hospitalization were unlikely to account for our findings, since the two groups of patients did

not differ significantly with respect to preadmission medications and elapsed time before hospitalization.

When considered separately as a risk factor, angina within 24 hours before infarction was associated with a significant reduction in the rate of right ventricular infarction and a more favorable outcome. These findings suggest that ischemic preconditioning plays a part in the protective effects of preinfarction angina.<sup>8,14</sup> Our analyses also suggest that angina 24 to 72 hours before infarction was a more powerful predictor of the absence of right ventricular infarction and combined hypotension and shock than angina within 24 hours. Therefore, it is possible that a delayed adaptive mechanism plays a part in these favorable outcomes. The effects of delayed ischemic preconditioning have been identified in experimental models.<sup>35–37</sup> Ischemic preconditioning occurs approximately 24 hours after the ischemic insult and lasts much longer than the classic preconditioning effect reported by Murry et al.<sup>17</sup> However, the clinical significance of delayed preconditioning has not

yet been established in patients with myocardial infarction.

Myocardial ischemia induced by gradual coronary occlusion may facilitate the development of collateral circulation.<sup>38,39</sup> In our study, the patients with preinfarction angina had more extensive development of collateral circulation than those without angina, although the difference was not statistically significant. Coronary angiographic studies do not provide information on microcirculation through vessels less than 100  $\mu\text{m}$  in diameter.<sup>40</sup> Therefore, it remains possible that collateral circulation is responsible in part for the infrequency of right ventricular infarction in patients with preinfarction angina. The anterior portion of the right ventricle has a dual blood supply that consists of right ventricular branches from the left anterior descending artery and the conus branch of the right coronary artery.<sup>1</sup> An association between preinfarction angina and the development of these intercoronary collaterals would also help explain our finding that ST-segment elevation in lead  $V_1$  was noted less frequently in the patients with preinfarction angina than in those without angina. These combined mechanisms may have led to more favorable outcomes in the patients with preinfarction angina.

In 50 percent of patients with inferior myocardial infarction, ST-segment elevation visible on the initial electrocardiogram disappears within 10 hours.<sup>24</sup> In our study, the elapsed time from the onset of infarction to the initial electrocardiogram was similar in the patients with and those without ST-segment elevation in lead  $V_{4R}$ . Hemodynamic measurements and infarct size differed significantly between the two groups. In our study, as in previous studies,<sup>24-27</sup> ST-segment elevation of more than 0.1 mV in lead  $V_{4R}$  was a reliable marker of additional right ventricular infarction with inferior myocardial infarction.

Zehender et al. reported that right ventricular infarction is an independent predictor of the short-term outcome in patients with inferior myocardial infarction.<sup>27</sup> In our study, the absence of preinfarction angina was the most powerful independent predictor of the three chief complications of inferior myocardial infarction, because the development of right ventricular infarction itself was also closely associated with preinfarction angina, as were complete atrioventricular block and combined hypotension and shock.

Our results establish the importance of preinfarction angina as an independent predictor of the absence of right ventricular infarction in patients with acute inferior myocardial infarction. Moreover, preinfarction angina is associated with better short-term outcomes in patients with acute inferior myocardial infarction. The delayed effect of angina may be responsible in part for these favorable outcomes; however, the underlying mechanisms are still unclear.

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## APPENDIX

In addition to the authors, the following investigators participated in the study: S. Hori, T. Miyazaki, K. Fukuda, S. Inoue, S. Iwanaga, S. Ishikawa, N. Tsutsumi, T. Meguro, K. Miyazaki, H. Nishimura, T. Adachi, M. Shimada, S. Abe, F. Ikeda, Y. Wainai, and M. Asanagi.

## REFERENCES

1. Isner JM, Roberts WC. Right ventricular infarction complicating left ventricular infarction secondary to coronary heart disease: frequency, location, associated findings and significance from analysis of 236 necropsy patients with acute or healed myocardial infarction. *Am J Cardiol* 1978;42:885-94.
2. Cabin HS, Clubb KS, Wackers FJ, Zaret BL. Right ventricular myocardial infarction with anterior wall left ventricular infarction: an autopsy study. *Am Heart J* 1987;113:16-23.
3. Ratliff NB, Hackel DB. Combined right and left ventricular infarction: pathogenesis and clinicopathologic correlations. *Am J Cardiol* 1980;45:217-21.
4. Andersen HR, Falk E, Nielsen D. Right ventricular infarction: frequency, size and topography in coronary heart disease: a prospective study comprising 107 consecutive autopsies from a coronary care unit. *J Am Coll Cardiol* 1987;10:1223-32.
5. Rackley CE, Russell RO Jr, Mantle JA, Rogers WJ, Papapietro SE, Schwartz KM. Right ventricular infarction and function. *Am Heart J* 1981;101:215-8.
6. Setaro JF, Cabin HS. Right ventricular infarction. *Cardiol Clin* 1992;10:69-90.
7. Yoshikawa T, Inoue S, Abe S, et al. Acute myocardial infarction without warning: clinical characteristics and significance of preinfarction angina. *Cardiology* 1993;82:42-7.
8. Ottani F, Galvani M, Ferrini D, et al. Prodromal angina limits infarct size: a role for ischemic preconditioning. *Circulation* 1995;91:291-7.
9. 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.
10. 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.
11. Muller DW, Topol EJ, Califf RM, et al. Relationship between antecedent angina pectoris and short-term prognosis after thrombolytic therapy for acute myocardial infarction: Thrombolysis and Angioplasty in Myocardial Infarction (TAMI) Study Group. *Am Heart J* 1990;119:224-31.
12. Hirai T, Fujita M, Yamanishi K, Ohno A, Miwa K, Sasayama S. Significance of preinfarction angina for preservation of left ventricular function in acute myocardial infarction. *Am Heart J* 1992;124:19-24.
13. Anzai T, Yoshikawa T, Asakura Y, et al. Effect on short-term prognosis and left ventricular function of angina pectoris prior to first Q-wave anterior wall acute myocardial infarction. *Am J Cardiol* 1994;74:755-9.
14. Kloner RA, Shook T, Przyklenk K, et al. Previous angina alters in-hospital outcome in TIMI 4: a clinical correlate to preconditioning? *Circulation* 1995;91:37-45.
15. Anzai T, Yoshikawa T, Asakura Y, et al. Preinfarction angina as a major predictor of left ventricular function and long-term prognosis after a first Q wave myocardial infarction. *J Am Coll Cardiol* 1995;26:319-27.
16. 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.
17. Murry CE, Jennings RB, Reimer KA. Preconditioning with ischemia: a delay of lethal cell injury in ischemic myocardium. *Circulation* 1986;74:1124-36.
18. Fujita M, Sasayama S, Ohno A, Nakajima H, Asanoi H. Importance of angina for development of collateral circulation. *Br Heart J* 1987;57:139-43.
19. Deusch E, Berger M, Kussmaul WG, Hirshfeld JW Jr, Herrmann HC, Laskey WK. Adaptation to ischemia during percutaneous transluminal coronary angioplasty: clinical, hemodynamic, and metabolic features. *Circulation* 1990;82:2044-51.
20. Cribier A, Korsatz L, Koning R, et al. Improved myocardial ischemic

- response and enhanced collateral circulation with long repetitive coronary occlusion during angioplasty: a prospective study. *J Am Coll Cardiol* 1992; 20:578-86.
21. Rentrop KP, Cohen M, Blanke H, Phillips RA. Changes in collateral channel filling immediately after controlled coronary artery occlusion by an angioplasty balloon in human subjects. *J Am Coll Cardiol* 1985;5: 587-92.
22. Haupt HM, Hutchins GM, Moore GW. Right ventricular infarction: role of the moderator band artery in determining infarct size. *Circulation* 1983;67:1268-72.
23. Kinch JW, Ryan TJ. Right ventricular infarction. *N Engl J Med* 1994; 330:1211-7.
24. Braat SH, Brugada P, de Zwaan C, Coenegracht JM, Wellens HJ. Value of electrocardiogram in diagnosing right ventricular involvement in patients with an acute inferior wall myocardial infarction. *Br Heart J* 1983; 49:368-72.
25. Croft CH, Nicod P, Corbett JR, et al. Detection of acute right ventricular infarction by right precordial electrocardiography. *Am J Cardiol* 1982;50:421-7.
26. Andersen HR, Nielsen D, Lund O, Falk E. Prognostic significance of right ventricular infarction diagnosed by ST elevation in right chest leads V3R to V7R. *Int J Cardiol* 1989;23:349-56.
27. Zehender M, Kasper W, Kauder E, et al. Right ventricular infarction as an independent predictor of prognosis after acute inferior myocardial infarction. *N Engl J Med* 1993;328:981-8.
28. Geft IL, Shah PK, Rodriguez L, et al. ST elevations in leads V1 to V5 may be caused by right coronary artery occlusion and acute right ventricular infarction. *Am J Cardiol* 1984;53:991-6.
29. Lew AS, Maddahi J, Shah PK, et al. Factors that determine the direction and magnitude of precordial ST-segment deviations during inferior wall acute myocardial infarction. *Am J Cardiol* 1985;55:883-8.
30. Opolski G, Kraska T, Ostrzycki A, Zielinski T, Korewicki J. The effect of infarct size on atrioventricular and intraventricular conduction disturbances in acute myocardial infarction. *Int J Cardiol* 1986;10:141-7.
31. Nicod P, Gilpin E, Dittrich H, Polikar R, Henning H, Ross J Jr. Long-term outcome in patients with inferior myocardial infarction and complete atrioventricular block. *J Am Coll Cardiol* 1988;12:589-94.
32. Love JC, Haffajee CI, Gore JM, Alpert JS. Reversibility of hypotension and shock by atrial or atrioventricular sequential pacing in patients with right ventricular infarction. *Am Heart J* 1984;108:5-13.
33. Goldstein JA, Tweddell JS, Barzilai B, Yagi Y, Jaffe AS, Cox JL. Importance of left ventricular function and systolic ventricular interaction to right ventricular performance during acute right heart ischemia. *J Am Coll Cardiol* 1992;19:704-11.
34. 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.
35. Marber MS, Latchman DS, Walker JM, Yellon DM. Cardiac stress protein elevation 24 hours after brief ischemia or heat stress is associated with resistance to myocardial infarction. *Circulation* 1993;88:1264-72.
36. Kuzuya T, Hoshida S, Yamashita N, et al. Delayed effects of sublethal ischemia on the acquisition of tolerance to ischemia. *Circ Res* 1993;72: 1293-9.
37. Yang XM, Baxter GF, Heads RJ, Yellon DM, Downey JM, Cohen MV. Infarct limitation of the second window of protection in a conscious rabbit model. *Cardiovasc Res* 1996;31:777-83.
38. Rentrop KP, Thornton JC, Feit E, Van Buskirk M. Determinants and protective potential of coronary arterial collaterals as assessed by an angioplasty model. *Am J Cardiol* 1988;61:677-84.
39. Yoshida N, Fujita M, Yamanishi K, Miwa K. Relation between collateral channel filling and flow grade in recipient coronary arteries in patients with stable effort angina. *J Am Coll Cardiol* 1993;22:426-30.
40. Gensini GG, Bruto da Costa BC. The coronary collateral circulation in living man. *Am J Cardiol* 1969;24:393-400.

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