Diabetes Mellitus Prevents Ischemic Preconditioning in Patients With a First Acute Anterior Wall Myocardial Infarction

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OBJECTIVES
This study was undertaken to assess whether prodromal angina could have beneficial effects in diabetic patients with acute myocardial infarction (AMI).

BACKGROUND
Prodromal angina occurring shortly before the onset of AMI is associated with favorable outcomes by the mechanism of ischemic preconditioning. However, little is known about the impact of diabetes on ischemic preconditioning.

METHODS
We studied 611 patients with a first anterior wall AMI who underwent emergency catheterization within 12 h after the onset of chest pain: 490 patients without diabetes and 121 patients with non–insulin treated diabetes. Prodromal angina was defined as angina episode(s) occurring within 24 h before the onset of AMI. Serial contrast left ventriculograms were obtained in 424 patients at the time of acute and predischarge catheterization.

RESULTS
In non-diabetic patients, prodromal angina was associated with lower peak creatine kinase (CK) value (3,068 ± 2,647 IU/l vs. 3,601 ± 2,462 IU/l, p = 0.037), larger increase in left ventricular ejection fraction (LVEF) (10.1 ± 13.0% vs. 5.8 ± 13.4%, p = 0.004) and lower in-hospital mortality (3.4% vs. 9.3%, p = 0.015). On the contrary, in diabetic patients, there was no significant difference in peak CK value (3,382 ± 2,520 IU/l vs. 3,233 ± 2,412 IU/l, p = NS), the change in LVEF (6.7 ± 13.8% vs. 7.1 ± 12.4%, p = NS) and in-hospital mortality (8.8% vs. 11.0%, p = NS) between patients with and patients without prodromal angina.

CONCLUSIONS
Prodromal angina limited infarct size, enhanced recovery of LV function and improved survival in non-diabetic patients with AMI. However, such beneficial effects of prodromal angina were not observed in diabetic patients, suggesting that diabetes might prevent ischemic preconditioning. (J Am Coll Cardiol 2001;38:1007–11) © 2001 by the American College of Cardiology

Diabetes mellitus is a risk factor for morbidity and mortality in acute myocardial infarction (AMI) (1–5). Although diabetes is associated with comorbid risk factors, diabetes is still an independent predictor of death after AMI. Angina pectoris occurring shortly before the onset of AMI limits infarct size, improves left ventricular (LV) function and enhances survival (6–10). Transient ischemic episodes have cardioprotective effects against subsequent ischemia, which is called ischemic preconditioning (11). Some experimental studies have reported that ischemic preconditioning is lost in the presence of diabetes (12,13). Loss of ischemic preconditioning may be responsible for the poor outcome of diabetic patients with AMI. However, there is no clinical data on the impact of diabetes on ischemic preconditioning in patients with AMI. This study was undertaken to assess the impact of diabetes on ischemic preconditioning in patients with a first anterior wall AMI.

METHODS
Study patients. Between January 1981 and December 1999, 611 patients with a first anterior wall AMI underwent coronary angiography within 12 h after the onset of chest pain. Anterior wall AMI was diagnosed by chest pain consistent with ongoing myocardial ischemia persisting >30 min and at least 1-mm ST elevation in at least two adjacent precordial electrocardiographic leads. Serum creatine kinase (CK) was measured every 3 h for at least 24 h, and peak CK value had to be more than twice the normal upper limit. Nine patients with diabetes who had been treated with insulin were excluded from this study.

Cardiac catheterization. Emergency cardiac catheterization was performed via the right femoral artery or left brachial artery approach after heparin administration. Selective coronary angiography was performed in multiple projections before the initiation of reperfusion therapy. Immediately after diagnostic angiography, reperfusion therapy was performed with coronary thrombolysis or angioplasty. The allocation of thrombolysis or angioplasty was not randomized and was based on the physician’s decision. In general, thrombolytic therapy was performed without adjunctive angioplasty during the first four years. During the
next 10 years, conventional balloon angioplasty was performed for severe stenosis after thrombolysis, after failed thrombolysis or without thrombolytic therapy. Since 1994, coronary stenting was performed if appropriate.

**Angiographic analysis.** All coronary angiograms were reviewed by two angiographers without knowledge of the clinical variables. The perfusion status of the left anterior descending artery was determined in accordance with the Thrombolysis In Myocardial Infarction (TIMI) study classification (14). An occluded artery was defined as TIMI flow grade 0 or 1. Reperfusion was defined as TIMI flow grade 3. Initial TIMI flow grade was assessed before the initiation of reperfusion therapy, and final TIMI flow grade on the final shot of the angiography. Multivessel coronary disease was defined as ≥75% stenosis in one or more vessels remote from the infarct artery. Left main coronary disease of ≥50% was considered to be at least two-vessel involvement. The extent of collateral circulation was assessed on pretreatment angiogram and classified in accordance with the method described by Rentrop et al. (15). Collateral circulation was considered to be present if the grade was ≥2. Contrast left ventriculography was performed in the 30° right anterior oblique projection before reperfusion therapy and at the time of predischARGE catheterization. The left ventricular ejection fraction (LVEF) was calculated by means of the area-length method.

**Definition of prodromal angina.** Data were collected on the study form regarding whether patients ever experienced angina before AMI. Prodromal angina was defined as typical chest pain episode(s) persisting ≤30 min either at rest or on effort within 24 h before the onset of AMI. Patients with stable angina pectoris were also included if they had chest pain episode(s) within 24 h before infarction.

**Data analysis.** Data were collected regarding whether patients had a previous or current diagnosis of diabetes mellitus during hospitalization. Statistical analysis was performed with the chi-square and t test. Differences were considered significant if the p value was <0.05. All group data are expressed as mean ± SD.

**RESULTS**

**Baseline characteristics.** There were 121 patients with diabetes (20%): 68 patients were treated with diet alone, and 53 patients with oral hypoglycemic drugs. Prodromal angina was found in 53 patients (44%) with diabetes and 147 patients (30%) without diabetes (p = 0.004).

There was no significant difference in age, gender, hypertension, Killip class upon admission, time to angiography, initial patency of the infarct artery, multivessel disease, collateral circulation, modality of reperfusion therapy and final reperfusion between diabetic patients with and diabetic patients without prodromal angina (Table 1). Also, there was no significant difference in the clinical and angiographic variables, except for more hypertension in non-diabetic patients with, than in non-diabetic patients without, prodromal angina (Table 2).

**Outcomes of non-diabetic patients.** In non-diabetic patients, peak CK value was obtained in 462 patients (94%). Peak CK value was significantly lower in non-diabetic patients with prodromal angina than it was in non-diabetic patients without (3,068 ± 2,647 IU/l vs. 3,601 ± 2,462 IU/l, p = 0.037; Fig. 1). Acute LVEF was obtained before reperfusion therapy in 421 patients (86%) and was not significantly different between non-diabetic patients with and non-diabetic patients without prodromal angiina.

| Table 1. Characteristics in Non-Diabetic Patients With Versus Without Prodromal Angina |
|-------------------------------------|----------|----------|----------|
| **Prodromal Angina**                | **Absent** (n = 343) | **Present** (n = 147) | **p Value** |
| Age (yr, SD)                        | 60 (12)  | 61 (11)  | 0.63 (NS) |
| Male gender (%)                     | 275 (80%) | 116 (79%) | 0.75 (NS) |
| Hypertension (%)                    | 214 (62%) | 95 (65%)  | 0.64 (NS) |
| Killip class ≥2 (%)                 | 45 (13%)  | 13 (9%)   | 0.17 (NS) |
| Time to angiography (h, SD)         | 4.0 (2.6) | 4.1 (3.1) | 0.78 (NS) |
| Initial TIMI flow grade ≥2 (%)      | 65 (19%)  | 35 (24%)  | 0.22 (NS) |
| Collateral circulation (%)          | 114 (33%) | 49 (33%)  | 0.98 (NS) |
| Multivessel disease (%)             | 77 (22%)  | 38 (26%)  | 0.42 (NS) |
| Reperfusion therapy (%)             |           |           | 0.31 (NS) |
| Angioplasty (%)                     | 238 (70%) | 109 (74%) |           |
| Thrombolysis (%)*                   | 76 (22%)  | 21 (21%)  |           |
| Bypass surgery (%)                  | 3 (2%)    | 4 (3%)    |           |
| None (%)                            | 20 (6%)   | 3 (2%)    |           |
| Final TIMI flow grade 3 (%)†        | 246 (74%) | 113 (79%) | 0.21 (NS) |

*Thrombolysis without rescue or immediate angioplasty; †data were not obtained in patients undergoing bypass surgery.

**Abbreviations and Acronyms**

AMI = acute myocardial infarction  
CK = creatine kinase  
TIMI = Thrombolysis In Myocardial Infarction  
LVEF = left ventricular ejection fraction
(49.6 ± 11.5% vs. 47.5 ± 11.1%, p = NS; Fig. 2). However, predischarge LVEF, obtained in 385 patients (79%), was significantly higher in non-diabetic patients with prodromal angina than it was in non-diabetic patients without (59.1 ± 14.1% vs. 53.2 ± 14.9%, p < 0.001; Fig. 2). Serial left ventriculograms were obtained in 348 patients (75%), and the change in LVEF was significantly larger in non-diabetic patients with prodromal angina than it was in non-diabetic patients without (10.1 ± 13.0% vs. 5.8 ± 13.4%, p = 0.004; Fig. 2). In-hospital mortality was significantly lower in non-diabetic patients with prodromal angina than it was in non-diabetic patients without (3.4% vs. 9.3%, p = 0.015; Fig. 3).

**Outcomes of diabetic patients.** In diabetic patients, peak CK value was obtained in 105 patients (87%) and was similar between patients with and patients without prodromal angina (3,461 ± 2,581 IU/l vs. 3,240 ± 2,459 IU/l, p = NS; Fig. 1). Acute LVEF, obtained in 92 patients (76%), was not significantly different between diabetic patients with, and diabetic patients without, prodromal angina (46.1 ± 12.6% vs. 49.0 ± 11.9%, p = NS; Fig. 4). Predischarge LVEF, obtained in 87 patients (72%), was not significantly different between diabetic patients with prodromal angina and diabetic patients without (53.0 ± 15.3% vs. 56.0 ± 16.7%, p = NS; Fig. 4). The change in LVEF, obtained in 76 patients (63%), was not significantly different between diabetic patients with prodromal angina and diabetic patients without (6.7 ± 13.8% vs. 7.1 ± 12.4%, p = NS; Fig. 4). In-hospital mortality was not significantly different between diabetic patients with prodromal angina and diabetic patients without (9.4% vs. 11.8%, p = NS; Fig. 3).

When only diabetic patients who had been treated exclusively with diet were studied, there was no significant difference in peak CK (3,586 ± 2,709 IU/l vs. 3,550 ± 2,821 IU/l, p = NS) and predischarge LVEF (55.1 ± 15.7% vs. 56.8 ± 19.8%, p = NS) between patients with and patients without prodromal angina. Also, among diabetic patients treated with oral hypoglycemic drugs, there

![Figure 1](image1.png)  
**Figure 1.** Peak creatine kinase value was significantly smaller in non-diabetic patients with prodromal angina (solid bars) than it was in non-diabetic patients without (open bars). It was not significantly different between diabetic patients with prodromal angina and diabetic patients without.

![Figure 2](image2.png)  
**Figure 2.** Acute left ventricular ejection fraction (LVEF), predischarge LVEF and the change in LVEF in non-diabetic patients with prodromal angina (solid bars) and non-diabetic patients without (open bars). Acute LVEF was not significantly different, but predischarge LVEF and the change in LVEF were significantly better in non-diabetic patients with prodromal angina than in non-diabetic patients without.
was no significant difference in peak CK (3,289 ± 2,446 IU/l vs. 2,843 ± 1,882 IU/l, p = NS) and predischarge LVEF (50.7 ± 14.9% vs. 55.2 ± 13.0%, p = NS) between patients with and patients without prodromal angina. The difference in peak CK and predischarge LVEF was not significant between diabetic patients treated with diet only and diabetic patients treated with oral hypoglycemic drugs.

DISCUSSION

Findings of this study. This study demonstrated that: 1) prodromal angina limited infarct size, enhanced improvement of LV function and improved in-hospital mortality in non-diabetic patients with AMI, and 2) these beneficial effects of prodromal angina were not obtained in non-insulin treated diabetic patients. These results suggest that ischemic preconditioning is prevented in diabetic patients with AMI.

Diabetes and AMI. Diabetes mellitus is a risk factor not only for the development of AMI but also for poor outcomes after AMI. Previous studies in the reperfusion era have demonstrated that the relative risk of mortality after AMI was approximately 50% greater in diabetic patients compared with non-diabetic patients (2–5). Although it has been reported that diabetic patients have more co-morbid risk factors including older age, more female gender, more previous infarction and more severe coronary artery disease, most studies have reported that diabetes is an independent predictor for mortality after AMI.

Prodromal angina and ischemic preconditioning. Murry et al. (11) first reported that brief episodes of ischemia in dogs limited infarct size resulting from a subsequent coronary occlusion and termed it “ischemic preconditioning.” Since then, several clinical studies have demonstrated that ischemic preconditioning occurs in patients with repetitive balloon inflation during coronary angioplasty and with intermittent aortic cross-clamping during coronary artery bypass surgery (16,17). It has been demonstrated that angina pectoris occurring shortly before the onset of AMI is associated with favorable outcomes, including smaller infarct size, improved LV function and enhanced survival after reperfusion therapy for AMI (6–10) and that angina episodes closest to the time of infarction have the most benefits, suggesting a relationship to ischemic preconditioning (7). Klomer et al. (10), reviewing 3,002 patients enrolled in the TIMI-9B study, have reported that the benefits of pre-infarction angina on clinical events were manifest only when the time between onset of angina and infarction was within 24 h and that a history of any angina alone was not associated with a reduced event rate. Thus, in the present study we defined “prodromal angina” as angina occurring ≤24 h before the onset of infarction.

Diabetes and ischemic preconditioning. Some previous experimental studies have reported that diabetic hearts are more sensitive to ischemic insults and that the cardioprotective effects of ischemic preconditioning are lost, but others have suggested that diabetic hearts are more protective against ischemia than non-diabetic hearts (12,13,18,19). The inconsistent results of these studies might be due to the difference in experimental conditions. It has been suggested that longer duration of diabetes, higher plasma glucose level and the presence of residual flow during ischemia were associated with the increased vulnerability of diabetic hearts (13). Most clinical episodes of AMI in diabetic patients occur in such conditions. Moreover, it has been consistently demonstrated that diabetic patients have poorer outcomes after AMI than non-diabetic patients. This study is the first to report that the cardioprotective effects of prodromal angina are lost in diabetic patients with AMI. This loss of ischemic preconditioning may be, at least in part, responsible for the poor outcomes of diabetic patients with AMI.

Patients with diabetes, particularly older diabetic patients, may present with more atypical features and may spend a longer time getting to a hospital. Delay in treatment might have affected the difference in outcomes. However, in the present study, there was no difference in time from the onset

**Figure 3.** In-hospital mortality was significantly lower in non-diabetic patients with prodromal angina (solid bars) than in non-diabetic patients without (open bars). There was no significant difference in in-hospital mortality between diabetic patients with and diabetic patients without, prodromal angina.

**Figure 4.** Acute left ventricular ejection fraction (LVEF), predischarge LVEF and the change in LVEF in diabetic patients with prodromal angina (solid bars) and in diabetic patients without (open bars). Acute LVEF, predischarge LVEF and the change in LVEF were not significantly different between diabetic patients with prodromal angina and diabetic patients without.
of chest pain to angiography between non-diabetic and diabetic patients (4.0 ± 2.8 h vs. 4.1 ± 2.7 h, p = NS). To clarify this issue, we performed additional analysis using only patients who underwent angiography within 6 h after the onset of chest pain, in which prodromal angina had beneficial effects on outcomes in non-diabetic patients but not in diabetic patients. Also, if only patients <70 years old were analyzed, results similar to those of the original analysis were obtained (data not shown).

There are several possible mechanisms that may explain the loss of ischemic preconditioning in diabetic hearts (20). Ischemic preconditioning is mediated by activation of the KATP channel. It has been reported that the nature of the KATP channel is altered in diabetic hearts (21). Several previous studies have reported that oral hypoglycemic drugs inhibit the KATP channel. Several previous studies have reported that oral hypoglycemic drugs prevent ischemic preconditioning and increase mortality after AMI (23,24). The loss of the cardioprotective effects of prodromal angina may be, in part, attributable to oral hypoglycemic drugs. However, it is still noteworthy that the cardioprotective effects of prodromal angina were lost even in patients with diabetes who had been treated without oral hypoglycemic drugs.

**Study limitations.** This study suffers from the limitations of all retrospective investigations. The allocation of reperfusion therapy was based on the physician’s decision. But the modality of reperfusion therapy and the incidence of reperfusion were similar between diabetic and non-diabetic patients. A small sample size is another limitation of this study. However, it is noteworthy that peak CK and predischARGE LVEF were not only significantly different but also tended to be worse in diabetic patients with prodromal angina. There were only nine insulin-treated diabetic patients, and the impact of insulin-treated diabetes on ischemic preconditioning could not be discussed, because of its small sample size. A patient was defined as having diabetes if a physician had diagnosed diabetes before, or at the time of, the current myocardial infarction. Because an oral glucose tolerance test was not routinely performed, some diabetic patients may not have been diagnosised as having diabetes. However, in this study, the incidence of diabetes was comparable with that of previous studies.

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