Preinfarction Angina Limits Myocardial Infarction Size in Nondiabetic Patients Treated With Primary Coronary Angioplasty*

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**Objective:** To evaluate myocardial necrosis extent after myocardial infarction (MI) and reperfusion with primary coronary angioplasty in nondiabetic patients and the relationship with unstable preinfarction angina (PA).

**Design:** Prospective cohort study.

**Setting:** Studies suggest PA limits infarct size. This effect is questioned in patients treated with primary coronary angioplasty.

**Patients:** Seventy-eight, nondiabetic, consecutive MI patients.

**Interventions:** Primary coronary angioplasty and scintigraphic study to assess the myocardial infarct size.

**Main outcome measures:** Scintigraphic myocardial infarct size.

**Results:** There were 32 patients with PA (PA+H11545) and 46 without PA (PA−H11546) in the 24-h period prior to MI onset. There were no significant differences in the baseline characteristics between the two groups. The scintigraphy indicated myocardial infarct size significantly smaller in PA+ patients: mean, 18.0% (SD, 14.7) vs 27.0% (SD, 20.1) [p = 0.033]. This occurs even though Thrombolysis in Myocardial Infarction grade 3 flow achieved in both groups was similar (84.8% vs 84.4%, p = 1.000). We found a higher percentage of ST-segment resolution (>70%) in PA+ patients (65.6% vs 45.7%, p = 0.082) together with a lower incidence of left ventricular systolic dysfunction (3.2% vs 18.6%, p = 0.071).

**Conclusions:** PA exerts a beneficial effect in nondiabetic patients with ST-segment elevation acute MI even when treated with primary PCI. The infarct size is limited, and left ventricular systolic function is preserved. The effects may be related to a better preservation of tissue reperfusion in patients with PA. (CHEST 2005; 127:1116–1121)

**Key words:** angina pectoris; diabetes mellitus; myocardial infarction

**Abbreviations:** CK = creatinine kinase; MI = myocardial infarction; PA = preinfarction angina; PA+ = with preinfarction angina; PA− = without preinfarction angina; PCI = primary coronary intervention; TIMI = Thrombolysis in Myocardial Infarction

In patients with acute myocardial infarction (MI), the presence of transient periods of symptomatic ischemia before the onset of the infarct has benefi-
compared with fibrinolysis, had a greater degree of myocardial salvage and smaller infarct sizes. In this setting, it is not known whether PA exerts an additional protective effect against myocardial cell death and cell loss. Some studies have reported that PA increases the probability of achieving a Thrombolysis in Myocardial Infarction (TIMI) grade 3 flow in the infarct-related artery, and that PA elicits a greater recovery of regional left ventricular function. However, other studies question the beneficial effect of PA in this specific subset of patients.

We designed this study to evaluate the effect of PA (< 24 h before the onset of the MI) on the eventual left ventricular infarction size in patients with ST-segment elevation acute MI treated with primary PCI. We excluded diabetic patients since the effect of PA in this specific group of patients has been specifically placed in doubt.

**Materials and Methods**

**Study Subjects**

All patients with an acute MI < 12 h in duration and who had been treated with primary coronary angioplasty in our unit were included in this study. MI was diagnosed when the following criteria had been fulfilled: (1) typical chest pain lasting ≥ 30 min; (2) ST-segment elevation of at least 0.2 mV in at least two contiguous leads of the standard 12-lead ECG; and (3) a serum creatinine kinase (CK)-MB concentration more than two times the upper limit of the reference range (25 IU/L in our laboratory) at 6 to 12 h after admission. Excluded from the study were patients who had significant valvular disease; a previous MI; participants with episodes of typical transient (< 30 min) chest pain while resting. None of our patients had chronic angina in the course of their normal daily activities. We selected a period of 24 h because the beneficial effect of PA appears to be highest if occurring within this period.

On hospital admission, all patients were interviewed regarding the timing of their most recent chest pains, if any. PA was defined as the presence, in the 24 h prior to the onset of the infarct, of episodes of typical transient (< 30 min) chest pain while resting. None of our patients had chronic angina in the course of their normal daily activities. We selected a period of 24 h because the beneficial effect of PA appears to be highest if occurring within this period.

**Evaluation of Infarct Size and Left Ventricular Function**

The infarct size was measured approximately 10 days after the MI with the IV injection of 740 MBq of 99mTc sestamibi. Dual-head camera systems with low-energy, high-resolution collimators were used for the study. Dedicated software was used to generate transverse slices and to create polar maps of the relative distribution of radionuclide activity throughout the left ventricle. The size of the defect was calculated with the use of a threshold of 50%, as previously described, and which provided the best estimate of infarct size in our laboratory (data not shown). This method allowed us to calculate the size of the infarct as a percentage of the left ventricle that was below the threshold level. Using the modified Simpson rule, left ventricular ejection fraction was assessed by two-dimensional echocardiography prior to the patient's discharge from hospital. The echocardiographers were asked to dichotomize the ejection fraction > 40% or < 40%. Both studies were performed by two members of the investigation team who were blinded with respect to the patients' clinical antecedents.

**Coronary Angiography and Angioplasty**

Coronary angiography followed by primary angioplasty was performed with standard techniques. Intra-aortic balloon counterpulsation and temporary pacing were left to the decision of the intervention team. In our laboratory, the indications for the implantation of intra-aortic balloon pump in our laboratory, besides cardiogenic shock, are signs of progressive heart failure despite conventional drug treatment, and severe no-reflow phenomenon. Similarly, in our institution, the indications for the implantation of a pacemaker are symptomatic bradycardia and persistent third-degree atrioventricular block. Although the use of intracoronary stents was not mandatory, our interventional team was encouraged to use them. An intravenous bolus of heparin was administered to maintain an activated clotting time that was > 250 s over the course of the procedure. Treatment with aspirin at a loading dose of 450 mg, and 100 mg/d thereafter, was begun in the emergency department. A loading dose of 300 mg of clopidogrel, followed by 75 mg/d, was administered to those patients who had an intra coronary stent deployed. The use of abciximab was left to the decision of the attending physician, but its use was encouraged. Arterial blood was collected in ethylenediamine tetra-acetic acid-coated tubes immediately after femoral artery puncture to measure specific cardiac troponin-I.

The initial and final flow in the infarct-related artery was assessed according to the classification of the TIMI trial. Significant stenosis of the coronary artery was defined as a narrowing of > 50% relative to the uninvolved segment of the artery. Collateral circulation was classified according to the Rentrop method.

**ST-Segment Resolution**

Serial 12-lead ECG recordings before departure from, and immediately on return to, the coronary care unit were analyzed by an observer blinded to the patient’s clinical data. The ST-segment in the lead showing maximal deviation was measured 60 ms after the J point. The reduction of the ST segment was expressed as percentage of reduction relative to baseline. Patients with bundle-branch block, pacemaker rhythm, or poorly interpretable ECG were excluded. We considered a complete ST-segment resolution as a reduction ≥ 70%.

**Data Analysis**

Continuous variables are expressed as mean ± SD, and categorical variables are presented as absolute numbers of cases (percentage of total). Statistical analyses were the χ² or Fisher exact test (categorical variables) and the Student t test (continuous variables). If the variances between both groups were unequal (as assessed by the Levene test), the Welch correction was applied. Linear regression analysis was performed to assess the correlation between two quantitative variables (r value of Pearson). Differences were considered statistically significant at values of p < 0.05.
RESULTS

Patients

Between March 2001 and October 2002, there were 116 patients with ST-segment elevation acute MI treated with primary angioplasty in our department. Thirty-eight patients were excluded from the study due to the following reasons: 12 died before the scintigraphic study, 17 had diabetes, 4 had had a previous MI, 3 chose not to participate in the study, 1 had an in-hospital reinfarction, and the scintigraphic study was not performed in 1 patient due to technical problems. Finally, 78 patients were included; 32 patients (41.0%) had PA and were assigned to the group with PA (PA +), and the rest were assigned to the group without PA (PA −).

Baseline Characteristics and Treatment of the Infarct

We did not find any statistically significant difference between the baseline characteristics of the patients in the two groups (Table 1), nor in the characteristics and treatment of the MI (Table 2). One patient in the PA − group had received ticlopidine (instead of clopidogrel), and all of the patients received aspirin.

There were no statistically significant differences in the PA − vs PA + patients with respect to the incidence of pacemaker implantation (6.5% vs 9.4%, p = 0.685), the use of intra-aortic balloon pump (10.9% vs 9.4%, p = 0.685), defibrillation (13.0% vs 25.0%, p = 0.176), or the use of mechanical ventilation (10.9% vs 9.4%, p = 1.000). A similar number of patients in each group had a poor Killip class > 1 (17.4% in PA − patients vs 18.8% in PA + patients, p = 0.878). There was no difference in the degree of collateral circulation (Rentsrop classification ≥ 2) between the two groups (34.8% in the PA − group vs 28.1% in the PA + group, p = 0.706). We did not find any significant differences between groups with respect to the patency of the infarct-related artery.

Table 1—Baseline Characteristics of the PA + and PA − Patients

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>PA − (n = 46)</th>
<th>PA + (n = 32)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (SD), yr</td>
<td>62 (11)</td>
<td>61 (10)</td>
<td>0.835</td>
</tr>
<tr>
<td>Female gender</td>
<td>5 (10.9)</td>
<td>5 (15.6)</td>
<td>0.732</td>
</tr>
<tr>
<td>Arterial hypertension</td>
<td>15 (32.6)</td>
<td>13 (40.6)</td>
<td>0.468</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>13 (28.3)</td>
<td>14 (43.8)</td>
<td>0.157</td>
</tr>
<tr>
<td>Current smoker</td>
<td>23 (50.0)</td>
<td>13 (40.6)</td>
<td>0.414</td>
</tr>
<tr>
<td>Family history of ischemic heart disease</td>
<td>6 (13.0)</td>
<td>9 (28.1)</td>
<td>0.096</td>
</tr>
</tbody>
</table>

*Data are presented as No. (%) unless otherwise indicated.

Table 2—Characteristics and Treatment of the Acute MI in the PA + and PA − Patients

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>PA − (n = 46)</th>
<th>PA + (n = 32)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inferior/anterior MI location, No.</td>
<td>23/23</td>
<td>19/13</td>
<td>0.414</td>
</tr>
<tr>
<td>Time lapse since symptoms onset (SD), min†</td>
<td>204 (108)</td>
<td>193 (89)</td>
<td>0.624</td>
</tr>
<tr>
<td>Door-to-needle (SD), min</td>
<td>75 (27)</td>
<td>84 (62)</td>
<td>0.458</td>
</tr>
<tr>
<td>Troponin I ≥ 0.1 ng/mL, (median)</td>
<td>23 (50.0)</td>
<td>17 (53.1)</td>
<td>0.392</td>
</tr>
<tr>
<td>TIMI-3 before PCI</td>
<td>1 (2.2)</td>
<td>0 (0.0)</td>
<td>1.000</td>
</tr>
<tr>
<td>TIMI-3 after PCI</td>
<td>39 (84.8)</td>
<td>27 (84.4)</td>
<td>1.000</td>
</tr>
<tr>
<td>Stenting</td>
<td>41 (89.1)</td>
<td>31 (96.9)</td>
<td>0.207</td>
</tr>
<tr>
<td>Triple-vascular disease</td>
<td>4 (8.7)</td>
<td>3 (9.4)</td>
<td>1.000</td>
</tr>
<tr>
<td>Oral β-blockers</td>
<td>22 (47.8)</td>
<td>19 (59.4)</td>
<td>0.315</td>
</tr>
<tr>
<td>IV β-blockers</td>
<td>7 (15.2)</td>
<td>3 (9.4)</td>
<td>0.513</td>
</tr>
<tr>
<td>Calcium antagonists</td>
<td>2 (4.3)</td>
<td>1 (3.1)</td>
<td>1.000</td>
</tr>
<tr>
<td>IV nitrates</td>
<td>34 (73.9)</td>
<td>25 (78.1)</td>
<td>0.670</td>
</tr>
<tr>
<td>Angiotensin-converting enzyme inhibitors</td>
<td>26 (56.5)</td>
<td>13 (40.6)</td>
<td>0.167</td>
</tr>
</tbody>
</table>

*Data are presented as No. (%) unless otherwise indicated.

Evaluating of Infarct Size

There was a significant correlation (r = 0.57, p < 0.001) between the maximum concentrations of CK-MB and the size of the infarction assessed with 99mTc sestamibi. We did not find significant differences in the maximum concentrations of CK-MB between the two groups: 353 IU/L (SD, 215) in PA − vs 343 IU/L (SD, 256) in PA + (p = 0.859). The isotopic study to determine the MI size was performed on the tenth day after the infarct (median, 25th percentile = 10; 75th percentile = 12). The percentage of the ventricle detected as being necrotic in this assessment was higher in PA − than PA + patients: 27.0% (SD, 20.1) vs 18.0% (SD, 14.7), respectively (p = 0.033). A higher proportion of PA − patients had an echocardiographic left ventricular systolic dysfunction (left ventricular ejection fraction ≤ 40%) at discharge from hospital than the patients in the PA + group (18.6% vs 3.2%, respectively; p = 0.071), albeit the difference was not quite statistically significant.

ST-Segment Resolution

All of the patients had the ST-segment resolution analyzed. There was a higher percentage of patients

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with a complete ST-segment resolution in the PA + group than in the PA − group, but this difference did not reach statistical significance: 21 (65.6%) vs 21 (45.7%), respectively (p = 0.082).

**Discussion**

The results of this study indicate that nondiabetic patients who have unstable angina pectoris in the 24 h prior to the onset of an acute MI, and who are treated with primary percutaneous coronary intervention, have smaller infarctions. Thus, PA appears to induce a beneficial effect that limits infarct size and preserves left ventricular systolic function within the setting of primary angioplasty. In this scenario, this beneficial effect is due, probably, not to a more rapid and sustained epicardial reperfusion of the infarct-related artery or to the development of epicardial collateral circulation, but more to a better myocardial tissue reperfusion if PA is present. We make this statement based on the similar patency of the infarct-related artery and of collateral circulation achieved in both groups, and the better ST-segment resolution encountered in PA + patients. Whether PA triggers an intracellular signal that intrinsically preserves cells from death was not an issue specifically assessed in this study, but this could be another potential beneficial mechanism.

On first view, there may appear to be a discrepancy in the data. The peak CK-MB concentrations were similar in both groups; 99mTc sestamibi differed significantly and both measures are significantly correlated. However, peak CK-MB concentration is not a reliable tool to assess infarct size. Currently, 99mTc sestamibi appears to be the best available tool to determine infarct size, and a significant linear relationship between two variables does not necessarily indicate a good concordance.

**Comparison With Previous Studies**

The beneficial effect of PA in MI treated with PCI has been questioned in some studies. Tomoda and Aoki reported a neutral effect of PA in patients with MI who are treated with primary PCI; however, the retrospective nature of that study poses important limitations when interpreting the data: only 27% of the patients had PA, and the infarct size was assessed by measuring the CK blood concentration peak that had been reached. This is an imprecise assessment; hence, it is not surprising that no differences had been observed between the groups. The authors went on to explain this lack of benefit of PA in this subset of patients on the basis of the rapid reperfusion achieved in both groups with primary PCI. Also, the benefit in patients treated with fibrinolytic agents was due to a more rapid reperfusion in patients with PA as had been previously reported.

However, the authors did not address the status of reperfusion in patients not treated with primary PCI. Only 38% of the patients in this group, who showed a benefit of PA, had been treated with tissue plasminogen activator, and with an unusual dose of 40 mg. Moreover, almost 21% of the patients included in the study had diabetes; in these patients, the PA appears not to have any beneficial effect.

In the Myocardial Infarction Registry, Zahn et al did not find statistically significant differences in the combined clinical endpoints of death, reinfarction, and stroke in PA + and PA − patients defined as angina pectoris occurring within the previous 4 weeks prior to the MI. When they segregated the study population into two groups, PA occurring in < 48 h before the infarct and PA occurring > 48 h before the infarct, they still did not find any significant differences. The comparison between PA + and PA − patients in the previous 48 h prior to the infarct was not reported. There were important baseline differences between groups in the study, particularly since 20% of the patients had diabetes.

Noda et al reported, in a small number of patients (n = 25), a beneficial effect of PA in patients with acute MI treated with a successful primary angioplasty and who had no macroscopic evidence of collateral circulation. They reported an increase in regional wall motion index at the 4-week follow-up with ventriculograms relative to the baseline ventriculograms. This suggested more myocardial salvage, less necrosis and more myocardial viability if PA was present.

**Angiographic Results**

Our results are concordant with those of Ishihara et al, but differ from those recently published by Colonna et al, in terms of reperfusion of the infarct artery achieved, as assessed by the TIMI flow grade in the group of patients treated with primary angioplasty. We did not find significant differences in the incidence of TIMI-3 flow in PA + and PA − patients. These data are of considerable importance because if the patency of the infarct-related artery is similar in both groups, an alternative mechanism needs to be invoked to explain the limiting of the infarct size if PA is present. This could be related to a lower incidence of reperfusion damage and/or to a better microvascular reperfusion if PA exists, as suggested by Colonna et al and Takahashi et al. With respect to this possibility, we observed a higher percentage, albeit statistically nonsignificant, of patients with PA having a complete ST-segment reso-
lution, a noninvasive method to assess the myocardial reperfusion achieved in revascularized infarcts.26

The imbalance in the use of abciximab between groups might have favorably influenced the results observed in the study. Although there was no statistically significant difference, more patients with PA received this drug. Abciximab has effects beyond the maintenance of large-vessel patency, and it can improve the recovery of distal coronary perfusion by different mechanisms.27 We do not think that this statistically nonsignificant imbalance in the use of stents between the two groups had a relevant impact in the results since the TIMI 3 perfusion flows achieved in both groups were almost identical.

The rate of preprocedure TIMI-3 flow in our study is very low compared with the rates reported in studies28,29 that assessed the use of abciximab in the setting of primary coronary angioplasty. Indeed, only one patient in the group without PA group had a TIMI-3 grade before the procedure. The only reasonable explanation for this finding is the short time lapse between drug administration and the performance of the first coronary angiogram. Abciximab was administered in the coronary care unit, and the patient was immediately transferred to the catheterization laboratory, or directly from the emergency room to the catheterization laboratory, where the drug was administered.

In conclusion, PA exerts a beneficial effect in nondiabetic patients with ST-segment elevation acute MI even if they are treated with primary PCI. The infarct size is limited and left ventricular systolic function is preserved.

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