Protective Effect of Pre-Infarction Angina on Microvascular Obstruction After Primary Percutaneous Coronary Intervention Is Blunted in Humans by Cardiovascular Risk Factors

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Background: Pre-infarction angina (PIA) has been shown to reduce the microvascular obstruction (MVO) rate in patients with ST-segment elevation myocardial infarction (STEMI). We sought to evaluate the potential modulator role of cardiovascular risk factors (CRFs) on this protective effect.

Methods and Results: Two hundred patients with STEMI were enrolled. PIA was defined as typical chest pain within the 48 h preceding STEMI onset. Angiographic MVO was defined as TIMI flow grade <2 or TIMI flow 3 with myocardial blush grade <2; electrocardiographic (ECG) MVO was defined as ST-segment elevation resolution <70%. Common CRFs were collected. In the absence of hypertension, both angiographic and ECG MVO rates were lower in patients with PIA as compared with those without, whereas, in the presence of hypertension, they were similar in both study groups (P for interaction=0.01 and P=0.014, respectively). Among nonsmokers, angiographic and ECG MVO rates were lower in patients with PIA as compared with those without, whereas within smokers, they were similar in both study groups (P for interaction=0.037 and P=0.037, respectively). In the absence of dyslipidemia, the angiographic and ECG MVO rates were lower in patients with PIA as compared with those without, whereas within dyslipidemic patients, they were similar in both study groups (P for interaction=0.012 and P=0.04, respectively).

Conclusions: The protective effect of PIA on MVO is blunted by CRFs. (Circ J 2014; 78: 1935–1941

Key Words: Acute myocardial infarction; Microcirculation; Percutaneous coronary intervention

Pre-infarction angina (PIA; ie, angina episodes preceding the onset of definite acute myocardial infarction: AMI),1–4 has been found to reduce infarct size5 and to prevent a major decrease of ejection fraction,6 therefore improving prognosis in patients with ST-segment elevation AMI (STEMI).7,8

Mechanisms underlying this association range from an improvement of collateral circulation to an increased sensitivity to thrombolysis.9–11 The most powerful protection conferred by PIA, however, is likely related to activation of ischemic preconditioning (IP), known to reduce infarct size by half in animal models.12–14 Of note, IP may also protect the microcirculation, as suggested by a study performed in pigs by Posa et al.15 Microvascular obstruction (MVO) is common after reperfusion in STEMI patients and carries a high risk of complications, including increased rates of adverse remodeling, heart failure and death.16–23 Interestingly, previous studies have shown a reduction “in vivo” of the MVO rate in patients experiencing PIA.24–26 Of note, although it is already known that cardiovascular risk factors (CRFs) may limit the protective effects of IP in human models,27–30 it is still unknown whether they may also limit the protective effect of PIA on MVO. Therefore, in this retrospective study we sought to investigate the effect of PIA on MVO after primary percutaneous coronary intervention (PPCI) and the modulator role of CRFs.

Methods

Study Population
Consecutive patients with a first STEMI admitted to hospital from September 2010 to September 2012 were screened. In-
history was obtained on hospital admission with specific assessment of possible occurrence of episodes of typical chest pain within days preceding onset of definite infarction pain that brought the patient to hospital. Specifically, PIA was defined as the occurrence, either at rest or during exercise, of at least 1 episode of typical chest pain of less than 30 min in duration occurring within the 48 h preceding the onset of definite infarction pain.

CRFs were carefully examined, including family history of early coronary artery disease (first-degree relative with a history of myocardial infarction <60 years), hypercholesterolemia (total cholesterol >200 mg/dl or treated hypercholesterolemia), smoking (current regular use (any amount) or cigarette withdrawal 2 months), diabetes mellitus (defined as A1C ≥ 6.5% or fasting plasma glucose ≥ 126 mg/dl or 2-h plasma glucose ≥200 mg/dl during oral glucose tolerance test or, in a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥200 mg/dl) and hypertension (systolic blood pressure >140 mmHg and/or diastolic blood pressure >90 mmHg or treated hypertension). Body mass index (BMI), defined as mass in kilograms divided by height in meters squared, was also obtained. Therapy on admission criteria were: prolonged chest pain (>30 min), ST-segment elevation >2 mV in 2 or more adjacent leads on standard electrocardiogram (ECG) and PPCI performed within 12 h of symptom onset. During the enrollment phase, 240 STEMI patients were eligible for the study (64±12 years, 75% male). Overall, 40 patients were excluded from the study because of: rescue PCI (n=11), stent thrombosis (n=14), or presence of morbidities (n=15) (acute or chronic infections, autoimmune disease, liver disease, neoplasia, immunologic disorder, anti-inflammatory or immunosuppressive therapy and recent surgical procedures or trauma). All PPCI patients received aspirin (250 mg IV) and clopidogrel (600 mg PO) in the emergency department, and intravenous heparin (100 UI/Kg) was administered before PCI. According to standard clinical practice, PCI was performed through a 6F sheath by femoral or radial artery approach. After wire crossing, thrombus aspiration (Diver CE, Invatec) was performed in all patients, followed by stent implantation preceded by balloon pre-dilation, if necessary. As routine clinical practice, all patients received a systemic bolus of abciximab (0.25 mg/kg bolus), followed by a 12-h continuous infusion (0.125 g · kg−1 · min−1 for 12 h). A detailed clinical history was obtained on hospital admission with specific assessment of possible occurrence of episodes of typical chest pain within days preceding onset of definite infarction pain that brought the patient to hospital. Specifically, PIA was defined as the occurrence, either at rest or during exercise, of at least 1 episode of typical chest pain of less than 30 min in duration occurring within the 48 h preceding the onset of definite infarction pain. 

**Table 1.** Clinical and Laboratory Data in the Overall Population and in Patients With and Without PIA

<table>
<thead>
<tr>
<th>Clinical characteristics</th>
<th>All population (200 (100%))</th>
<th>PIA+ group (63 (31.5%))</th>
<th>PIA– group (137 (68.5%))</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &lt;65 years</td>
<td>113 (56.5)</td>
<td>39 (62)</td>
<td>74 (54)</td>
<td>0.39</td>
</tr>
<tr>
<td>Sex (male), n (%)</td>
<td>150 (75)</td>
<td>39 (62)</td>
<td>111 (81)</td>
<td>0.004</td>
</tr>
<tr>
<td>Arterial hypertension, n (%)</td>
<td>111 (56)</td>
<td>36 (57)</td>
<td>75 (55)</td>
<td>0.44</td>
</tr>
<tr>
<td>Smoker, n (%)</td>
<td>76 (38)</td>
<td>24 (44)</td>
<td>48 (35)</td>
<td>0.38</td>
</tr>
<tr>
<td>Dyslipidemia, n (%)</td>
<td>96 (48)</td>
<td>25 (40)</td>
<td>71 (52)</td>
<td>0.07</td>
</tr>
<tr>
<td>Diabetic mellitus, n (%)</td>
<td>49 (25)</td>
<td>10 (16)</td>
<td>39 (29)</td>
<td>0.04</td>
</tr>
<tr>
<td>Family history of CAD, n (%)</td>
<td>63 (32)</td>
<td>21 (33)</td>
<td>42 (31)</td>
<td>0.41</td>
</tr>
<tr>
<td>BMI (kg/m²±DS)</td>
<td>26.3±2.3</td>
<td>25.7±2.3</td>
<td>26.5±2.3</td>
<td>0.02</td>
</tr>
<tr>
<td>Precorony time (min±SD)</td>
<td>290±224</td>
<td>266±198</td>
<td>301±235</td>
<td>0.31</td>
</tr>
<tr>
<td>Pathological Q wave</td>
<td>18 (9)</td>
<td>1 (1.6)</td>
<td>17 (12.4)</td>
<td>0.008</td>
</tr>
</tbody>
</table>

**Therapy on admission**

- β-blockers, n (%) 40 (20) 15 (24) 25 (18) 0.23
- ACE-inhibitors, n (%) 36 (18) 13 (21) 23 (17) 0.32
- Statins, n (%) 24 (12) 8 (13) 16 (12) 0.50
- Aspirin, n (%) 149 (75) 43 (76) 101 (74) 0.42

**Laboratory data**

- Glycemia (mg/dl) 122±52 117±46 125±54 0.27
- Total cholesterol (mg/dl) 180±54 182±59 179±51 0.66
- LDL (mg/dl) 107±42 112±48 105±39 0.26
- HDL (mg/dl) 43±12 43±13 43±12 0.81
- Triglycerides (mg/dl) 140±62 138±56 140±65 0.81
- Creatinine (mg/dl) 1.11±0.26 1.12±0.27 1.11±0.26 0.92
- Creatinine-clearance (nl/min) 64.2±14.59 66.1±11.95 63.3±15.72 0.21
- Platelets (10^9/L) 234±75 246±84 229±71 0.13
- Fibrinogen (mg/dl) 361±136 355±123 363±142 0.69
- Creatin-chinase (UI/L) 347±486 387±532 328±464 0.43
- Creatin-chinase isoenzyme MB (ng/ml) 29±57 22±34 32±65 0.29
- Troponin T (ng/ml) 1.8±4.7 1.2±2.9 2.1±5.3 0.25

ACE, angiotensin-converting enzyme; CAD, coronary artery disease; HDL, high-density lipoprotein; LDL, low-density lipoprotein; PIA, pre-infarction angina.
admission was recorded for all patients. The study was approved by the Ethics Committee of the Catholic University and all patients gave their consent before entering the study.

**Angiographic and ECG Analyses**

Angiographic analyses were performed by 2 expert angiographers (G.N. and G.S.) blinded to PIA occurrence. Coronary Thrombolysis In Myocardial Infarction (TIMI) flow grading and myocardial blush grade (MBG) were evaluated. Anterograde coronary flow was graded using the standard TIMI criteria, and MBG was graded. Angiographic MVO was defined as TIMI flow grade <2 after vessel reopening or TIMI flow 3 with a final MBG <2. A 12-lead ECG was recorded before and 90 min after PPCI and analyzed by a trained cardiologist (N.C.) blinded to PIA. ECG-MVO was defined as an ST-segment elevation resolution <70%.

**Statistical Analysis**

Data distribution was assessed by the Kolmogorov-Smirnov test. Variables that did not follow a normal distribution are expressed as medians and interquartile ranges, whereas other continuous variables are expressed as mean±SD; categorical variables are expressed as proportions. Comparisons between categorical variables were done using chi-square test or Fischer exact test, as appropriate. Student’s t-test or Mann-Whitney U test were used for comparisons between continuous variables among groups, as appropriate according to data distribution. Interaction between independent variables was evaluated by 2-way factorial ANOVA. The statistical software SPSS 20.0 (SPSS Italia, Florence, Italy) was used for all statistical analysis.

**Results**

**Study Population**

Clinical features of enrolled patients are reported in Table 1 and angiographic data are reported in Table 2. Patients with unheralded STEMI (68.5%) were more frequently male (81% vs. 62%, P=0.004), diabetics (29% vs. 16%, P=0.04), had higher BMI (26.5±2.3 kg/m² vs. 25.7±2.3 kg/m², P=0.02), higher thrombus score (83% vs. 65%, P=0.008) and higher rate of pathological Q wave on ECG (12.4% vs. 1.6%, P=0.008) as compared with those with PIA (31.5%).

Angiographic MVO and MVO evaluated by ST-segment elevation resolution <70% were observed in 49 (24.5%) and 94 (47%) patients, respectively. Of note, angiographic MVO and MVO evaluated by ST-segment elevation resolution <70% rates were lower in patients with PIA as compared with those without PIA (9 [14.3%] vs. 40 [29.2%], P=0.016 and 23 [37%] vs. 71 [52%], P=0.03, respectively).

In the absence of hypertension, the angiographic MVO rate was lower in patients with PIA as compared with those without PIA (4 [11.1%] vs. 26 [34.7%], P=0.007), whereas, in the presence of hypertension, it was similar between the 2 study groups (5 [18.5%] vs. 14 [22.6%], P=0.45; P for interaction=0.01) (Figure 1A). Among nonsmokers, the MVO rate was lower in patients with PIA as compared with those without PIA (9 [14.3%] vs. 40 [29.2%], P=0.016 and 23 [37%] vs. 71 [52%], P=0.03, respectively).

In the absence of dyslipidemia, the MVO rate was lower in patients with PIA as compared with those without PIA (1 [4%] vs. 24 [33.8%], P=0.002), whereas, in the presence of dyslipidemia, it was similar between the 2 study groups (4 [12.5%] vs. 17 [20.2%], P=0.25; P for interaction=0.037) (Figure 1B). In the absence of dyslipidemia, the MVO rate was lower in patients with PIA as compared with those without PIA (1 [4%] vs. 24 [33.8%], P=0.002), whereas, in the presence of dyslipidemia, it was similar between the 2 study groups (4 [12.5%] vs. 17 [20.2%], P=0.25; P for interaction=0.037) (Figure 1B). In the absence of diabetes, family history of cardiovascular disease or BMI (data not shown).
PIA, CRFs and ECG-MVO

In the absence of hypertension, the ECG-MVO rate was lower in patients with PIA as compared with those without PIA (6 [22%] vs. 32 [52%], P=0.009), whereas, in the presence of hypertension, it was similar between the 2 study groups (17 [47%] vs. 39 [52%], P=0.39, P for interaction=0.014) (Figure 2A). Among nonsmokers, the ECG-MVO rate was lower in patients with PIA as compared with those without PIA (10 [31%] vs. 47 [56%], P=0.01), whereas, among the smokers, it was similar between the 2 study groups (12 [43%] vs. 23 [48%], P=0.25; P for interaction=0.037) (Figure 2B).

In the absence of dyslipidemia, the ECG-MVO rate was lower in patients with PIA as compared with those without PIA (4 [37%] vs. 35 [53%], P=0.002), whereas, in the presence of dyslipidemia, it was similar between the 2 study groups (9 [36%] vs. 36 [51%], P=0.43; P for interaction=0.04) (Figure 2C). Among patients without a family history of cardiovascular disease, the ECG-MVO rate was lower in patients with PIA as compared with those without PIA (13 [31%] vs. 50 [53%], P=0.015), whereas, among patients with a family history of cardiovascular disease, it was similar between the 2 study groups (9 [17%] vs. 27 [27.6%], P=0.54; P for interaction=0.036) (Figure 2D). No interaction between PIA and MVO was observed for diabetes or BMI (data not shown).

Discussion

This retrospective study further strengthens the evidence that, among patients presenting with a first STEMI, both the angiographic and ECG MVO rates are lower in patients with PIA as compared with those with an unheralded AMI. More importantly, this study shows that the protective effect of PIA on MVO is considerably modulated by CRFs.

PIA has been suggested to improve prognosis in patients with STEMI in several previous studies. 

Mechanisms underlying this association are multiple, including better collateral circulation and increased sensitivity to thrombolysis. However, the most powerful protection conferred by PIA seems to be related to activation of the IP cascade. IP, in its early and delayed forms, is currently the most important paradigm for experimental studies aiming at minimizing infarct size and reducing the incidence of other adverse events related to ischemia-reperfusion (IR) damage. Heusch et al demonstrated that early IP appears quickly (within a few minutes) and lasts almost 2, up to 3 hours; conversely, delayed IP appears from 12 up to 24 hours later and lasts from 3 to 4 days.

The time frame of PIA onset has varied widely in previous studies focused on PIA, and, therefore, it was not possible to attribute the protective effects of PIA to either early or delayed IP. Beyond reduction of infarct size, IP may also protect the microcirculation after reperfusion, as previously shown in animal models. This effect may be related to improvement of endothelial dysfunction and to prevention of neutrophil activation caused by IR.

Accordingly, PIA is also associated with preservation of myocardial microvasculature as assessed by echocardiography in STEMI patients. Of note, among STEMI patients presenting with TIMI flow grade 3, microvascular damage as assessed by myocardial contrast echocardiography has been demonstrated to be a more powerful independent predictor of left ventricular remodeling after myocardial infarction as compared with persistent ST-segment elevation and MBG. Furthermore, Jesel et al have recently shown that the absence of PIA is the only independent predictor of MRI-detected MVO. Of note, previous studies demonstrated that ischemic postconditioning is also able to reduce infarct size, myocardial edema and, therefore, the area at risk and to improve coronary microvascular perfusion. Moreover, Mewton et al showed that the protective effect of ischemic postconditioning on coronary MVO is greater than that observed for myocardial infarction. Despite these encouraging results, several studies have emphasized the hypothesis that the use of at least some drugs and the presence of CRFs may modulate these protective effects of PIA. Of course, a major confounding issue of specific drugs. Indeed, some drugs could themselves induce a protective effect (eg, β-blockers, angiotensin-converting enzyme inhibitors and angiotensin II recep-

![Figure 1. Rates of angiographic microvascular obstruction (MVO) according to the presence or absence of pre-infarction angina (PIA) among patients with and without (A) hypertension, (B) smoking habit and (C) dyslipidemia.](image-url)
intrinsic inhibitors, might explain our and other clinical results.

Nakamura et al demonstrated that smoking habit abolishes IP-induced augmentation of endothelium-dependent vasodilation. Possible mechanisms explaining this finding derive from experimental studies and might involve downregulation of vascular endothelial growth factor (VEGF) receptor-2 expression, endothelial nitric oxide synthase (eNOS) protein levels, and VEGF-induced VEGF receptor-2 phosphorylation, leading to impaired VEGF-induced cell migration and angiogenesis. Our study showed that, among nonsmokers, both the angiographic and ECG MVO rates were lower in patients with PIA as compared with those without PIA, whereas among smokers, it was similar between the 2 groups.

Animal studies provide conflicting results concerning the effect of hypercholesterolemia on the protective effects of IP. Ferdinandy et al demonstrated that pacing-induced preconditioning was lost in hypercholesterolemic rabbits. Yet another group showed that hypercholesterolemia did not abolish the protective effects of IP. Clinical results seem to be more consistent. Recently, Takeuchi et al demonstrated that left ventricular hypertrophy accompanying hypertension was a crucial determinant of the effects of IP.

In particular, PIA resulted in significantly less myocardial damage, better left ventricular ejection fraction and greater MBG on dual-isotope (thallium-201/technetium-99 m pyrophosphate) single-photon emission computed tomography in normotensive than in hypertensive patients. Accordingly, the myocardial salvage effects of PIA showed a significant negative correlation with left ventricular mass index. Impaired coronary endothelial function and vasomotor responsiveness, up to an abnormal balance between the JAK-STAT pathway and its intrinsic inhibitors, might explain our and other clinical results. Nakamura et al demonstrated that smoking habit abolishes IP-induced augmentation of endothelium-dependent vasodilation. Possible mechanisms explaining this finding derive from experimental studies and might involve downregulation of vascular endothelial growth factor (VEGF) receptor-2 expression, endothelial nitric oxide synthase (eNOS) protein levels, and VEGF-induced VEGF receptor-2 phosphorylation, leading to impaired VEGF-induced cell migration and angiogenesis. Our study showed that, among nonsmokers, both the angiographic and ECG MVO rates were lower in patients with PIA as compared with those without PIA, whereas among smokers, it was similar between the 2 groups.

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formation of reactive oxygen species, attenuation of heat shock response, and accumulation of cholesterol in sarcocellular and mitochondrial membranes, up to significant alterations in the expression of several genes in animal models.

Diabetes mellitus is a well-known predictor of morbidity and mortality after AMI. One experimental study demonstrated PI-mediated cardioprotection in the diabetic heart. In contrast, consistent evidence suggests that the protective effects of IP are abolished in the presence of chronic diabetes mellitus.

In this complex scenario, our data support the hypothesis that diabetes does not modulate the favorable effect of PIA on MVO.

Finally, in our study we demonstrated that, among patients without a family history of cardiovascular disease, the ECG-MVO rate was lower in patients with PIA as compared with those without PIA, whereas, within patients with a family history of cardiovascular disease, it was similar between the 2 groups. These findings might suggest a potential role played by genetic factors in influencing the individual response to IP/PIA.

Of note, the slight differences in modulation by CRFs of the protective effect of IP/PIA on angiographic or ECG MVO might be explained by the fact that angiography and ECG reflect different aspects of MVO. Therefore, in order to fully exploit the favorable effect of PIA on MVO, careful treatment of CRFs is strongly recommended.

Study Limitations

Firstly, we did not perform MRI, which is the most specific method of assessing MVO. However, a good correlation has been reported for angiographic and ECG indexes of MVO and MRI-defined MVO. Secondly, the size of the study population may have been too small to detect other relevant interactions between CRFs and PIA. Finally, we were not able to clarify the mechanism of myocardial protection, which should be investigated in future studies.

Conclusions

We showed that PIA is able to reduce the rates of angiographic and ECG MVO after STEMI and that some CRFs may blunt this beneficial effect. Therefore, in order to fully exploit the protective effect of PIA on MVO, careful treatment of CRFs is warranted.

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Disclosures

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