Pre-Conditioning in Non-ST Elevation Myocardial Infarction
Fact or Fiction

The Department of Cardiology, Faculty of Medicine, Ain Shams University Hospitals

Abstract

Background: Several studies have demonstrated the protective effects of preconditioning in STEMI but it remained uncertain in patients with non STEMI.

Aim: To evaluate preconditioning in non STEMI.

Patients and Methods: 80 patients with first non-STEMI who were admitted to Ain Shams University Hospitals were divided into group one: 40 patients without preinfarction angina and group two: 40 patients with preinfarction angina and subdivided into group 2A: With preinfarction angina within 12 hours before admission and group 2B: With delayed preinfarction angina >12 hours preinfarction angina.

Methods: All patients received standard treatment for non-STEMI.ECG, cardiac enzymes, coronary angiography and informed consents were done for all patients. Echocardiography was done to every patient before discharge.

Results: Higher myocardial biomarkers and lower LV ejection fraction was found in group 1 than group 2 (51 ± 6.7 vs 57±6.5 respectively p-value 0.006) total CPK in group 1: 162±45 vs 680±90 in group 2 with p-value 0.016. All major cardiac events were more in group 1. Incidence of recurrent ischemia was 65% in group 1 and 30% in group 2 (p-value 0.008). Timing of preinfarction angina did not affect the inhospital outcome and did not influence myocardial protection.

Conclusion: Preinfarction angina is a protective mechanism in patients with non STEMI regardless the timing of preinfarction angina.

Key Words: Preconditioning – Preinfarction angina.

Introduction

SEVERAL studies have demonstrated the protective effects of pre-infarction angina in setting of Q wave myocardial infarction, implicating the role of ischemic preconditioning (IPC), but this role remains uncertain in patients with NSTEMI. Sub-endocardial viability in NSTEMI patients is thought to be less dependent on collateral circulation, and thus more likely to be protected by other mechanisms such as preconditioning [1].

Brief episodes of transient myocardial ischemia are tolerated by myocytes. Although no cell death results from ischemia, the myocytes are damaged. In canine heart, total proximal coronary artery occlusions up to 15 minutes result in reversible injury and beyond that irreversible injury. The 15-minute period of ischemia, however, induces marked change in the high-energy phosphates and the adenine nucleotide pool, depletion of glycogen, accumulation of lactate and H+ and mild intracellular edema observed on ultrastructure: But once blood flow is reestablished, the myocytes eventually recover, the clinical counterparts to brief periods of transient ischemia include angina, unstable angina, coronary vasospasm and transient ischemia induced by inflation of an angioplasty balloon in the coronary arteries. Patients with coronary artery disease may experience episodes of transient ischemia on daily basis without developing myocardial necrosis [2].

Aim of the work:

The aim of this study was to evaluate the effect of pre-infarction angina in the clinical setting of Non-ST segment elevation myocardial infarction (NSTEMI).

Patients and Methods

The current study was conducted on 80 patients with first NSTEMI who were admitted to the Coronary Care Unit–Ain Shams University Hospital in the period between 5/2010 to 5/2011 and fulfilled the following predetermined criteria:

Correspondence to: Dr. Bassem Wadie, The Department of Cardiology, Faculty of Medicine, Ain Shams University Hospitals

Abbreviations:
Non-STEMI : Non ST segment elevation myocardial infarction.
L.V.W.M.S.I : Left ventricular wall motion scoring index.
**Inclusion criteria:**
- Patients’ age less than 75 years.
- Typical angina like chest pain on admission lasting more than 20 minutes and not exceeding 6 hours (in order to record the peak levels of myocardial necrosis markers).
- ECG showing ST segment depression >0.1mv and/or the appearance of new negative T waves >0.1mv, in at least two contiguous leads on the surface ECG with raised biochemical markers of total serum creatinine kinase (CPK), creatinine kinase MB (CPK-MB) isoenzyme.
- Positive qualitative troponin I test.
- Ischemic preconditioning is the prodromal angina that is defined as typical chest pain episodes persisting <20 minutes either at rest or on effort within 24 hours before the onset of NSTEMI in group 2 (preconditioned patients) [1].

**Exclusion criteria:**
- Patients with ECG abnormalities, which mask the accurate assessment of ECG changes with acute myocardial infarction as left bundle branch block, paced rhythm and digitalis therapy.
- Diabetic patients being on Glibenclamide treatment that may affect the results of this study by inhibiting preconditioning phenomenon.
- Patients with congestive heart failure, advanced renal or hepatic disease.
- Patients with collateral circulation more than grade 1 according to Rentrop classification in coronary angiography [3].

The patients were classified into two groups according to the presence or absence of preinfarction anginal attacks:

**Group 1:** Included 40 patients presented with first NSTEMI not preceded by preinfarction angina.

**Group 2:** Included 40 patients presented with first NSTEMI preceded by preinfarction angina.

Then patients in group 2 were classified into two subgroups according to time of the preinfarction anginal attacks:

**Subgroup A (classic preconditioning):**
Patients who reported preinfarction angina within 12 hours prior to admission with NSTEMI.

**Subgroup B (delayed pre-conditioning):**
Patients who reported pre-infarction angina within 13-24 hours prior to admission with NSTEMI.

Lastly, patients of group 2 were divided into another two subgroups according to the number of pre-infarction anginal attacks.

**Subgroup C:** Patients who reported less than five preinfarction anginal attacks within the 24 hours prior to admission.

**Subgroup D:** Patients who reported five or more preinfarction anginal attacks within the 24 hours prior to admission.

All the patients were treated with the standard medical therapy for NSTEMI according to the decision of treating physician and were subjected to:

a- Detailed history taking and examination.

b- A standard 12 lead ECG on admission for recording the predetermined ECG criteria, and every morning until discharge and at any typical anginal pain.

c- Blood samples for measuring CPK and CKMB plasma level were taken on admission and every 8 hours for the 1st day and subsequently every morning until discharge.

d- During hospitalization all patients underwent coronary angiography after informed consent aiming at: Assessment of the severity of coronary disease according the number of the diseased coronary arteries, and evaluation of collateral circulation was done according to Rentrop classification.

e- Predischarge complete transthoracic echocardiography examination was performed for assessment of left ventricular systolic function and segmental wall motion score index [3].

**Patients were followed-up in hospital for the following events:**
- Episodes of recurrent ischemia, heart failure, reinfarction and arrhythmia.

**Statistical Methods:**
Data were collected, coded, tabulated, and then analyzed using SPSS® v.16 computer package. Data were presented as mean (±standard deviation) and frequency (%) for numerical variables and categorical variables respectively. Analysis of numerical variables was done using unpaired t-test if its assumptions were fulfilled. Otherwise, Mann-Whitney’s test was used instead. Comparisons of categorical variables were done using Fisher’s exact test or chi-square test as appropriate. Any difference with p-value <0.05 was considered statistically significant.
Results

Eighty patients were recruited and divided into two groups according to the presence or absence of preinfarction angina.

Comparing both groups as regard the demographic data, there was no statistically significant difference as shown in Table (1). Admission ECG was compared in both groups as regard total sum of ST-segment depression, depth of T wave inversion and admission QTc. These ECG changes showed no significant difference among both groups. Coronary angiographic data was revised in both groups and revealed: Group 1: Two patients with left main disease (5%), twenty patients with single vessel disease (50%), ten patients with two vessel disease (25%) and another eight patients with three vessel disease (20%), while only sixteen patients (40%) out of the forty patients in group 2 had single vessel disease, fourteen patients (35%) had two vessel disease and the remaining ten patients (25%) had three vessel disease.

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>Group 1</th>
<th>Group 2</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>59.20 ± 10.55</td>
<td>52.85 ± 13.05</td>
<td>0.10</td>
</tr>
<tr>
<td>Sex</td>
<td>M: 26</td>
<td>32</td>
<td>0.48</td>
</tr>
<tr>
<td></td>
<td>F: 14</td>
<td>8</td>
<td>0.48</td>
</tr>
<tr>
<td>Current smoking</td>
<td>No: 16</td>
<td>12</td>
<td>0.507</td>
</tr>
<tr>
<td></td>
<td>Yes: 24</td>
<td>28</td>
<td>0.507</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>No: 20</td>
<td>15</td>
<td>0.018</td>
</tr>
<tr>
<td></td>
<td>Yes: 20</td>
<td>34</td>
<td>0.018</td>
</tr>
<tr>
<td>D.M.</td>
<td>No: 28</td>
<td>28</td>
<td>1.000</td>
</tr>
<tr>
<td></td>
<td>Yes: 12</td>
<td>12</td>
<td>1.000</td>
</tr>
<tr>
<td>H.T.N</td>
<td>No: 18</td>
<td>20</td>
<td>0.752</td>
</tr>
<tr>
<td></td>
<td>Yes: 22</td>
<td>20</td>
<td>0.752</td>
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<tr>
<td>FH of IHD</td>
<td>No: 30</td>
<td>28</td>
<td>0.723</td>
</tr>
<tr>
<td></td>
<td>Yes: 10</td>
<td>12</td>
<td>0.723</td>
</tr>
</tbody>
</table>

Myocardial markers and echocardiography were assessed in both groups.

There was significant myocardial damage among patients in group (1) compared with group (2) as proved by higher myocardial markers and lower left ventricular ejection fraction in group (1) patients as shown in Table (2).

The comparison between both main groups as regard in-hospital outcome is shown in Table (3). All major cardiac events were more common among patients in group (1). Recurrent ischemia was reported in 26 patients (65%) in Group 1, while only 12 patients (30%) in group (2) experienced recurrent ischemia (p-value 0.027). Sixteen patients (40%) in group 1, and two patients (5%) in group 2 had congestive heart failure (p-value 0.008). Ten patients in this study suffered from ventricular arrhythmia. Eight of them were in group 1 (p-value 0.035). There were no reported cases of death or reinfarction in the current study.

Patients in group 2 were furtherly subdivided into group A (26 patients) and group B (14 patients) according to number of pre-infarction anginal attacks. Both subgroups were compared to find out the impact of the frequency of pre-infarction anginal attacks on in-hospital outcome and myocardial protection. It was found that regardless of the number of pre-infarction anginal attacks the in-hospital outcome, left ventricular ejection fraction and myocardial enzymatic elevation were not affected.

Patients in group 2 were reclassified into group C (22 patients) and group D (18 patients) according to time of pre-infarction angina and were compared as regard myocardial markers, echocardiographic findings and in-hospital outcome. This comparison showed clearly that the timing of pre-infarction angina did not affect the in-hospital outcome and did not add to myocardial protection as shown by absence of significant differences as regard left ventricular ejection fraction and myocardial enzymatic elevation (Tables 3,4).

<table>
<thead>
<tr>
<th>Echocardiographic and enzymatic data</th>
<th>Group 1</th>
<th>Group 2</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean ± SD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total C.P.K (mg/dl)</td>
<td>1162.45</td>
<td>702.43</td>
<td>0.016</td>
</tr>
<tr>
<td>C.K.M.B (ng/dl)</td>
<td>163.45</td>
<td>143.85</td>
<td>0.008</td>
</tr>
<tr>
<td>L.V.E.F (%)</td>
<td>50.00</td>
<td>67.60</td>
<td>0.006</td>
</tr>
<tr>
<td>L.V.W.M.S.I</td>
<td>1.34</td>
<td>0.25</td>
<td>0.002</td>
</tr>
</tbody>
</table>

Table (3): Comparison between Subgroup (A) versus Subgroup (B) as regard echocardiographic data and enzymatic infarct size.

<table>
<thead>
<tr>
<th>N</th>
<th>Mean ± SD</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total C.P.K</td>
<td>26</td>
<td>749.15</td>
</tr>
<tr>
<td>Subgroup (A)</td>
<td>14</td>
<td>554.14</td>
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<tr>
<td>C.K.M.B</td>
<td>26</td>
<td>73.15</td>
</tr>
<tr>
<td>Subgroup (A)</td>
<td>14</td>
<td>54.00</td>
</tr>
<tr>
<td>L.V.E.F (%)</td>
<td>26</td>
<td>58.23</td>
</tr>
<tr>
<td>Subgroup (A)</td>
<td>14</td>
<td>56.57</td>
</tr>
<tr>
<td>L.V.W.M.S.I</td>
<td>26</td>
<td>1.18</td>
</tr>
<tr>
<td>Subgroup (A)</td>
<td>14</td>
<td>1.00</td>
</tr>
</tbody>
</table>
Pre-infarction angina and left ventricular systolic function.

-Discussion-

The present study demonstrated that pre-infarction angina has a beneficial role in the clinical setting of NSTEMI through the mechanism of IPC. This study demonstrated that preconditioned patients are associated with more favorable in-hospital outcome, smaller infarct size and better left ventricular systolic function.

Pre-infarction angina offered better in-hospital outcome:

Patients reporting pre-infarction angina in the 24 hours prior to admission suffered less angina, congestive heart failure, and arrhythmic events, compared to non-preconditioned patients. The study findings are consistent with results of other studies; Iwaska et al. [4]; Anzani et al. [5]; Kloner et al. [6] in the Major TIMI9B study.

Pre-infarction angina induced infarct size reduction:

The current study revealed infarct size reduction as assessed by serial myocardial serum markers (enzymatic infarct size) and this result is consistent with several studies focusing on pre infarction angina effect on STEMI; Anzani et al. [5]; Nakagwa et al. [7]; Kloner [6] Kloner [8]; in the Major TIMI9B study.

Pre-infarction angina and left ventricular systolic function:

The results of the current study revealed that preconditioned patients had a better global systolic function and better regional myocardial systolic function assessed by LVEF and Wall motion score index.

Several mechanisms including mainly preconditioning and collateral development and to a lesser extent, accelerated thrombolysis may explain the beneficial effect of pre-infarction angina. This study was designed in order to exclude other possible mechanisms and elucidate the presence of preconditioning phenomenon.

Ottani et al. [9] reported that the new onset prodromal angina appears to afford protection to ischemic myocardium at least in patients with evolving myocardial infarction who have undergone successful thrombolytic therapy less than 2 hours from the onset of symptoms. Patients with new onset preinfarction angina showed a significantly smaller infarct size compared with patients without preinfarction angina. Since the two groups had similar times to reperfusion and no evidence of collateral circulation to infarct related artery, the protection afforded by angina in the group preceded by angina might be explained by ischemic preconditioning (IPC).

In the major TIMI9B study, Kloner et al. [6] demonstrated that pre-infarction angina was only beneficial for event rate when the time between the onset of angina and myocardial infarction was within 24 hours.

Christitodoulos et al. [10] demonstrated that the prodromal angina in patients with history of coronary heart disease who develop NSTEMI is associated with a more favorable in-hospital outcome, smaller infarct size and less incidence of future arrhythmias. Moreover, postulated that preconditioning is responsible for these results.

Ottani et al. [10] reported that prodromal angina limits infarct size in the setting of anterior STEMI treated with primary PCI and attributed these results to the effect of preconditioning phenomenon. However, the authors reported that prodromal angina patients achieved TIMI flow grade 3 slightly earlier suggesting that its presence might have caused a more unstable clot structure due to less activated platelets.

On the other hand, other studies explain the beneficial role of pre infarction angina in the setting of acute myocardial infarction by the development of collaterals. Ishihara et al. [11] reported that the cardio protective effect of pre infarction angina could be explained by opening and development of thin walled coronary collateral vessels.

Zijlstra [12] reported that patients with pre-infarction angina are associated with reduced myocardial infarct size in patients treated with thrombolysis and explained that due to better collateral...
failing of the infarct related artery and due to ischemic preconditioning. In the study of Zijlstra et al. [12] total patients with pre infarction angina 254 patients about 163 (65%) had collateral grade 0 and 75 patients (30%) had collaterals grade 1 according to Rentrop classification and only few patients have grade 2 and 3. So, the conclusion of the authors that collateral development is the explanation of the results of the protective mechanism of preinfarction angina is not accepted as the majority of the patients have collaterals grade 0-1.

The classic and delayed preconditioning:

As mentioned before IPC consists of two phases first phase is apparent within minutes and lasts for 2-3 hours, a second phase of delayed preconditioning appears 12-24 hours later and lasts for 3-4 days as reported by Baxter et al. [13] and Stein et al. [14].

The present study demonstrated that IPC elicits delayed or second window of protection to the human myocardium that lasts 24 hours following preconditioning stimulus (pre-infarction angina). In the current study subgroup analysis of population study experiencing pre infarction angina revealed some proof about the existence of this delayed preconditioning. Statistical analysis showed no significant difference between patients reporting preinfarction angina within 12-24 hours prior to admission with NSTEMI and those reporting pre infarction angina only within the last 12 hours prior to admission.

This delayed preconditioning is well documented in the experimental studies and in human [15].

Kloner et al. [6] in the Major TIMI9B study demonstrated that the pre infarction angina was only beneficial for event rate when the time between onset of angina and myocardial infarction was within 24 hours.

Christitodoulos et al. [1] demonstrated that patients reporting pre infarction angina within 12-48 hours prior to admission were similarly protected as patients reporting pre infarction only within the last 12 hours concluded that both forms of preconditioning either early or late offer the same level of protection.

Study Limitations:

1. The number of the patients enrolled in this study is relatively small.
2. The detection of silent ischemia, which may influence the study results, was not feasible.

References