Beneficial Impact of Preconditioning During PTCA on Creatine Kinase Release

Warren K. Laskey, MD

Background—Previous studies in humans have indicated that there is less ischemic dysfunction during PTCA when ischemic preconditioning is elicited. However, the clinical relevance of these observations remains unclear. The present study design tests the hypothesis that PTCA performed to elicit the preconditioning response would result in less myocardial necrosis as assessed by postprocedure creatine kinase (CK) levels.

Methods and Results—Patients (n=150) undergoing PTCA for unstable ischemic syndromes were randomly assigned to receive a previously validated approach to PTCA-mediated preconditioning (PC) or an unrestricted approach to balloon angioplasty (UC). CK levels were determined at 8, 12, and, if necessary, 24 hours. Clinical success rates were equivalent for the 2 groups. However, the frequency of any CK elevation was significantly higher in the UC group (25%) than in the PC group (7.1%) (P<0.005). Multivariable analysis confirmed a significant effect of preconditioning on CK release.

Conclusions—A standardized protocol to elicit preconditioning during PTCA results in a significant reduction in the rate of CK elevation in a high-risk population. These observations support the clinical relevance of ischemic preconditioning in humans. (Circulation. 1999;99:2085-2089.)

Key Words: ischemia ■ angioplasty ■ creatine kinase ■ balloon

A growing number of experimental and clinical studies have identified the ability of myocardial tissue to protect itself from lethal ischemia. The name given to this phenomenon, ischemic preconditioning, was originally taken from studies in which the extent of myocardial necrosis after coronary artery occlusion was limited when preceded by a brief period of ischemia and subsequent reperfusion.1 Since these seminal studies, inquiries into the mechanism(s) and mediator(s) of preconditioning have proliferated.2 Moreover, extension of these original observations to clinical contexts have proceeded in parallel. There is a growing body of data supporting the occurrence of preconditioning in humans under a variety of spontaneous3,4 and investigational circumstances.5–10 In the latter instance, however, surrogate markers of myocardial “protection” during PTCA, eg, ST-segment shift and clinical pain response, have been used as end points. The clinical relevance of these observations remains unclear.

Creatine kinase (CK) elevations after percutaneous coronary interventions have been reported.11 There is a growing awareness that elevation of this marker enzyme after coronary intervention has important prognostic significance11,12 and may be predictive of future events.12–14 The present study design tests the hypothesis that in a population of patients with unstable ischemic syndromes, PTCA performed in accordance with a standardized method of eliciting preconditioning would result in less CK elevation than would procedures performed without such an approach.

Methods

The study population consisted of 150 patients undergoing percutaneous coronary revascularization of a native coronary artery for a variety of unstable ischemic syndromes. Patients were randomly assigned (computer-generated code) to receive a previously validated sequence of balloon inflations that would elicit preconditioning (PC) or to an unrestricted approach to PTCA (UC). In all other respects, the remainder of the procedure was conducted at the discretion of the operator with respect to subsequent devices, use of adjunctive antithrombotic agents, and type of contrast media. All patients had determinations of creatine kinase (CK) blood levels at 8 and 12 hours after the procedure. In patients with elevated levels of either CK (normal range, 55 to 170 U/L in men, 30 to 135 U/L in women) or CK-MB (normal range, 0% to 3%) at 12 hours, repeat determinations at 24 hours were made.

The standardized protocol for inducing preconditioning during PTCA has been described4 and subsequently validated in additional populations.15,16 The protocol consists of a 90-second period of balloon occlusion of the target artery followed by a 5-minute period of reperfusion with the balloon withdrawn proximal to the lesion. A second 90-second period of balloon occlusion at the same inflation pressure is then performed. The ST segment response during these 2 periods of balloon occlusion is assessed from either the surface ECG or the intracoronary guidewire. An unrestricted approach to PTCA was defined as a single period of balloon occlusion for >1 minute (n=65) or multiple inflations of <60 seconds each without an intervening period of reperfusion (n=15).

Data Analysis

Summary data are represented as mean±SD for continuous variables and percentages for dichotomous variables. CK data were categorized as 1X<CK<2X, 2X<CK<5X, and CK>5X, where X is the...
upper limit of normal. Between-group comparisons were made with unpaired t tests or contingency tables. Multivariable logistic regression was performed to assess the independent contribution of clinical and procedural variables to the end point of any CK elevation. A value of $P < 0.05$ was considered statistically significant.

### Results

There were no significant differences (Table 1) in demographic, clinical, or angiographic features between patients in the preconditioning group (PC) and those in the usual-care (UC) group. Moreover, there were no differences between groups in the use of adjunctive IIb/IIIa platelet antagonists during the procedure (PC, 9%; UC, 11%; $P = NS$), use of ionic (I) versus nonionic (NI) contrast media (PC I/NI, 73%; UC I/NI, 70%; $P = NS$), or specific device used.

The overall clinical success rate (residual stenosis $\leq 50\%$ and the absence of death, in-laboratory myocardial infarction, or emergent bypass surgery) for the entire population was 94%. Therefore, by definition, there was a 6% major adverse event rate, which was equally distributed between groups (Table 2). There were too few individual major adverse events to allow for meaningful statistical analysis. Other periprocedural (in-laboratory and within 24 hours of the procedure) adverse events are recorded in Table 3. Again, there were too few events in each group to allow for meaningful comparison.

The overall rate of any CK elevation after percutaneous revascularization procedures in this population was 16% (25 of 150 patients), and the rate of any CK-MB elevation was 22%. All subsequent analyses, however, will be restricted to the patients with elevated total CK. The distribution of CK elevations is shown in Figure 1. Notably, only 3 of the 25 patients with an elevated CK had a $>5$-fold increase. As expected, there was a significant relationship between CK elevation and all adverse events ($P = 0.0001$) as well as major in-laboratory adverse events ($P = 0.04$).

There was a significant difference in the rate of any CK elevation between the PC and UC groups (Figure 2). CK elevations were detected in 7.1% of the PC patients and in 25% of the UC patients. This difference was highly significant ($P < 0.005$). The individual event rates within each group are shown in Table 4. For any level of CK elevation, the number of patients in the control group always exceeded the number of patients undergoing PC. Because of the limited size of the individual groups, meaningful statistical analysis is precluded.

The strength of the relationship between preconditioning and CK release is expressed in the univariate odds ratio of 0.23 (95% CI, 0.06 to 0.69; $P = 0.0034$). This relationship is preserved after adjustment for potential confounders. Multi-

### Table 1. Patient Population Characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>PC (n=70)</th>
<th>UC (n=80)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>61±9</td>
<td>59±9</td>
</tr>
<tr>
<td>Sex, % male</td>
<td>73</td>
<td>70</td>
</tr>
<tr>
<td>Clinical presentation, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Postinfarct angina</td>
<td>66</td>
<td>65</td>
</tr>
<tr>
<td>Unstable angina</td>
<td>34</td>
<td>35</td>
</tr>
<tr>
<td>Culprit vessel, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LAD</td>
<td>56</td>
<td>62</td>
</tr>
<tr>
<td>RCA</td>
<td>30</td>
<td>28</td>
</tr>
<tr>
<td>LCx</td>
<td>4</td>
<td>10</td>
</tr>
<tr>
<td>AHA/ACC class, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>38</td>
<td>41</td>
</tr>
<tr>
<td>B</td>
<td>45</td>
<td>40</td>
</tr>
<tr>
<td>C</td>
<td>17</td>
<td>19</td>
</tr>
<tr>
<td>Thrombus</td>
<td>20</td>
<td>25</td>
</tr>
<tr>
<td>Device, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>POBA</td>
<td>58</td>
<td>55</td>
</tr>
<tr>
<td>Stent</td>
<td>40</td>
<td>42</td>
</tr>
<tr>
<td>Atherectomy</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>

LAD indicates left anterior descending artery; RCA, right coronary artery; LCx, left circumflex artery; AHA, American Heart Association; ACC, American College of Cardiology; and POBA, balloon angioplasty.

### Table 2. Major Adverse Clinical Events

<table>
<thead>
<tr>
<th></th>
<th>PC, %</th>
<th>UC, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>In-laboratory MI</td>
<td>2 (3)</td>
<td>2 (2.5)</td>
</tr>
<tr>
<td>Emergent CABG</td>
<td>2 (3)</td>
<td>3 (3.7)</td>
</tr>
<tr>
<td>Any MACE</td>
<td>4 (6)</td>
<td>5 (6.2)</td>
</tr>
</tbody>
</table>

MI indicates myocardial infarction; MACE, major adverse clinical event.

### Table 3. Miscellaneous Adverse Events

<table>
<thead>
<tr>
<th></th>
<th>PC</th>
<th>UC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Significant dissection, n</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Side-branch occlusion, n</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Thromboembolism, n</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Urgent recatheterization, n</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Abrupt closure (&lt;24 h), n</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Total events, %</td>
<td>8 (11.4)</td>
<td>10 (12.5)</td>
</tr>
</tbody>
</table>

There were too few events in each group to allow for meaningful comparison.

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### Figure 1. Distribution of CK elevation among patients with abnormal postprocedure CK determinations (n=25). Of these, 52% exhibited mild elevation (1X<CK<2X), 36% exhibited modest elevation (2X<CK<5X), and 12% exhibited substantial elevation (CK>5X).
variable analysis of preprocedural and intraprocedural variables revealed only the PC group (odds ratio, 0.25; 95% CI, 0.04 to 0.70) and all adverse events (odds ratio, 1.6; 95% CI, 1.05 to 5.4) as significant predictors of any CK elevation.

**Discussion**

In this randomized, prospectively designed study, the use of a protocol designed to elicit preconditioning during PTCA resulted in clinically relevant cardioprotection. Specifically, the likelihood of postprocedure CK release was reduced by 77% in patients undergoing a standardized preconditioning protocol in comparison with patients not receiving this protocol. These findings are particularly relevant given that the study population consisted entirely of patients with unstable ischemic syndromes, who are at a high risk of ischemic complications.

A considerable literature on ischemic preconditioning consists of characterization of the phenomenon, generalizability across species, mechanisms and potential metabolic pathways, modes of induction, and applicability to humans. With respect to the latter, there is ongoing controversy with respect to the phenomenon itself and its clinical relevance. Controversy surrounding the mechanism of cardioprotection conferred by sequential periods of brief ischemia separated by a period of reperfusion has engendered considerable discussion. A role for collateral blood flow enhancement during PTCA-mediated preconditioning has been adduced, although the majority of published studies support a collateral independent mechanism. Indirect evidence of the clinical relevance of PC exists in studies performed during PTCA in which ECG and metabolic markers of myocardial ischemia were diminished with preconditioning. Estimates of infarct size and clinical outcome in retrospective analyses of thrombolytic trials were improved in the setting of antecedent angina. More direct evidence exists in studies performed during open-heart surgery, in which markers of lessened ischemia and membrane integrity were observed in hearts subjected to a preconditioning stimulus. However, clinical outcomes were not reported.

Percutaneous revascularization procedures have been associated with markers of myocardial necrosis, particularly in high-risk settings. Notably, even in the absence of major intraprocedural or periprocedural adverse events, there appears to be a relationship between detectability of these markers and intermediate and long-term clinical outcome. Although the strength of this relationship is somewhat controversial, the significance of these observations is of great interest. Clearly, pharmacological or procedural strategies designed to minimize these perturbations may translate into improved clinical outcomes during percutaneous revascularization. In the present study, a simple, previously validated protocol designed to elicit the preconditioning response resulted in a lower frequency of CK release in a population at significant risk of CK release. Whether such a beneficial effect on CK release translates into improved long-term clinical outcome is as yet unanswered. It is of interest that preconditioning was not associated with fewer (major or minor) periprocedural adverse events ($P=0.1$), although the event rates were low in both groups. It is also important to note that of the 70 patients in the PC arm, 65 manifested either lessened pain and/or ST-segment shift during sequential balloon occlusion. Analysis confined to these patients yields conclusions identical to those reported above.

The mechanism whereby preconditioning exerts a beneficial effect on procedure-related CK elevation cannot be answered by this type of study. The results reported here, however, are entirely consistent with the form of myocardial protection associated with experimental and clinically observed preconditioning. The time course for the induction of ischemic preconditioning observed during PTCA has been well characterized. It has been noted that a minimum of 60 to
90 seconds of initial balloon occlusion is necessary to demonstrate lessened ischemia during subsequent occlusion. Furthermore, the necessity for a sufficient intervening period of reperfusion is critical. The distribution of initial balloon occlusion times in the UC group is shown in Figure 3. The mean occlusion time was 3.3 ± 1.2 minutes in the group overall and 3.6 ± 0.8 minutes in the 65 patients with an occlusion >1 minute. Thus, the UC group sustained a period of total occlusion time comparable to that in the PC group. The fact that CK elevation was more frequent in the UC group than the PC group, given the similarity in overall total ischemic duration, provides additional support for the induction of preconditioning with sequential 90-second occlusions.

It is important to point out that previous studies have reported CK elevation in the absence of clinically evident periprocedural adverse events. Thus, it would appear that the adverse prognosis associated with CK release during coronary intervention may be independent of procedural mishaps. In the present study, there was a relationship between CK elevation and adverse events, although no relationship exists between preconditioning and adverse events. Although the failure to detect a relationship between preconditioning and adverse events may be the result of the small number of events, the acute (beneficial) effects of preconditioning on CK elevation may be the result of a true effect on adverse periprocedural events and/or a more fundamental cardioprotective effect.

This study was conducted in a population of patients with unstable ischemic syndromes. Such patients are known to be at high risk of ischemic complications during percutaneous intervention. No patient had elevated CK levels at baseline. The frequency of overall (any) CK elevation is within the range of previous reports, although the frequency of substantial elevations (>5 times normal) was surprisingly low. This may reflect the underrepresentation of various atherectomy modalities, the exclusion of saphenous vein graft interventions from the study, differences in patient population, or differences in procedural conduct. The protocol used for the induction of preconditioning, however, precludes the initial use of atherectomy devices. In addition, the use of intracoronary stents to minimize ischemic sequelae in high-risk situations also may contribute to a lower than expected adverse event rate. However, the frequencies of clinical, demographic, and anatomic correlates of procedural complications, including CK release, were equally distributed between the groups. Both univariate and multivariable analysis confirmed the potent influence of preconditioning on CK release and lend further support to the clinical relevance of preconditioning.

In summary, a standardized protocol of inducing preconditioning during PTCA resulted in a significant reduction in the rate of CK elevation in a high-risk population. Given the increasing evidence for such elevations as markers of altered medium- and long-term prognosis, the ability to favorably alter the rate of enzyme release provides important support for the clinical relevance of preconditioning. Studies designed to examine differences in clinical outcomes during long-term follow-up are in order.

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References


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