Conclusions—The occurrence of preinfarction angina is associated with significant myocardial protection in the setting against a subsequent episode of prolonged ischemia. With preinfarction angina, larger trials showed no protective benefit of this phenomenon translates to patients undergoing primary percutaneous coronary intervention (PCI). Whereas randomized evidence for the benefits of preinfarction angina in the setting of primary percutaneous coronary intervention with stenting is inconclusive because of the greater achievement of infarct artery patency and speed of reperfusion.

Methods and Results—To identify a homogeneous population, we performed a retrospective analysis of 1031 patients admitted with a first ST-elevation myocardial infarction with ischemic times between 1 and 6 hours who received primary percutaneous coronary intervention. We identified 245 patients who had occluded arteries on presentation, of which 79 patients had documented preinfarction angina defined as chest pain within 24 hours of infarction. Infarct size was measured as the peak creatine kinase level, a metric supported in a subgroup by late enhancement on cardiac magnetic resonance imaging. Patients with preinfarction angina (n=79) had a 50% reduction in infarct size compared with those patients without preinfarction angina (n=166) by both peak creatine kinase (1094±75 IU/L versus 2270±102 IU/L; P<0.0001) and creatine kinase area under curve (18 420±18 941 versus 36 810±21 741 IU/h per liter; P<0.0001) despite having identical ischemic times (185±8 minutes versus 181±5 minutes; P=0.67) and angiographic area at risk (24.1±1.2% versus 25.3±0.9%; P=0.43). There was an absolute 4% improvement in left ventricular ejection fraction before discharge in those patients with preinfarction angina (P<0.02).

Conclusions—The occurrence of preinfarction angina is associated with significant myocardial protection in the setting of primary percutaneous coronary intervention with stenting during ST-elevation myocardial infarction. Because preinfarction angina is relatively common, it is important that these patients be identified in clinical trials investigating therapies designed to reduce reperfusion injury and infarct size. (Circ Cardiovasc Interv. 2013;6:52-58.)

Key Words: angina ■ myocardial infarction ■ reperfusion ■ stents

Ischemic preconditioning (IP) is the phenomenon by which transient episodes of ischemia protect the myocardium against a subsequent episode of prolonged ischemia.1 IP represents the most potent form of myocardial protection yet discovered. In humans, angina pectoris preceding myocardial infarction is thought to represent a clinical correlate of ischemic preconditioning. Multiple studies have shown that preinfarction angina before ST-elevation myocardial infarction (STEMI) limits infarct size, improves left ventricular function, and enhances survival.2-5 However, the majority of these studies were performed when reperfusion was achieved with thrombolysis.2-7 To date, significant uncertainty remains regarding whether the benefit of this phenomenon translates to patients undergoing primary percutaneous coronary intervention (PCI). Whereas 1 small study demonstrated decreased infarct size in patients with preinfarction angina,8 2 larger trials showed no protective effect in the setting of primary PCI with angioplasty alone or in conjunction with stenting.9,10 However, confounding factors that affect infarct size such as collateral blood flow and accurate measurements of ischemic time and myocardial area at risk (AAR) were not accounted for in these trials. Thus, the true benefit of preinfarction angina in the primary PCI era remains unclear. To clarify if preinfarction angina reduces infarct size after a well-defined duration of myocardial ischemia, we analyzed its protective effect in 245 patients with well-defined ischemic times who presented with an occluded coronary artery during primary PCI in the setting of STEMI.

Methods

Study Design
A retrospective analysis was performed on all patients who were admitted to the Minneapolis Heart Institute at Abbott Northwestern...
WHAT IS KNOWN

- Chest pain in the 24 hours before myocardial infarction, called preinfarction angina, is common.
- Preinfarction angina is thought to reduce infarct size by a preconditioning mechanism.
- In the thrombolytic era, preinfarction angina was shown to limit infarct size and to improve left ventricular function and survival.
- It is not known if preinfarction angina remains protective in the era of primary percutaneous coronary intervention, when reperfusion can be achieved more quickly.

WHAT THE STUDY ADDS

- This article is the largest cohort to date to examine the effect preinfarction angina in patients with ST-elevation myocardial infarction in the setting of primary percutaneous coronary intervention with well-defined ischemic times and angiographic areas at risk.
- The occurrence of preinfarction resulted in a 50% reduction in infarct size compared with patients without preinfarction angina despite having similar ischemic times and areas at risk.
- Patients with preinfarction angina had improved ejection fractions at discharge compared with those patients without preinfarction angina.

Hospital from January 2006 through September 2010 as part of the level 1 acute myocardial infarction program.12 This is a regionalized transfer network developed for primary PCI involving 31 community hospitals and emergency departments throughout Minnesota and Western Wisconsin. Patients were enrolled in a prospective registry with detailed baseline clinical, time to treatment, laboratory, angiographic, and follow-up data.

A total of 1031 patients were identified in the level 1 program database who presented with STEMI and had well-defined ischemic times and angiographic areas at risk.13 Patients were excluded from further analysis because they had one or more of the following exclusion criteria: thrombolysis by 1.75 mg/kg per hour) and underwent routine primary PCI and drug-eluting stents.

Comparison of infarct size, ischemic times, AAR, and LVEF was performed by 2-tailed Student t test. P<0.05 was considered statistically significant. Pearson correlation coefficient was used to determine the relationship between ischemic time and peak CK. A 2-tailed P<0.05 was considered statistically significant. Quantile–quantile plot was constructed by calculating the quantiles of the preinfarction angina (PIA) population and plotting the corresponding ejection fraction and CK values on the x axis of the respective graphs. The y axis shows the ejection fraction and CK values of the non-PIA population. Graph Pad Prism was used for all statistical calculations.

### Measurement of Infarct Size

The peak creatine kinase (CK) level was used as a surrogate of infarct size as previously validated by us13 and others14,15 using delayed enhancement measurements with cardiac magnetic resonance imaging. Measurements of CK were performed on presentation and every 6 to 8 hours for 24 to 48 hours after reperfusion with the highest value designated as the peak CK. Measurement of left ventricular ejection fraction (LVEF) by echocardiography was obtained in 220 patients within 48 hours after reperfusion. Confirmatory measurements of infarct size difference between groups also was performed by measuring the CK area under curve.

### Measurement of the AAR

The angiographic AAR was calculated for each patient using the modified Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease (APPROACH) score.16 This method is based on previous pathological studies estimating the percentage of myocardium perfused by each coronary artery. For each patient, an AAR score, expressed as percentage of myocardium, was calculated based on the location of the culprit lesion in the infarct artery (proximal, mid, distal) in relation to major side branches and dominance of the vessel. This method has been previously validated by magnetic resonance imaging measurements of AAR by us13 and others.17

### Statistical Analysis

Comparison of infarct size, ischemic times, AAR, and LVEF was performed by 2-tailed Student t test. P<0.05 was considered statistically significant. Pearson correlation coefficient was used to determine the relationship between ischemic time and peak CK. A 2-tailed P<0.05 was considered statistically significant. Quantile–quantile plot was constructed by calculating the quantiles of the preinfarction angina (PIA) population and plotting the corresponding ejection fraction and CK values on the x axis of the respective graphs. The y axis shows the ejection fraction and CK values of the same quantiles in the non-PIA population. Graph Pad Prism was used for all statistical calculations.
Results

Baseline Characteristics

Preinfarction angina within 24 hours of admission was present in 79 patients and absent in 166 patients. As summarized in the Table, there were no significant differences in terms of age, sex, body mass index, ischemic time, and classical risk factors for coronary artery disease.

Primary PCI Characteristics

There were no differences between the 2 groups regarding fluoroscopy time, contrast use, and number of stents delivered. A similar number of patients in both groups received glycoprotein IIb/IIIa receptor antagonists and aspiration thrombectomy (Table).

Infarct Size, Ischemic Times, and Angiographic AAR

Infarct size was significantly lower in patients with preinfarction angina compared with those without (1094±75 IU/L versus 2270±102 IU/L; P<0.0001; Figure 2A). Similar results were obtained when peak troponin T was used as a marker for myocardial damage (4.2±0.4 ng/mL versus 6.7±0.4 ng/mL; P<0.0001; Figure 2B). CK area under the curve was significantly reduced in the patients with preinfarction angina (18 420±18 941 versus 36 810±21 741 IU/h per liter; P<0.0001; Table). Ischemic times were similar between the 2 groups (185±8 minutes versus 181±5 minutes; P=0.67; Figure 3), and no difference in the AAR was observed between patients with and without preinfarction angina (24.1±1.2% versus 25.3±0.9%; P=0.43; Figure 4).

Table. Patient Demographics

<table>
<thead>
<tr>
<th></th>
<th>No Preinfarction Angina (n=166)</th>
<th>Preinfarction Angina (n=79)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y, mean, SD</td>
<td>58.9±12.5</td>
<td>60.7±12.7</td>
<td>0.31</td>
</tr>
<tr>
<td>Males (%)</td>
<td>133 (80.1)</td>
<td>59 (74.7)</td>
<td>0.33</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>79 (47.6)</td>
<td>39 (50.0)</td>
<td>0.73</td>
</tr>
<tr>
<td>Dyslipidemia (%)</td>
<td>83 (50.9)</td>
<td>39 (49.4)</td>
<td>0.82</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>22 (13.3)</td>
<td>10 (12.7)</td>
<td>0.90</td>
</tr>
<tr>
<td>Culprit artery</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LAD (%)</td>
<td>65 (39.2)</td>
<td>32 (40.5)</td>
<td>0.69</td>
</tr>
<tr>
<td>RCA (%)</td>
<td>73 (44.0)</td>
<td>37 (46.8)</td>
<td></td>
</tr>
<tr>
<td>LCx (%)</td>
<td>28 (16.9)</td>
<td>10 (12.7)</td>
<td></td>
</tr>
<tr>
<td>Killip class</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0/1 (%)</td>
<td>149 (89.8)</td>
<td>74 (93.7)</td>
<td>0.65</td>
</tr>
<tr>
<td>2/4 (%)</td>
<td>17 (10.2)</td>
<td>5 (6.3)</td>
<td></td>
</tr>
<tr>
<td>CK AUC, IU/h per L</td>
<td>36 810±21 741</td>
<td>18 420±18 941</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Time-to-peak CK after reperfusion, min</td>
<td>550±29</td>
<td>581±42</td>
<td>0.54</td>
</tr>
<tr>
<td>N of stents placed</td>
<td>1.4±0.1</td>
<td>1.5±0.1</td>
<td>0.58</td>
</tr>
<tr>
<td>Fluoroscopy time, min</td>
<td>11.9±0.6</td>
<td>11.9±1.0</td>
<td>0.97</td>
</tr>
<tr>
<td>Contrast use, mL</td>
<td>168±4</td>
<td>164±7</td>
<td>0.64</td>
</tr>
<tr>
<td>Bivalirudin, %</td>
<td>10.6±2</td>
<td>15.6±4</td>
<td>0.28</td>
</tr>
<tr>
<td>GP IIb/IIIa, %</td>
<td>78.1±3.3</td>
<td>77.9±4.7</td>
<td>0.97</td>
</tr>
<tr>
<td>Aspiration thrombectomy, %</td>
<td>38.1±3.9</td>
<td>43.6±5.7</td>
<td>0.42</td>
</tr>
</tbody>
</table>

Baseline characteristics of patients who had preinfarction angina before STEMI compared with patients without preinfarction angina. AUC indicates area under the curve; CK, creatine kinase; GP, glycoprotein; LAD, left-anterior descending; LCx, circumflex; RCA, right coronary artery; and STEMI, ST-elevation myocardial infarction.

Figure 2. Peak creatine kinase (CK) and peak Troponin I according to the presence or absence of preinfarction angina. Peak CK (A) and peak Troponin I (B) were plotted according to the presence or absence of preinfarction angina. Mean peak CK, indicated by horizontal line, is significantly different in patients with and without preinfarction angina 1094±75 IU/L versus 2270±102 IU/L (P<0.0001; Student t test). Mean peak Troponin I was 4.2±0.4 ng/mL vs 6.7±0.4 ng/mL (P<0.0001).
We investigated if the significant difference in infarct size in patients with and without preinfarction angina was associated with a significant difference in left ventricular function. A total of 220 patients had measurements of LVEF obtained within 2 days of STEMI. Ejection fraction was 4% higher in patients with preinfarction angina (51.4±1.1%; median, 55%; interquartile range, 45%–60%) compared with patients without (47.5±1.0%; median, 50%; interquartile range, 40%–57.5%; P<0.02; Figures 5 and 6).

To determine if PIA acts to limit large infarctions, we compared the 2 populations using a quantile-quantile plot of the peak CK values and LVEF. Data points on the CK plot follow a straight line with a slope >1. This suggests that the 2 populations have a similar distribution and differ in scale only. It indicates that the protective effect of PIA is present regardless of infarct size. The LVEF curve also is straight except for the bottom left of the curve, where the slope is greater. This suggests that the distribution of the LVEF in the non-PIA population is skewed to the left, showing a comparatively larger number of patients with low ejection fraction (Figure II in the online-only Data Supplement).

Protective Effect of Preinfarction Angina Is Dependent on Ischemic Time

Previous studies showed improved clinical outcome in patients with preinfarction angina only if reperfusion by thrombolysis occurred after 2 hours of chest pain, whereas no beneficial effect was seen in early reperfusion. We therefore investigated if a similar time dependence of the protective effect of preinfarction angina in patients treated with PCI could be seen. We plotted ischemic time against peak CK and performed linear regression. In patients without preinfarction angina, we observed a linear increase in infarct size with increasing ischemic time (r=0.35; P<0.0001; Figure 7A). In contrast, patients with preinfarction angina demonstrated no correlation between ischemic time and peak CK within 6 hours of ischemia (r=0.07; P=0.53; Figure 7B). This suggests that the protection potentially conferred by preinfarction angina may extend for at least 6 hours of ischemia and becomes more protective with increasing ischemic times.

Discussion

Our results suggest that preinfarction angina is associated with significant myocardial protection in the setting of primary PCI for STEMI. Multiple mechanisms have been proposed to account for these protective effects, including accelerated thrombolysis,18 opening of pre-existing collateral vessels,19 reduced microvascular obstruction,20 and a myocardial conditioning effect similar to IP. Several clinical studies have demonstrated significant cardioprotective effects of preinfarction angina in the setting of thrombolytic therapy, including reduced infarct size2–7,9,21 and improved short-term and long-term mortality.22 In contrast,
its beneficial effect in patients treated with primary PCI with and without stenting has been inconclusive. A small prospective study by Ottani et al in 22 patients with anterior STEMI undergoing primary PCI with stenting demonstrated that the occurrence of angina within 24 hours of infarction significantly reduced infarct size and improved myocardial salvage by 32%, which translated into an 8% improvement in LVEF at 6 months. Kosuge et al presented data from the Japan Acute Coronary Syndrome Study in 913 patients with STEMI undergoing primary PCI (78% stenting) with ischemic times up to 12 hours. Preinfarction angina described as <30 minutes of chest pain within 24 hours of myocardial infarction was observed in 358 patients (39%). Patients with preinfarction angina and anterior STEMIIs had significant reductions in infarct size and improved mortality compared with those without preinfarction angina. However, 2 other studies observed no clinical benefit of preinfarction angina. Zahn et al analyzed 774 patients STEMI from the German Myocardial Infarction Registry treated with primary PCI without stenting who had ischemic durations of up to 12 hours. Preinfarction angina was defined as any episode of chest pain within 4 weeks of infarction occurred in 69% of all patients. They observed no clinical benefit of preinfarction angina regarding mortality or development of heart failure, suggesting that its benefit was potentially overshadowed in the setting of primary angioplasty because of the much greater achievement of rapid reperfusion compared with thrombolytic therapy. Tomoda and Aoki presented data from 613 STEMI patients with up to 12 hours of ischemia treated with thrombolysis or medical therapy alone (group 1, n=306) or primary PCI (group 2, n=307). In patients with preinfarction angina, defined as chest pain within 24 hours of infarction, only those patients with preinfarction angina in group 1 demonstrated significant reductions in peak CK and development of heart failure, whereas there was no additional benefit observed in group 2 patients that had preinfarction angina.

In contrast, in a homogeneous population with similar ischemic times and myocardial AAR, we observed >50% reduction in infarct size associated with patients with preinfarction angina who underwent primary PCI, suggesting a powerful myocardial protective effect of this correlate of IP. It is likely that patient selection and study design in previous studies significantly contributed to the inconsistent benefits of preinfarction angina. Our highly selected patient cohort was chosen by design to determine more accurately the benefits of preinfarction angina on infarct size reduction in STEMI. To achieve this, we excluded patients with previous myocardial infarction, infarct artery patency before PCI (thrombolysis in myocardial infarction >0), or visible collateral blood flow to the infarct region. Importantly, this potent infarct-sparing mechanism was never accounted for in any of the other trials with the exception of the small study by Ottani et al. Ischemic duration was further limited to 6 hours, because the benefit of IP may be lost with prolonged ischemic duration. Using these selection criteria, we observed a linear increase in infarct size with ischemic duration in the control group that was abrogated in those patients with preinfarction angina (Figure 6).

These observations may have implications for studies investigating novel therapies to reduce reperfusion injury and infarct size in the setting of STEMI. It is remarkable that preinfarction angina is rarely accounted for in clinical trials despite its high prevalence, which may exceed 50% of all patients presenting with STEMI in some trials. This could contribute to the largely negative outcomes of clinical trials in this area, despite encouraging preclinical data in animals.

Whereas eventual reperfusion is essential for the protective effect of preinfarction angina, the time course is less
The finding that the time-to-peak CK was similar between the 2 groups argues against this possibility. However, the only way to exclude this completely would be to have patients undergo continuous ST-segment monitoring during STEMI, which was not feasible in this study. We did not include patients with short ischemic times (<2 hours) because the relationship with infarct size in patients with PIA may reflect difficulty in establishing the true ischemic time as much as a physiological effect.

Conclusions
This study represents the most detailed analysis to date describing the potential myocardial protective effects of preinfarction angina in patients with STEMI undergoing primary PCI with stenting. These findings may have implications for clinical trials investigating agents designed to reduce reperfusion injury and infarct size. Because preinfarction angina is relatively common and may result in significant myocardial protection, it is imperative for patients with preinfarction angina to be identified in clinical trials.

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Disclosures
None.

References
pectoris on outcome in patients with acute myocardial infarction treated with primary angioplasty (results from the Myocardial Infarction Registry. Am J Cardiol. 2001;87:1–6.


Preinfarction Angina Reduces Infarct Size in ST-Elevation Myocardial Infarction Treated With Percutaneous Coronary Intervention
Ronald Reiter, Timothy D. Henry and Jay H. Traverse

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Supplemental Material

Supplemental Figure 1

Peak CK is highly correlated with infarct size measured by cardiac MRI: Infarct size was measured by cMRI (n=45), expressed as % of total myocardium and plotted against peak CK. Correlation is highly significant (r=0.76, p<0.0001) From Reiter et al. Circ Res 2012;110:105-110.
Supplemental Figure 2

Medians and Interquartile ranges for LVEF (%) and peak CK (IU/L) and Ischemic time (min) in patients with and Without pre-infarction angina.
Supplemental Figure 3

Q-Q plot of LVEF and peak CK in patients with pre-infarction angina versus patients without pre-infarction angina.