Prospective Study Correlating Fibrinopeptide A, Troponin I, Myoglobin, and Myosin Light Chain Levels With Early and Late Ischemic Events in Consecutive Patients Presenting to the Emergency Department With Chest Pain

Ali Sonel, MD; Brett M. Sasseen, MD; Naomi Fineberg, PhD; Nils Bang, MD; Robert L. Wilensky, MD

Background—Although thrombus formation plays a major role in acute coronary syndromes, few studies have evaluated a thrombus marker in risk stratification of patients with chest pain. Furthermore, the relation between markers that reflect myocardial injury and thrombus formation that may predict events in a heterogeneous patient population is unknown. This study correlated markers of thrombus and myocardial injury with early and late ischemic events in consecutive patients with chest pain.

Methods and Results—Serum troponin I (TnI), myoglobin, and myosin light chain levels were obtained from 247 patients and urinary fibrinopeptide A (FPA) from 178 of the 247. By multivariate analysis, patients with an elevated FPA level were 4.82 times more likely to die or have myocardial infarction, unstable angina, and coronary revascularization at 1 week (P<0.002, 95% CI 1.78, 13.03), whereas those with an elevated TnI (>0.2 ng/mL) were 9.41 times more likely (P<0.001, 95% CI 2.84, 31.17). At 6 months (excluding the index event), an elevated FPA level was an independent predictor of events, with an odds ratio of 9.57 (P<0.001, CI 3.29, 27.8), and was the only marker to predict a shorter event-free survival (P<0.001). The other markers did not independently correlate with cardiac events, although MLC incrementally increased early predictive accuracy in combination with the FPA and TnI.

Conclusions—Elevated FPA and TnI correlated with cardiac events during the initial week in patients presenting to the Emergency Department with chest pain. FPA predicted adverse events and a shorter event-free survival at 6 months. (Circulation. 2000;102:1107-1113.)

Key Words: myoglobin ■ myosin light chain ■ ischemia

A rupture or erosion of an atherosclerotic plaque with ensuing intracoronary thrombus often results in an acute coronary syndrome. The extent and duration of thrombus and subsequent myocardial injury determines whether a patient has unstable angina (UA) or a myocardial infarction (MI), and so the early clinical differentiation from noncardiac causes of chest pain is often difficult. Most patients with presumed acute coronary syndromes are admitted for observation until the cause has been elucidated. Despite this strategy, some patients are inappropriately discharged from the Emergency Department.1

Although thrombus plays an important role in acute coronary syndromes, there have been no prospective studies evaluating a marker of in vivo thrombosis to predict future ischemic events. Elevations in myocardial injury markers, such as troponin I (TnI) and T, myoglobin (Myo), and myosin light chain (MLC), reflect sustained ischemic insult and are associated with adverse clinical ischemic events.2–6 However, the results may not apply to a heterogeneous population presenting with chest pain of uncertain cause. This study was designed to evaluate the utility of urinary fibrinopeptide A (FPA), a marker of thrombin activity, in a general population of chest pain patients presenting to the Emergency Department. FPA levels were compared with TnI, Myo, and MLC levels to evaluate the use of these markers in predicting adverse clinical events during the initial week and the subsequent 6-month follow-up. FPA was evaluated because elevated levels predict angiographic intracoronary thrombus formation in patients with acute coronary syndromes.7,8

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From the University of Pennsylvania (B.M.S., R.L.W.), University of Pittsburgh, and the Pittsburgh VA Health System (A.S.), Pittsburgh, Pa, and Indiana University Medical Center, Indianapolis, Ind (N.F., N.B.).


Correspondence to Robert L. Wilensky, MD, Hospital of the University of Pennsylvania, 3400 Spruce St, Philadelphia, PA 19104. E-mail rwilensk@mail.med.upenn.edu

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Methods
This was a prospective, single-center observational study of 247 consecutively enrolled patients who presented to the Emergency Department with chest pain. Patients admitted and those discharged from the Emergency Department were included if they were >21 years and presented with precardial chest pain or shortness of breath within the previous 24 hours. Patients were excluded if determined to have a noncardiac cause. All patients provided informed consent, and the Institutional Review Board of the Indiana University approved the study.

Treatment decisions and patient disposition were not influenced by enrollment into the study. A 12-lead ECG was obtained at presentation (0 hours), 4 hours later, and for recurrent chest pain. Blood specimens for creatine kinase (CK) and CK-MB% were obtained at 0, 8, 16, and 24 hours. TnI, Myo, and MLC samples were obtained at 0, 4, and 8 hours and FPA samples at 0 and 4 hours. The initial FPA sample was obtained before heparin administration.

Clinical Definitions
Major adverse clinical events (MACE) were death, nonfatal MI, UA, or a revascularization procedure performed for recurrent ischemia. An MI was diagnosed with ≥2 of the following criteria: (1) ischemic pain lasting ≥30 minutes, (2) a rise and fall of CK and MB% with ≥1 value >2 times the upper limits of normal, and (3) acute ischemia or the new development of a left bundle-branch block on ECG. Unstable angina was diagnosed according to the National Heart, Lung, and Blood Institute guidelines. Noncardiac chest pain was diagnosed in those patients without a MI or UA and a subsequent negative stress test or cardiac catheterization. Coronary revascularization was performed to treat ischemic symptoms only for stenosis ≥70% in severity or left main coronary artery stenosis of >50%. Investigators blinded to the marker results determined end points. Events at 1 week included admission-related events, whereas the 6-month event rate only included events between the 1st week and the 6-month follow-up, excluding the index event.

Patients released from the Emergency Department returned within 72 hours for a history and physical examination, ECG, and CK-MB and LDH isoenzymes determination. Patients then underwent appropriate testing to document coronary artery disease. Additional follow-up was obtained 6 months after presentation. All patients were questioned about recurrent chest pain or a subsequent hospital admission, and hospital databases were reviewed. No patient was admitted to another hospital during the study period.

Samples for TnI, Myo, and MLC were obtained in serum separator tubes, immediately centrifuged, and stored at −70°C. Urine for FPA analysis was stored and analyzed as previously described. The upper limit of normal for FPA, 3.2 ng/mg creatinine, was the mean plus 2 SD determined from 25 healthy volunteer samples. FPA was normalized to the urine creatinine level to adjust for renal function and hydration state. The assay for TnI determinations was a 2-site enzyme immunoassay (Spectral Diagnostics), with the upper reference limit 0.20 ng/mL. Myoglobin levels were analyzed with the Dade Stratus II Immunoassay (Dade International, Inc.). MLC levels were analyzed with a quantitative 2-antibody ELISA assay. The upper reference limit for Myo was 100 μg/mL and for MLC 1 μg/mL.

Continuous variables between the 3 clinical groups were compared by means of ANOVA with Tukey’s honestly significant differences test for multiple comparisons. Discrete variables were compared by means of Fisher’s exact test. Comparisons between subjects with and without events used the Student’s t tests and Fisher’s exact test. Odds ratios and 95% confidence intervals were calculated with univariate logistic regression. A multivariate logistic regression model was used to determine the relation between abnormal markers and the occurrence of events after correcting for other significant predictors. Variables with univariate significance levels of <0.10 were considered in a forward stepwise logistic regression analysis. A log rank test was used to compare survival curves for discrete variables and a Cox regression analysis was used to analyze the effect on survival of continuous predictor variables.

Any calculations evaluating FPA used patients with urine samples only. Values reported represent the highest value obtained. Any 2-tailed value of P<0.05 was considered significant.

Results
Of the 247 sampled patients, 30 were diagnosed with an acute MI, 107 with UA, and 110 with noncardiac chest pain (Table 1). Patients with noncardiac symptoms were younger (P=0.005), whereas patients with UA were more likely to have established coronary artery disease (P<0.001). Patients who had a MI or UA were more likely to have diabetes, hypertension, or hyperlipidemia (P=0.01).

In the initial week, 137 patients had 187 events (Table 2). All events occurred in patients with MI and UA, reflecting, in part, the distribution of index events. Thirteen patients discharged from the Emergency Department had episodes of unstable angina. Six-month clinical follow-up was available for 244 patients (98.8%), of whom 68 (28%) had 102 adverse events.

Sixty-nine of the 247 patients (28%) could not provide a urine sample at presentation and so 178 patients had results of all 4 markers. A single patient (0.04%) had results from only 2 markers. The event rates of patients with and without FPA measurements did not differ at 1 week (P=0.260) or 6 months (P=0.272).

At least 1 marker was elevated in 73% of MI patients, 68% of the UA patients, and in 44% of patients in the noncardiac group. In the MI group, 5 patients (16.6%) had all 4 positive markers. No other patient demonstrated elevations of all markers. A scatterplot demonstrating highest marker levels is shown in the Figure. The mean peak FPA and TnI levels were higher in the MI groups than the UA groups, which was also higher than the noncardiac chest pain group. The mean peak Myo values in the MI and unstable angina groups were greater than the noncardiac chest pain group, whereas MLC peak values were not significantly different among the 3 groups.

Patients with an elevated FPA level had a significantly greater incidence of adverse events within the first week (Table 3). The odds ratio of any MACE in a patient with an elevated FPA level was 2.75 (P=0.005, 95% CI 1.35, 5.6). By multivariate analysis, after adjusting for age, race, history of coronary artery disease, cardiac risk factors, peripheral vascular disease, use of β-blockers, ACE-I inhibitors or aspirin, ECG changes, and elevations in any of the other markers, patients with an elevated FPA level had a 4.82 times greater likelihood of having an adverse event during the initial week (P<0.002, 95% CI 1.78, 13.03). At the 6-month follow-up, patients with an elevated FPA level had significantly more cardiac events than those with normal levels (Table 3), with the univariate odds ratio 4.85 (P<0.001, 95% CI 2.34, 10.05). By multivariate analysis, the odds ratio was 9.57 (P<0.001, 95% CI 3.29, 27.8).

Patients with an elevated TnI level had a significantly greater incidence of cardiac events within 1 week, with a MACE odds ratio of 4.89 (P<0.001, 95% CI 2.33, 10.27). By multivariate analysis, patients with an abnormal TnI level were 9.41 times more likely to have an adverse event (P<0.001, 95% CI 2.84, 31.17). At 6 months, the odds ratio of any MACE was 1.88.
(P=0.052, 95% CI 0.995, 3.56). By multivariate analysis, an elevated TnI was not an independent predictor of MACE.

Patients with an elevated Myo level had a higher MACE rate (odds ratio 2.47, P=0.004, 95% CI 1.33, 4.6). In the first week, those patients with an abnormal MLC level had a greater MACE rate (odds ratio 2.02, P=0.008, 95% CI 1.2, 3.41). By multivariate analysis, neither Myo or MLC was a significant predictor of adverse outcomes at 1 week or 6 months.

Table 4 shows the sensitivity, specificity, and predictive values of the markers in predicting major adverse clinical events. MLC demonstrated the highest sensitivity but the lowest specificity. TnI had the highest positive predictive value (PPV). During the 6 months follow-up period, FPA had the highest sensitivity in detecting events (51%) and the highest PPV and NPPV, whereas FPA, TnI, and Myo had similar specificities. The combination of markers increased the predictive accuracy at 1 week and 6 months (Table 5).

**Table 1. Patient Demographics**

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>Total</th>
<th>Myocardial Infarction (n=30)</th>
<th>Unstable Angina (n=107)</th>
<th>Noncardiac Chest Pain (n=110)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, y</td>
<td>56.3±13.6</td>
<td>54.4±13.4</td>
<td>49.4±12.6</td>
<td>0.005</td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>60% (18)</td>
<td>57.9% (62)</td>
<td>48.2% (53)</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>66.7% (20)</td>
<td>70.1% (75)</td>
<td>60.0% (66)</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Known CAD</td>
<td>33.3% (10)</td>
<td>54.2% (58)</td>
<td>13.6% (15)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

**Risk factors**

- Diabetes mellitus: 36.7% (11) 34.6% (37) 17.3% (19) 0.011
- Tobacco: 83.3% (25) 70.1% (75) 67.3% (74) NS
- Hypertension: 66.7% (20) 67.3% (72) 50.0% (55) 0.014
- Hyperlipidemia: 60.0% (18) 64.5% (69) 46.4% (51) 0.014
- Family history: 46.7% (14) 39.3% (42) 46.4% (51) NS

**Other factors**

- Cocaine use: 0% (0) 2.8% (3) 11.8% (13) 0.009
- Peripheral vascular disease: 10.0% (3) 12.0% (13) 2.7% (3) NS

**Medications**

- β-Blocker: 70.0% (21) 46.7% (50) 15.5% (17) <0.001
- ACE-I: 56.7% (17) 37.3% (40) 27.3% (30) 0.008
- Aspirin: 78.7% (23) 75.7% (81) 53.6% (59) 0.001
- Warfarin: 6.7% (2) 10.2% (11) 7.3% (8) NS

**Disposition**

- Admitted: 96.7% (29) 87.8% (94) 54.5% (60) ...
- ED discharge: 3.3% (1) 12.2% (13) 45.5% (50) ...

**CAD** indicates coronary artery disease; ED, Emergency Department. Values are percentage of patients (n) unless otherwise indicated.

**Table 2. Clinical Events**

<table>
<thead>
<tr>
<th>1 wk</th>
<th>Myocardial Infarction</th>
<th>Unstable Angina</th>
<th>Noncardiac Chest Pain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>30</td>
<td>107</td>
<td>110</td>
</tr>
<tr>
<td>Death</td>
<td>0 (0%)</td>
<td>2 (1.9%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>MI</td>
<td>30 (100%)</td>
<td>3 (2.8%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>UA</td>
<td>7 (23.3%)</td>
<td>107 (100%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Revascularization</td>
<td>20 (66.7%)</td>
<td>18 (16.8%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Total</td>
<td>57</td>
<td>130</td>
<td>0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>6 mo</th>
<th>Myocardial Infarction</th>
<th>Unstable Angina</th>
<th>Noncardiac Chest Pain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>29</td>
<td>105</td>
<td>110</td>
</tr>
<tr>
<td>Death</td>
<td>1 (3.4%)</td>
<td>8 (7.6%)</td>
<td>1 (0.9%)</td>
</tr>
<tr>
<td>MI</td>
<td>5 (17.2%)</td>
<td>8 (7.6%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>UA</td>
<td>11 (37.9%)</td>
<td>38 (36.2%)</td>
<td>2 (1.8%)</td>
</tr>
<tr>
<td>Revascularization</td>
<td>7 (24.1%)</td>
<td>20 (19.0%)</td>
<td>1 (0.9%)</td>
</tr>
<tr>
<td>Total</td>
<td>24</td>
<td>74</td>
<td>4</td>
</tr>
</tbody>
</table>

**Discussion**

This study prospectively evaluated the role of markers of thrombus and myocardial injury to predict adverse cardiac ischemic events in a heterogeneous patient population presenting to the Emergency Department with chest pain. It is unique in that it included both inpatients and outpatients. The results show that FPA and TnI independently predicted an increased rate of adverse clinical events within the first week. The presence of an elevated FPA level, regardless of the initial diagnosis at presentation to the Emergency Department, was the most significant variable in determining adverse clinical events at 6-month follow-up, whereas TnI approached significance (P=0.052).

Diagnosis and risk stratification of patients presenting to the hospital with a possible acute coronary syndrome remains...
challenging. In this study, 10.2% of patients with ischemia or infarction were discharged from the Emergency Department, whereas 54.5% of patients at low risk for adverse cardiac events were admitted to the hospital for monitoring (Table 1). The incidence of adverse events over the 6-month follow-up was 28%, percentages similar to published data. Although ST-segment deviation on the admission ECG predicts an increased rate of ischemia related events, a specific ECG diagnosis is present in only ~40% of patients with an acute MI and 5% of all patients who present with chest pain. CK-MB isoenzymes correlate with the extent of a MI but are not elevated in UA or within the initial hours of an infarct. Therefore, new markers have been evaluated to aid in risk stratification.

Hypercoagulability is an important determinant of adverse outcomes in patients with coronary artery disease. Patients with increased fibrinogen levels have a 2-fold greater risk of MI. Decreased fibrinolytic activity has been associated with a 40% increased risk of ischemic heart disease and cardiac events. Elevated levels of PAI-1, the endogenous
inhibitor of tissue plasminogen activator (TPA), has been associated with reinfarction in young patients, whereas elevated levels of PAI-1 and TPA have been associated with development of a first MI. Increased activated factor VII levels have been associated with a 45% increase in fatal cardiac events. Results of the current study support the hypothesis that elevated thrombin activity predicts acute coronary ischemic events for up to 6 months. Thrombin may cause ischemic events by several potential mechanisms. In addition to promoting coagulation, the proinflammatory actions of thrombin on monocytes, neutrophils, and endothelial cells and proliferative effects on mesenchymal cells may result in accelerated development of atherosclerosis. Increased thrombin activity in patients with unstable angina correlate with intracoronary thrombus and reversible ST-segment changes. Plasma concentrations of the prothrombin fragment F$_{1+2}$ and FPA are elevated in patients with UA and MI, and F$_{1+2}$ remains persistently elevated. Elevated plasma FPA levels correlate with abrupt coronary occlusion and MI after angioplasty, as well as failed reperfusion after thrombolytic therapy. Furthermore, elevated thrombin activity in patients with UA or MI has been associated with an increased adverse event rate, whereas the use of thrombin inhibitors reduces adverse cardiac events.

Although elevated troponin levels predict a higher mortality and infarction rate in patients with acute MI and UA, the utility of troponins in predicting future events in a general population is unclear. In one study of patients with chest pain lasting ≤6 hours, Tnl had a sensitivity of 58% and TnT 62% for diagnosing a MI. For a late MI diagnosis, the sensitivities of the troponins approached that of CK-MB. In 128 patients with chest pain in whom a MI was excluded, de Winter et al showed that an elevated TnI predicted adverse events and a shorter event-free survival. Polancyzk et al showed in 1047 patients with chest pain that a peak Tnl >0.4 ng/mL had a 47% sensitivity, an 80% specificity, and a 19% PPV for predicting major cardiac events. In our population, Tnl was the most powerful predictor of cardiac events in the first week, with a sensitivity of 34%, a specificity of 91%, and an 82% PPV. Our study differs from the analysis by Polancyzk et al because we included those patients initially discharged from the hospital. In addition, we obtained troponin levels only from the 0-, 4-, and 8-hour time points, whereas Polancyzk et al collected Tnl over the initial 24 hours.

### TABLE 3. Events at 1 Week and 6 Months

<table>
<thead>
<tr>
<th>Marker</th>
<th>FPA (&gt;3.2 ng/mg Cr)</th>
<th>TnI (&gt;0.2 ng/mL)</th>
<th>Myo (&gt;100 µg/mL)</th>
<th>MLC (&gt;1 µg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elevated</td>
<td>Normal</td>
<td>Elevated</td>
<td>Normal</td>
<td>Elevated</td>
</tr>
<tr>
<td>Events at 1 wk</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No.</td>
<td>48</td>
<td>130</td>
<td>56</td>
<td>191</td>
</tr>
<tr>
<td>Death (n)</td>
<td>2% (1)</td>
<td>0</td>
<td>2% (1)</td>
<td>1% (1)</td>
</tr>
<tr>
<td>MI (n)</td>
<td>19% (9)</td>
<td>7% (9)</td>
<td>25% (14)</td>
<td>9% (17)</td>
</tr>
<tr>
<td>UA (n)</td>
<td>50% (24)</td>
<td>40% (52)</td>
<td>55% (31)</td>
<td>38% (73)</td>
</tr>
<tr>
<td>Revascularization alone, n</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Any MACE (n)</td>
<td>71% (34)</td>
<td>47% (61)</td>
<td>82% (46)</td>
<td>48% (91)</td>
</tr>
<tr>
<td>P</td>
<td>&lt;0.005</td>
<td>&lt;0.001</td>
<td>0.004</td>
<td>0.008</td>
</tr>
</tbody>
</table>

Events at 6 mo | | | | |
| No. | 47 | 130 | 55 | 189 | 65 | 181 | 102 | 142 |
| Death (n) | 11% (5) | 1% (1) | 7% (4) | 3% (6) | 8% (5) | 3% (5) | 6% (6) | 3% (4) |
| MI (n) | 6% (3) | 2% (3) | 5% (3) | 3% (5) | 3% (2) | 3% (6) | 5% (5) | 2% (3) |
| UA (n) | 32% (15) | 13% (17) | 24% (13) | 17% (33) | 22% (14) | 17% (31) | 17% (17) | 20% (29) |
| Revascularization alone, n | 0 | 2% (2) | 4% (2) | 1% (2) | 2% (1) | 2% (3) | 1% (1) | 2% (3) |
| Any MACE (n) | 51% (24) | 18% (23) | 40% (22) | 24% (46) | 34% (22) | 25% (45) | 28% (29) | 27% (39) |
| P | <0.001 | 0.052 | NS | NS |

Cr indicates creatinine.

P value between elevated and normal levels of the individual marker, by univariate analysis. Upper limit of normal for each marker is noted.

### TABLE 4. Marker Sensitivity, Specificity

<table>
<thead>
<tr>
<th>Marker</th>
<th>≤1 wk</th>
<th>1 wk to 6 mo</th>
<th>≤6 mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>FPA</td>
<td>Sensitivity, %</td>
<td>Specificity, %</td>
<td>PPV, %</td>
</tr>
<tr>
<td>TnI</td>
<td>36</td>
<td>83</td>
<td>71</td>
</tr>
<tr>
<td>Myo</td>
<td>34</td>
<td>91</td>
<td>82</td>
</tr>
<tr>
<td>MLC</td>
<td>33</td>
<td>84</td>
<td>71</td>
</tr>
</tbody>
</table>

Positive (PPV) and negative (NPV) predictive values of predicting major adverse clinical events.
Elevated Myo and MLC levels identified adverse events in the early phase but did predict events not at the 6-month follow-up. Myo appears earlier in the serum (within 4 hours of MI onset), with a sensitivity of 43% and a specificity of 89%, although others have shown that myoglobin did not identify adverse events. In the current study, MLC identified adverse events in 89%, although others have shown that myoglobin did not significantly predict long-term outcomes as well as a shorter event-free survival in a larger cohort. However, this was an adequate reflection of the percentage of patients presenting to the Emergency Department with MI. We did not obtain serum samples 16 hours after presentation, and a 16-hour TnI sample may add prognostic information. The TnI assay used was a first-generation assay, and newer-generation assays may be more sensitive in detecting smaller degrees of myocardial injury.

In conclusion, FPA and TnI independently predicted major adverse cardiac events within the initial week in a general population of patients presenting to the Emergency Department with chest pain. At 6-month follow-up, FPA was the most significant and accurate predictor of long-term outcomes and the only marker that predicted a shorter event-free survival. A combination of markers enhanced the sensitivity of predicting adverse cardiac events.

Acknowledgments
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References
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