Symptom onset and treatment in acute myocardial infarction
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CHAPTER 4

Biochemical validation of patient-reported symptom onset time in patients with ST-elevation myocardial infarction undergoing primary percutaneous coronary intervention

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**Abstract**

**Background:** Symptom onset time is an important metric in patients with ST-elevation myocardial infarction (STEMI) but has never been formally validated. We performed a biochemical validation of patient-reported symptom onset time.

**Methods:** The Mayo Clinic Percutaneous Coronary Intervention (PCI) Registry was interrogated to obtain baseline, procedural, and outcome data on 607 STEMI patients undergoing primary PCI. Biochemical onset time was determined by backward extrapolation of serial rising cardiac troponin T (cTnT) measurements.

**Results:** Overall, biochemical onset time was earlier than patient-reported onset time (median -4.2 hours; interquartile range -11.1; -1.9; P<0.001); a trend that was especially pronounced in subgroups based on age ≥65 years, body mass index <28 kg/m², no prior PCI, and preprocedural TIMI flow >0. Conventional ischemic time showed no association with infarct size (correlation with peak cTnT r=0.023; P=0.61) or 1-year mortality (hazard ratio 0.97 per doubling; 95% confidence interval 0.68-1.40; P=0.88). However, after recalculation of ischemic time with biochemical onset time, significant associations with infarct size (r=0.14; P=0.001) and 1-year mortality (hazard ratio 1.70 per doubling; 95% confidence interval 1.20-2.40; P=0.003) were found. When underestimation of ischemic time by patient-reported onset time increased, so did the risk of mortality.

**Conclusions:** Our study indicates that the actual onset of STEMI is likely to be earlier than patient-reported onset time and that this phenomenon is aggravated in certain subgroups. Recalculation of ischemic time with biochemical onset time greatly enhanced its prognostic value. Underestimation of ischemic time by patient-reported onset time occurred more often in high-risk patients.

**Introduction**

 Patients with ST-elevation myocardial infarction (STEMI) require rapid reperfusion therapy of the infarct related coronary artery.¹ In this context, patient-reported symptom onset time is a key metric. Symptom onset time is used in conjunction with time of treatment to determine the total ischemic time, which has been associated with myocardial reperfusion, infarct size, and mortality at short- and long-term follow-up.²⁻⁴ In addition, symptom onset time may aid in selecting a reperfusion strategy in patients with STEMI. Observational studies and a recent clinical trial have suggested that a pharmaco-invasive
approach consisting of (prehospital) fibrinolysis with timely angiography may result in a superior outcome as compared with primary percutaneous coronary intervention (PCI) in STEMI patients presenting early (i.e. within 3 hours of symptom onset) in whom delays to primary PCI are expected to be substantial.\textsuperscript{5-7} Similarly, current guidelines do not recommend routine reperfusion therapy in stable STEMI patients without clinical and electrocardiographic evidence of ongoing ischemia when time from symptom onset to presentation is more than 12 to 24 hours.\textsuperscript{1} Despite this growing importance of symptom onset time, prior reports have pointed out that reported symptom onset time is subjective information and is likely to be an inaccurate measure of true time of onset of myocardial infarction.\textsuperscript{6,9} Some subgroups of patients are known for their often atypical symptoms such as women, diabetics, and the elderly,\textsuperscript{10-12} which may further jeopardize the accuracy of reported symptom onset time. Furthermore, patients may report an episode of angina prior to coronary artery occlusion as time of symptom onset. To the best of our knowledge, symptom onset time in STEMI has never been formally validated. In the present study, we validated patient-reported symptom onset time with biochemical onset time, which was estimated using cardiac troponin T (cTnT) concentrations. We determined the accuracy of patient-reported symptom onset time in the overall population and in relevant subgroups. Furthermore, we assessed the prognostic value of ischemic time using reported symptom onset time versus ischemic time using biochemical onset time.

**METHODS**

**Study design**

The Mayo Clinic PCI Registry was interrogated to obtain baseline, procedural, and outcome data on consecutive patients with STEMI undergoing primary PCI between 2004 and 2012 at the Mayo Clinic, Rochester, Minnesota. For this registry, data are prospectively collected by experienced interventional cardiology data technicians. After discharge, follow-up is collected by a periodical standardized telephone survey with the patient. All adverse events are confirmed by reviewing the medical records of the patients followed up at our institution and by contacting the patients’ physicians and reviewing the hospital records of patients treated elsewhere. The database supervisor randomly audits 10\% of the records for quality control purposes. STEMI was defined as symptoms suggestive of myocardial ischemia and an electrocardiogram (ECG) with either
new or presumed new ST-elevation or left bundle branch block. ST-elevation was defined as ≥1 mm elevation of ST segments in 2 or more limb leads or ≥2 mm in 2 or more contiguous precordial leads. Patients were included if they had at least 2 rising cTnT measurements within 24 hours of patient-reported symptom onset time. Furthermore, the peak cTnT concentration had to be at least 5 times greater than the minimal value to allow for an accurate calculation of biochemical onset time. Exclusion criteria were moderate to severe renal disease (defined as creatinine >265 μmol/L [>3.0 mg/dL] or on dialysis or previous kidney transplant), a prior PCI procedure within 7 days of the primary PCI procedure, unreported symptom onset time, and patient refusal to have their medical records reviewed for research. The study protocol was approved by the institutional review board.

Methods of measurement
All baseline data were documented upon admission. Hypertension was defined as a documented history or treatment with medication. Current smoking was defined as having smoked cigarettes within the past 6 months. Diabetes was defined as a documented diagnosis requiring treatment with medication or diet. Hypercholesterolemia was defined as total cholesterol >6.2 mmol/L (>240 mg/dL) or on drug therapy. Positive family history was defined as a family history of coronary heart disease at young age (≤55 years). Preprocedural shock was defined as a systolic blood pressure <95 mmHg or <110 mmHg on inotropic support. Multivessel disease was defined as a stenotic lesion of at least 50% in a vessel other than the culprit coronary artery. Symptom onset time was defined as patient-reported date and time of onset of symptoms. To calculate biochemical onset time, serial blood levels of cTnT were used. cTnT levels are routinely measured in all STEMI patients following a standardized protocol on admission and at 3 and 6 hours on an electrochemiluminescence immunoassay (Elecsys; Roche Diagnostics, Indianapolis, Indiana) with a coefficient of variation <10% at 0.035 ng/mL, a lower limit of detection of 0.01 ng/mL, and a 99th percentile reference limit <0.01 ng/mL in accordance with current guidelines for the diagnosis of myocardial infarction. Treatment time was the date and time documented in the catheterization procedure note as the time of first device used to open the coronary artery including balloon, stent, or thrombectomy device. Conventional ischemic time was derived from reported symptom onset time and treatment time, while biochemical ischemic time was derived from biochemical onset time and treatment time. Thrombolysis
In Myocardial Infarction (TIMI) flow was scored by the operator during the PCI procedure. Measures of outcome included peak cTnT which is a validated measure of infarct size and all-cause mortality during hospitalization and at 1-year follow-up. One-year follow-up was completed in 93% of the included patients.

Statistical analysis
Continuous variables were summarized as mean ± standard deviation or median and interquartile range (IQR). Discrete variables were presented as numbers and percentages. Bivariate associations were assessed with Spearman’s correlation, group differences were tested with the Mann–Whitney U-test, and differences between paired observations were tested with the Wilcoxon Signed-Rank test. To calculate the biochemical onset time, we adopted an approach as reported in a historical study that validated the circadian variation in acute myocardial infarction with creatine kinase MB levels.

Assuming a monoexponential rise of cTnT in STEMI patients, a regression line was fitted to the rising cTnT levels in each patient after logarithmic transformation of both time and cTnT. By using a Tobit model, cTnT levels below 0.01 ng/mL could be considered as censored data in the modeling process. Backward extrapolation of the regression function allowed us to estimate the time of initial elevation of cTnT (defined as cTnT=0.01 ng/mL). We then subtracted a predefined constant term from this time point, to account for the time between coronary occlusion and initial elevation of cTnT (Figure 1). Based on prior preclinical and clinical studies, we chose a constant term of 4 hours for all patients. Reported symptom onset time was compared with biochemical onset time in the overall population and in prespecified subgroups based on age (≥65 years), gender, body mass index ([BMI], above the median), hypertension, diabetes, hypercholesterolemia, current smoking, positive family history, prior myocardial infarction, prior PCI, prior coronary artery bypass grafting (CABG), reported symptom onset at night (midnight through 05:59),

Figure 1. Determination of biochemical onset time. After logarithmic transformation of both axes, a regression line was fitted to the rising cardiac troponin T (cTnT) values in each patient. Extrapolation of this line allowed estimation of the time of first cTnT elevation. Finally, a constant factor (C) was added to account for time between coronary occlusion and first cTnT elevation.
Table 1. Baseline, procedural, and outcome data

<table>
<thead>
<tr>
<th>Baseline</th>
<th>Included patients (n=607)</th>
<th>Excluded patients (n=1202)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>62.6 ± 13.4</td>
<td>64.0 ± 13.7</td>
<td>0.036</td>
</tr>
<tr>
<td>Female gender</td>
<td>140 (23)</td>
<td>355 (30)</td>
<td>0.004</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>28.9 ± 5.3</td>
<td>29.1 ± 6.1</td>
<td>0.44</td>
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<tr>
<td>Hypertension</td>
<td>347 (62)</td>
<td>791 (69)</td>
<td>0.004</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>101 (17)</td>
<td>210 (18)</td>
<td>0.68</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>372 (69)</td>
<td>755 (68)</td>
<td>0.61</td>
</tr>
<tr>
<td>Smoking status</td>
<td></td>
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<td>0.52</td>
</tr>
<tr>
<td>Current</td>
<td>195 (33)</td>
<td>412 (35)</td>
<td></td>
</tr>
<tr>
<td>Former</td>
<td>199 (34)</td>
<td>391 (33)</td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>197 (33)</td>
<td>385 (32)</td>
<td></td>
</tr>
<tr>
<td>Family history</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Positive</td>
<td>154 (25)</td>
<td>253 (21)</td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>260 (43)</td>
<td>673 (56)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>193 (32)</td>
<td>276 (23)</td>
<td></td>
</tr>
<tr>
<td>Prior myocardial infarction</td>
<td>96 (16)</td>
<td>206 (17)</td>
<td>0.47</td>
</tr>
<tr>
<td>Prior PCI</td>
<td>115 (19)</td>
<td>268 (22)</td>
<td>0.10</td>
</tr>
<tr>
<td>Prior CABG</td>
<td>32 (5)</td>
<td>79 (7)</td>
<td>0.29</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td></td>
<td></td>
<td>0.14</td>
</tr>
<tr>
<td>Current</td>
<td>46 (8)</td>
<td>110 (9)</td>
<td></td>
</tr>
<tr>
<td>Prior</td>
<td>8 (1)</td>
<td>24 (2)</td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>543 (91)</td>
<td>1044 (89)</td>
<td></td>
</tr>
<tr>
<td>Preprocedural shock</td>
<td>74 (12)</td>
<td>129 (11)</td>
<td>0.34</td>
</tr>
<tr>
<td>Conventional ischemic time (hours)</td>
<td>3.7 (2.4-6.1)</td>
<td>4.8 (2.7-10.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Procedural</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multivessel disease</td>
<td>392 (65)</td>
<td>779 (66)</td>
<td>0.67</td>
</tr>
<tr>
<td>Preprocedural TIMI 0 flow</td>
<td>331 (62)</td>
<td>562 (52)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Target coronary artery*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left anterior descending</td>
<td>208 (34)</td>
<td>522 (44)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Right</td>
<td>320 (53)</td>
<td>486 (41)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Circumflex</td>
<td>87 (14)</td>
<td>206 (17)</td>
<td>0.12</td>
</tr>
<tr>
<td>Left main</td>
<td>0 (0)</td>
<td>21 (2)</td>
<td>0.001</td>
</tr>
<tr>
<td>Graft</td>
<td>16 (3)</td>
<td>36 (3)</td>
<td>0.66</td>
</tr>
<tr>
<td>Number of segments treated</td>
<td>1.3 ± 0.6</td>
<td>1.4 ± 0.6</td>
<td>0.71</td>
</tr>
<tr>
<td>Number of stents placed</td>
<td>1.2 ± 0.7</td>
<td>1.2 ± 0.8</td>
<td>0.59</td>
</tr>
<tr>
<td>Use of drug-eluting stents</td>
<td>424 (70)</td>
<td>794 (66)</td>
<td>0.13</td>
</tr>
<tr>
<td>Periprocedural GP IIb/IIIa use</td>
<td>511 (84)</td>
<td>983 (82)</td>
<td>0.20</td>
</tr>
<tr>
<td>Outcome</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Postprocedural TIMI 3 flow</td>
<td>531 (93)</td>
<td>1050 (91)</td>
<td>0.26</td>
</tr>
<tr>
<td>Peak cardiac troponin T (ng/mL)</td>
<td>3.7 (1.7-7.2)</td>
<td>1.3 (0.1-4.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Death</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inhospital</td>
<td>11 (1.8)</td>
<td>61 (5.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>1-year</td>
<td>34 (5.7)</td>
<td>119 (10)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Values are mean ± standard deviation, n (%), or median (interquartile range)

*sum is >100% due to multivessel procedures

CABG, coronary artery bypass grafting; GP, glycoprotein; PCI, percutaneous coronary intervention; TIMI, Thrombolysis In Myocardial Infarction
congestive heart failure on admission, preprocedural shock, multivessel disease, and preprocedural TIMI flow (>0). After logarithmic transformation of ischemic time, we used univariable Cox proportional hazards models to assess the association between ischemic time and 1-year mortality. For this analysis, ischemic time was calculated both with reported symptom onset time and biochemical onset time. In sensitivity analyses, the study results were recalculated after exclusion of 1) patients with postprocedural TIMI flow <3 and 2) patients with only 2 cTnT measurements when one of these measurements was <0.01 ng/mL. All statistical analyses were performed using SAS version 9.3 (SAS Institute Inc., Cary, North Carolina) and statistical significance was set at P<0.05 (two-tailed).

RESULTS

There were 1809 eligible primary PCI cases in patients with STEMI between January 1, 2004 and December 31, 2012. Of these, we excluded 1174 patients in whom cTnT measurements were not suitable for biochemical onset time calculation, 15 patients who had had a prior PCI procedure within the last 7 days, and 13 patients with moderate to severe renal failure (Figure 2). Thus, 607 STEMI patients were included in the present analysis. Baseline and procedural characteristics of the included and excluded patients are listed in Table 1. Among included patients, the mean age was 62.6 years, 23% were female, and mean BMI was 28.9 kg/m². The rate of current smokers was 33%, diabetes was present in 17% of patients, and 19% of patients had a history of PCI. Upon coronary angiography, TIMI 0 flow was found in 62% of patients and multivessel disease in 65%. The average number of cTnT measurements was 3.2 of which an average of 2.7 measurements was rising.

Patients excluded from this study were more likely to be female, had higher rates of hypertension and longer ischemic time, but were less likely to have a positive family history (Table 1). Preprocedural TIMI 0 flow was
less often found in excluded patients. Treatment was similar in excluded patients, except for less right coronary artery interventions at the expense of more left anterior descending artery interventions. Mortality was higher among excluded patients.

**Reported onset time versus biochemical onset time**

Overall, biochemical onset time tended to be earlier than reported symptom onset time with a median difference of -4.2 hours (IQR -11.1 to -1.9; P<0.001; Figure 3). Of note, this indicated that median reported symptom onset time was 12 minutes later than the estimated time of first cTnT elevation. Subgroup differences are shown in Figure 4. As compared with the reference population, biochemical onset time was especially earlier than reported symptom onset time in patients aged ≥65 years (median -4.8 hours; IQR -13.4 to -2.2; P=0.001), patients with a BMI <28 (median -4.7 hours; IQR -12.9 to -2.1; P=0.006), patients without a history of PCI (median -4.3; IQR -11.1 to 2.2; P=0.038), and patients with a preprocedural TIMI flow >0 (median -5.5; IQR -15.3 to -2.0; P=0.001). There were trends towards earlier biochemical onset in non-smokers (P=0.059) and patients with preprocedural shock (P=0.083). No differences were seen in subgroups based on gender, diabetes, or reported symptom onset at night.

**Relation with ischemic time**

When calculated using reported symptom onset time, median

![Figure 3](image-url)  

Figure 3. Distribution of the difference between biochemical onset time and reported symptom onset time. Median biochemical onset time was 4.2 hours earlier than reported onset time (IQR 1.9 to 11.1; P<0.001). The line shows the estimated density function using a kernel estimator.
Figure 4. Subgroup differences in biochemical onset time relative to patient-reported symptom onset time. CABG, coronary artery bypass grafting; CHF, congestive heart failure; MI, myocardial infarction; PCI, percutaneous coronary intervention; TIMI, Thrombolysis In Myocardial Infarction.
conventional ischemic time was 3.7 hours (IQR 2.4 to 6.1). Recalculation by using biochemical onset time, resulted in a median biochemical ischemic time of 8.6 hours (IQR 5.1 to 17.4). Biochemical ischemic time tended to be longer than conventional ischemic time, although the two measures showed good agreement in patients with ischemic times >12 hours (overall correlation r=0.39; P<0.001; Figure 5).

**Relation with outcome**

To verify the internal validity of biochemical onset time and compare the prognostic value of conventional ischemic time and biochemical ischemic time, their relation with biochemical infarct size and mortality was assessed. Overall, median peak cTnT was 3.7 ng/mL (IQR 1.7 to 7.2). While conventional ischemic time did not correlate with peak cTnT (r=0.023; P=0.61; Figure 6A), there was a highly significant positive correlation between biochemical ischemic time and peak cTnT (r=0.14; P=0.001; Figure 6B).

At follow-up, inhospital mortality was 1.8% and 1-year mortality was 5.7% (Table 1). No association was found between conventional ischemic time and 1-year mortality (hazard ratio 0.97 per doubling; 95% confidence interval [CI] 0.68-1.40; P=0.88). In contrast, longer biochemical ischemic time was predictive of 1-year mortality (hazard ratio 1.70 per doubling; 95%CI 1.20-2.40; P=0.003). To gain further insight into this pattern, we also assessed the predictive value of the ratio of biochemical ischemic time over conventional ischemic time. An increase of this ratio was also predictive of 1-year mortality (hazard
ratio 1.60 per doubling; 95%CI 1.18-2.18; P=0.003), indicating that shorter conventional ischemic time relative to biochemical ischemic time was more common in patients at higher risk of 1-year mortality.

**Sensitivity analyses**

To assess the impact of completeness of epicardial reperfusion on our results, we excluded patients with postprocedural TIMI flow <3 (n=76) in a sensitivity analysis. In the remaining 531 patients, the difference between biochemical onset time and reported symptom onset time was similar to the overall population (median -4.1 hours; IQR -10.6 to -2.0; P<0.001), and biochemical ischemic time remained associated with infarct size (correlation with peak cTnT r=0.12; P=0.013) and 1-year mortality (hazard ratio 1.59 per doubling; 95%CI 1.06-2.39; P=0.025). Thus, this analysis argued against a significant bias in the modeling process due to cTnT washout after reperfusion. In a second sensitivity analysis, patients with only 2 cTnT measurements were excluded when the first measurement was <0.01 ng/mL (n=85). This represented the group of patients with the most scarce data to model cTnT and the Tobit model showed a slight bias towards later biochemical onset time in these patients. The median difference between biochemical onset time and reported symptom onset time was greater in the remaining patients (n=522; median -5.5 hours; IQR -12.4 to -2.2; P<0.001). The correlation between biochemical ischemic time and infarct size was weaker in this subset (correlation with peak cTnT r=0.08; P=0.081), although performance was still better than conventional ischemic time. The association between biochemical ischemic time and 1-year mortality also persisted in this subset (hazard ratio 1.50 per doubling; 95%CI 1.05-2.16; P=0.027).

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**Figure 6. Correlation between ischemic time and biochemical infarct size as assessed by peak cardiac troponin T. Panel A.** correlation between conventional ischemic time and infarct size (r=0.023; P=0.61) and **Panel B.** correlation between biochemical ischemic time and infarct size (r=0.14; P=0.001). The line represents a spline smoother to help visualize the trend.
To the best of our knowledge, we are the first to validate symptom onset time in patients with STEMI. Patient-reported symptom onset time was compared with biochemical onset time, which was derived from serial cTnT measurements. We found that reported symptom onset time tended to be later than biochemical onset time and that this phenomenon was even more pronounced in the elderly, patients with a BMI <28, patients without a history of PCI, and patients with residual flow in the culprit artery upon coronary angiography. Conventional ischemic time – reported symptom onset to treatment time – did not correlate with infarct size and mortality. Conversely, biochemical ischemic time – biochemical onset to treatment time – was closely associated with infarct size and mortality. An increase in the ratio of biochemical ischemic time over conventional ischemic time was also associated with mortality, indicating that larger differences between these measures were more frequent among patients at higher risk of death.

While our findings are novel and compelling, a thorough understanding of the methodology applied to determine biochemical onset time is crucial to the interpretation of our results. As shown in Figure 1, backward extrapolation of serial rising cTnT measurements was used to estimate the time of initial cTnT elevation. From this time point, 4 hours were subtracted in all patients to account for the time between coronary occlusion and first cTnT elevation. This constant term was predefined and based on prior studies. In an experimental model, cardiac troponin I was elevated after 4 hours of balloon occlusion of the circumflex artery in pigs. Human studies have shown cardiac troponin I elevation 2 to 4 hours after onset of myocardial infarction in most patients. However, the human studies relied on reported symptom onset time and are prone to the very bias we tried to assess in this study. Thus, the choice of the constant remains arbitrary to some extent as the true time of coronary occlusion cannot be known. Accordingly, the point estimate of the median difference between biochemical onset time and reported symptom onset time found in our study (~4.2 hours) should be interpreted with caution. Still, regardless of the constant factor, the median reported symptom onset time in our study roughly coincided with the estimated time of first cTnT elevation, thereby representing clear evidence that reported symptom onset time is later than the actual time of onset of STEMI. Moreover, most of our analyses are not affected by the application of a constant factor to the overall population. Specifically, modification of the constant factor would only have a marginal impact on
In a sensitivity analysis, the association between biochemical ischemic time and infarct size was no longer significant after exclusion of patients with 1 cTnT measurement below the lower limit of detection and 1 elevated cTnT value. While this could be related to the modeling of cTnT, other explanations are also plausible. Clearly, a sample size reduction limits statistical power to detect any association. More importantly, patients with initially undetectable cTnT values are likely to be early presenters and generally have a favorable outcome. Selective exclusion of these patients may compromise the association between ischemic time and outcome. We found greater deviation between reported symptom onset time and biochemical onset time in elderly patients. This finding is consistent with prior studies, showing that elderly patients with acute myocardial infarction more often present with atypical symptoms such as dyspnea and faintness. In addition, remembrance of time of onset may be less accurate in elderly patients. Reported symptom onset time also tended to be later than biochemical onset time in patients with TIMI flow >0 upon coronary angiography. This group of patients may suffer a “stuttering myocardial infarction” where transient episodes of (sub)total coronary occlusion are accompanied by waxing and waning of ischemic symptoms, thereby complicating determination of actual time of onset of symptoms. Furthermore, reported symptom onset time was later than could be expected from biochemical onset time in patients with a lower BMI and patients without a history of PCI procedures. These patients have not been identified as subgroups with an atypical symptom presentation in previous studies. A possible explanation is that these patients were not made aware of the symptoms associated with myocardial infarction by their physicians due to their lower risk of cardiovascular events. Hence, they may not have attributed the initial symptoms as being cardiac. In this context, however, it should also be stressed that atypical symptoms such as dyspnea and nausea – although harder to attribute as cardiac – do not necessarily preclude adequate recollection of onset time. This may explain why we did not find differences in other subgroups known for their atypical symptom presentation such as women and diabetics.

The pathophysiological importance of total ischemic time in patients with STEMI is well recognized. However, some prior studies in patients undergoing primary PCI have failed to show associations between ischemic time and infarct size, myocardial salvage index, left ventricular ejection fraction, and mortality. Remarkably,
associations with these measures of outcome could be demonstrated when ischemic time was replaced with a more objective measure such as system delay. Our findings help to explain these observations, by showing that the prognostic value of ischemic time was greatly enhanced when it was systematically determined in a manner that was less prone to bias than the use of reported symptom onset time. Importantly, reported symptom onset time tended to underestimate ischemic time to a greater extent in patients at higher risk of mortality, thereby further obscuring the association between ischemic time and clinical outcome.

The retrospective methodology we applied to determine biochemical onset time limits its applicability for reperfusion strategy selection in clinical practice. Nonetheless, clinicians should be aware that reported symptom onset time is typically later than the actual time of onset of STEMI, especially in the subgroups identified in this study and in high-risk patients. Our results suggest that other readily available measures that reflect time from onset of STEMI should also be considered when selecting a reperfusion strategy, such as the presence of Q waves on the baseline ECG. However, we do not argue against the current guideline recommendations to consider conservative management in stable STEMI patients without evidence of ongoing ischemia when symptom onset to presentation is more than 12 to 24 hours, since conventional ischemic time correlated well with biochemical ischemic time in patients with ischemic time beyond 12 hours.¹

**Limitations**

Several limitations of our study should be considered. As stated earlier, the most important limitation of our study is the fact that true time of onset of STEMI cannot be known and that there is neither a gold standard for onset time nor for ischemic time. Nonetheless, biochemical ischemic time greatly outperformed conventional ischemic time with regard to prognostic value, thus showing good internal validity. Second, biochemical onset time could only be reliably calculated in patients with sufficient and rising cTnT measurements. Exclusion of a substantial number of patients with inadequate cTnT measurements introduced some selection bias to our study population as outlined in our results. Third, it is conceivable that a minor plaque disruption before the actual STEMI-related coronary event already caused cTnT release, resulting in a too early onset time when determined biochemically. Similarly, despite exclusion of patients with renal failure, some of the included patients may still have had chronically elevated cTnT levels due to other conditions such as left ventricular hypertrophy, heart failure, or diabetes which could...
also introduce a bias towards earlier biochemical onset time.\textsuperscript{25}

\textbf{CONCLUSIONS}

Our study provides evidence that patient-reported symptom onset time is later than the actual time of onset of STEMI among patients undergoing primary PCI. This phenomenon is especially pronounced in the elderly, patients with a lower BMI, patients without a history of PCI, and patients with residual flow in the culprit artery upon coronary angiography. Unlike conventional ischemic time, biochemically determined ischemic time correlated well with infarct size and mortality. As compared with biochemical onset time, reported symptom onset time tended to underestimate ischemic time more in patients at higher risk of 1-year mortality. Our study shows that minimizing ischemic time should remain a key goal in STEMI care. Future studies are required to corroborate our findings and assess the association between biochemically determined ischemic time and infarct size measured by imaging modalities such as magnetic resonance imaging.
REFERENCES


