Symptom onset and treatment in acute myocardial infarction
Mahmoud, Karim

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2014

Citation for published version (APA):

Copyright
Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

The publication may also be distributed here under the terms of Article 25fa of the Dutch Copyright Act, indicated by the “Taverne” license. More information can be found on the University of Groningen website: https://www.rug.nl/library/open-access/self-archiving-pure/taverne-amendment.

Take-down policy
If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): http://www.rug.nl/research/portal. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.
CHAPTER 3

Independent association between symptom onset time and infarct size in patients with ST-elevation myocardial infarction undergoing primary percutaneous coronary intervention

Karim D. Mahmoud\textsuperscript{1,2}  
Maarten W. Nijsten\textsuperscript{3}  
Wouter G. Wieringa\textsuperscript{1}  
Jan P. Ottervanger\textsuperscript{4}  
David R. Holmes Jr.\textsuperscript{2}  
Hans L. Hillege\textsuperscript{1}  
Arnoud W. van ‘t Hof\textsuperscript{4}  
Erik Lipsic\textsuperscript{1}

\textsuperscript{1}Department of Cardiology, University Medical Center Groningen, The Netherlands  
\textsuperscript{2}Division of Cardiovascular Diseases, Mayo Clinic, Rochester, Minnesota, USA  
\textsuperscript{3}Department of Critical Care, University Medical Center Groningen, The Netherlands  
\textsuperscript{4}Department of Cardiology, Isala Klinieken, Zwolle, The Netherlands

Submitted
Abstract

Background: Recent studies have reported on circadian variation in infarct size in ST-elevation myocardial infarction (STEMI) patients. Controversy remains as to whether this finding indicates circadian dependence of myocardial tolerance to ischemia/reperfusion injury or that it can simply be explained by confounding factors such as baseline profile and ischemic time. We assessed the clinical impact and independent association between symptom onset time and infarct size, accounting for possible subgroup differences.

Methods: From a multicenter registry, 6799 consecutive STEMI patients undergoing primary percutaneous coronary intervention (PCI) between 2004 and 2010 were included. Infarct size was measured using peak creatine kinase (CK).

Results: Infarct size exhibited circadian variation with largest infarct size in patients with symptom onset around 03:00 at night (peak CK 1322 U/l; 95%CI 1217-1436) and smallest infarct size around 11:00 in the morning (peak CK 1071 U/l; 95%CI 1001-1146; relative reduction 19%; P=0.001). Circadian variation in infarct size followed an inverse pattern in patients with prior myocardial infarction ($P_{\text{interaction}}<0.001$) and prior PCI ($P_{\text{interaction}}=0.006$), although the later did not persist in multivariable analysis. Symptom onset time remained associated with infarct size after accounting for these interactions and adjusting for baseline characteristics and ischemic time. Symptom onset time did not predict 1-year mortality (P=0.081).

Conclusions: There is substantial circadian variation in infarct size which cannot be fully explained by variations in baseline profile or ischemic time. Our results lend support to the hypothesis of circadian myocardial ischemic tolerance and suggest a different mechanism in patients with prior myocardial infarction.

Introduction

It is well-known that the incidence of acute myocardial infarction is low during the night and tends to peak in the morning between 06:00 and 12:00.\textsuperscript{1-3} This circadian pattern has been explained by a sudden increase in sympathetic nervous system activity and a prothrombotic state during the morning hours.\textsuperscript{4} Recently, several studies have described circadian variation in infarct size in patients with ST-elevation myocardial infarction (STEMI), suggesting the possibility of circadian dependence of myocardial...
tolerance to ischemia/reperfusion injury in man.\textsuperscript{5-9} This concept has previously been demonstrated in a rodent model, showing profound variation in infarct size depending on the time of coronary artery occlusion.\textsuperscript{10} However, the human studies on circadian variation in infarct size to date were small and controversy remains as to whether the circadian variation in infarct size truly reflects endogenous myocardial response to ischemia/reperfusion injury or is confounded by the circadian variation in baseline profile\textsuperscript{2,3,11} and the circadian variation in symptom onset to treatment time (ischemic time) reported in STEMI patients.\textsuperscript{2,3,12} Furthermore, common subgroups have not been assessed and it is also unknown if circadian variation in infarct size translates into differences in mortality.

In the present observational study we used data from consecutive patients with STEMI undergoing primary percutaneous coronary intervention (PCI) at 2 high-volume referral centers. We systematically assessed circadian variation in enzymatic infarct size in the overall population and relevant subgroups with adjustment for baseline characteristics and ischemic time. We also assessed if circadian variation in infarct size translated into a circadian mortality pattern.

**METHODS**

**Study design**

We used a registry from 2 large PCI-capable centers in the northern part of The Netherlands (University Medical Center Groningen, Groningen and Isala Clinics, Zwolle). Consecutive patients with STEMI undergoing primary PCI from January 2004 through December 2010 were included. STEMI was defined as chest pain suggestive of myocardial ischemia, time from onset of symptoms <12 hours, and an electrocardiogram (ECG) with new ST-segment elevation in $\geq 2$ contiguous leads of $\geq 0.2\text{mV}$ in leads $V_2$-$V_3$ and/or $\geq 0.1\text{mV}$ in other leads or a new-onset left bundle branch block. All patients with available symptom onset time and enzymatic infarct size were studied. For this observational study on anonymized patient data, informed consent was not required by our medical ethics committees.

**Treatment**

Both centers provided 24/7 primary PCI and emergency cardiac care facilities with on-site cardiothoracic surgical support throughout the study period. Regional STEMI networks for 12-lead ECG based prehospital diagnosis and direct referral for primary PCI were in place and fully operational. Primary PCI was the preferred reperfusion strategy for all patients with STEMI and interhospital
transfer for primary PCI was performed in case of failed prehospital diagnosis or self-referral to a non-PCI-capable center. Pharmacological pretreatment was usually initiated in the ambulance and consisted of aspirin (500mg), heparin (5000IU), and clopidogrel (300mg or 600mg, according to at that time valid guidelines). Periprocedural glycoprotein IIb/IIIa inhibitors were used unless contra-indicated. Bare-metal stents as well as drug-eluting stents were used at the operator’s discretion.

**Methods of measurement**

Data on all patients with STEMI undergoing primary PCI were routinely collected in a dedicated database. Baseline characteristics were documented upon admission and vital signs were collected upon entrance to the catheterization laboratory. Symptom onset time was defined as self-reported time of onset of symptoms compatible with myocardial infarction. Ischemic time was defined as time from symptom onset to initial intracoronary therapy by means of thrombus aspiration, balloon inflation, or stenting of the infarct related artery. The time of emergency medical services arrival at the PCI-capable center was deemed the ‘door’ time or, in case of self-referrals, time of presentation at the emergency department. Thrombolysis In Myocardial Infarction (TIMI) flow was scored by the operator during the PCI procedure. Enzymatic infarct size was determined using serum peak creatine kinase (CK) as previously validated.\textsuperscript{13,14} CK levels were measured in all patients following a standardized protocol on admission and 3, 6, 12, and 24 hours after primary PCI. Levels of CK were determined using an UV assay and an immunologic UV assay (Mega, Merck, Darmstadt, Germany for Groningen between January 2004 and February 2006; Modular P, Roche, Mannheim, Germany for Zwolle and for Groningen as of March 2006). All-cause mortality was collected using hospital records, telephone interviews with either the patient or general practitioner, and coupling with municipal civil registries. All reported variables and outcome measures were available in $\geq 90\%$ of patients except for body mass index (77%), symptom-onset-to-door time (73%), and door-to-balloon time (72%). Follow-up with regard to 30-day and 1-year mortality was completed in all patients.

**Statistical analysis**

Continuous variables were summarized as mean $\pm$ standard deviation or median and interquartile range. Discrete variables were presented as numbers and percentages. To compare groups, we used analysis of variance for normally distributed continuous variables, Kruskal-Wallis test for nonparametric continuous variables, and Pearson’s $\chi^2$ test for
Circadian variation in infarct size in ST-elevation myocardial infarction

Part 1 – Symptom onset

Table 1. Baseline characteristics by symptom onset time and impact on enzymatic infarct size

<table>
<thead>
<tr>
<th>Symptom onset time</th>
<th>Univariable association with infarct size</th>
<th>P</th>
<th>P_interaction *</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Estimate (95% CI)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>00:00-08:00 (n=1751)</td>
<td>-7.0% (-9.0; -4.8)</td>
<td>&lt;0.001</td>
<td>0.434</td>
</tr>
<tr>
<td>08:00-16:00 (n=3198)</td>
<td>+26% (+18; +34)</td>
<td>&lt;0.001</td>
<td>0.263</td>
</tr>
<tr>
<td>16:00-00:00 (n=1850)</td>
<td>+1.1% (+0.3; +1.9)</td>
<td>0.008</td>
<td>0.274</td>
</tr>
<tr>
<td></td>
<td>Pinteraction</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)†</td>
<td>-7.0% (-9.0; -4.8)</td>
<td>&lt;0.001</td>
<td>0.434</td>
</tr>
<tr>
<td>Male gender</td>
<td>+26% (+18; +34)</td>
<td>&lt;0.001</td>
<td>0.263</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>+1.1% (+0.3; +1.9)</td>
<td>0.008</td>
<td>0.274</td>
</tr>
<tr>
<td>Hypertension</td>
<td>-3.3% (-8.9; +2.6)</td>
<td>0.269</td>
<td>0.917</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>-7.5% (-16; +1.3)</td>
<td>0.093</td>
<td>0.581</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>-6.8% (-13; -0.06)</td>
<td>0.048</td>
<td>0.425</td>
</tr>
<tr>
<td>Current smoking</td>
<td>+6.5% (+0.4; +13)</td>
<td>0.035</td>
<td>0.696</td>
</tr>
<tr>
<td>Positive family history</td>
<td>-0.3% (-6.0; +5.7)</td>
<td>0.918</td>
<td>0.528</td>
</tr>
<tr>
<td>Prior myocardial infarction</td>
<td>-24% (-31; -16)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Prior PCI</td>
<td>-22% (-30; -13)</td>
<td>&lt;0.001</td>
<td>0.006</td>
</tr>
<tr>
<td>Prior CABG</td>
<td>-24% (-36; -8.8)</td>
<td>0.003</td>
<td>0.202</td>
</tr>
<tr>
<td>Anterior myocardial infarction</td>
<td>+32% (+24; +40)</td>
<td>&lt;0.001</td>
<td>0.378</td>
</tr>
<tr>
<td>Preprocedural TIMI 0 flow</td>
<td>-131% (+119; +144)</td>
<td>&lt;0.001</td>
<td>0.489</td>
</tr>
<tr>
<td>Single vessel disease</td>
<td>-7.9% (-13; -2.5)</td>
<td>0.005</td>
<td>0.388</td>
</tr>
</tbody>
</table>

Descriptive data is presented as mean ± standard deviation or n (%). CABG, coronary artery bypass grafting; CI, confidence interval; PCI, percutaneous coronary intervention; TIMI, Thrombolysis In Myocardial Infarction

*Interaction between symptom onset time on a continuous scale and the baseline variable in predicting infarct size; †per decade in the infarct size analysis.
categorical variables. The distribution of symptom onset time over the 24-hour clock was tested against the null hypothesis of a uniform likelihood with the Rayleigh test. Symptom onset time was subsequently grouped into three 8-hour periods based on the distribution of symptom onset time and the circadian variation in infarct size: night (00:00-08:00), daytime (08:00-16:00), and evening (16:00-00:00). This 3-group approach is comparable with previous studies and was only used for descriptive analysis. For all other analyses, symptom onset time was transformed into a 4 degrees-of-freedom sinusoid consisting of a 1-period sine, 1-period cosine, 2-period sine, and 2-period cosine variable and handled on a continuous scale. Statistical significance of symptom onset time was tested using the likelihood ratio test.

To study the independent association between enzymatic infarct size (peak CK) and symptom onset time, mixed-effects regression models were used with peak CK as the dependent variable. A random center effect was added to the models. Peak CK and ischemic time were first transformed logarithmically, to account for their skewed distribution. Parameter estimates and 95% confidence intervals (CI) were retransformed into meaningful units in the final models. First, univariable associations between the baseline characteristics listed in Table 1 and peak CK were investigated. Second, subgroup differences in the pattern of circadian variation in infarct size among these baseline characteristics were tested by entering interaction terms between the baseline characteristics and symptom onset time into the regression model. Third, multivariable mixed-effects regression models were constructed to assess if circadian variation in infarct size persisted after adjustment for confounders. In 4 models we adjusted for A) all baseline characteristics listed in Table 1, B) ischemic time, C) baseline characteristics and ischemic time, and D) baseline characteristics, ischemic time, and hemodynamic status on admission. The subgroup interactions found in the initial analysis were accounted for in the multivariable analyses where appropriate. In sensitivity analyses, the multivariable models were recalculated with the omission of body mass index (this variable was missing in >10% of patients) and application of more extensive eligibility criteria as reported in a prior study (additional exclusion of patients with ischemic time >6 hours, preprocedural TIMI flow >0, prior myocardial infarction, prior coronary artery bypass grafting, and postprocedural TIMI flow <1).

Finally, the impact of symptom onset time and infarct size on 30-day and 1-year mortality was tested in univariable Cox proportional hazards
models using stratification by center. Discriminative performance of infarct size in predicting mortality was assessed by calculating the c-statistic. For all analyses, statistical significance was set at P<0.05 (two-tailed). Statistical analyses were performed with IBM SPSS Statistics, version 20.0 (IBM, Armonk, New York) and Stata, version 11.0 (StataCorp, College Station, Texas).

RESULTS

From January 2004 through December 2010, 7252 consecutive patients with STEMI underwent primary PCI. After exclusion of patients with missing symptom onset time (n=282) and missing infarct size (n=171), the total study population consisted of 6799 patients (94%) of which 2908 patients from Groningen and 3891 patients from Zwolle. In the overall study population, the mean age was 63±13 years, 4943 patients (73%) were male, 618 patients (9.2%) had a history of myocardial infarction, and 559 patients (8.3%) had a history of PCI.

Circadian variation

Our study population exhibited the classical circadian variation in symptom onset time with a low incidence of myocardial infarction during the night and a peak in symptom onset during the morning (P<0.001; Figure 1).

Figure 1. Circadian variation in symptom onset time (gray bars) and infarct size (black line with dashed 95% confidence interval). The vertical dashed lines demonstrate how symptom onset was broken down into night, daytime, and evening categories for the descriptive analysis.
Circadian variation was also seen in infarct size ($P=0.001$; Figure 1). Infarct size was largest for patients with symptom onset around 03:00 at night (estimated peak CK 1322 U/l; 95% CI 1217-1436) and smallest for patients with symptom onset around 11:00 in the morning (estimated peak CK 1071 U/l; 95% CI 1001-1146), thus representing a relative reduction in infarct size of 19% between peak and nadir levels. As described earlier, symptom onset time was broken down into 3 groups (Figure 1): night (00:00-08:00), daytime (08:00-16:00), and evening (16:00-00:00). Baseline characteristics by group are shown in Table 1. Patients with symptom onset during the daytime were slightly older ($64\pm12$) as compared with patients with symptom onset at night ($63\pm13$) and in the evening ($62\pm13$; $P<0.001$). The proportion of smokers was lowest in patients with symptom onset during the daytime (43%) and higher in patients with symptom onset at night (47%) and in the evening (49%; $P<0.001$). Patients with symptom onset at night had a markedly longer median symptom onset to door time (170 minutes) as compared with patients with symptom onset during the daytime (137 minutes) and evening (135 minutes; $P<0.001$; Table 2). While differences in door-to-balloon time were statistically significant, the absolute difference in median door-to-balloon time was only 4 minutes (night 40 minutes; daytime 41 minutes; evening 37 minutes; $P<0.001$). There was a clear and significant circadian variation in ischemic time ($P<0.001$; Figure 2). Ischemic time was longest in patients with symptom onset around 03:00 at night (estimate 246 minutes; 95% CI 230-262) and shortest in patients with symptom onset around 18:00 (178 minutes; 95% CI 167-189).

### Table 2. Delay and inhospital parameters by symptom onset time

<table>
<thead>
<tr>
<th>Symptom onset time</th>
<th>00:00-08:00 (n=1751)</th>
<th>08:00-16:00 (n=3198)</th>
<th>16:00-00:00 (n=1850)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemodynamic parameters on admission</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>131 ± 26</td>
<td>129 ± 26</td>
<td>131 ± 27</td>
<td>0.046</td>
</tr>
<tr>
<td>Systolic blood pressure &lt;90 mmHg</td>
<td>53 (3.4)</td>
<td>138 (4.8)</td>
<td>85 (5.1)</td>
<td>0.035</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>78 ± 16</td>
<td>76 ± 16</td>
<td>78 ± 16</td>
<td>0.008</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>75 ± 18</td>
<td>76 ± 18</td>
<td>78 ± 20</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Heart rate &gt;100 bpm</td>
<td>120 (7.7)</td>
<td>223 (7.7)</td>
<td>175 (11)</td>
<td>0.002</td>
</tr>
<tr>
<td>Symptom onset to door time (min)*</td>
<td>170 (110-290)</td>
<td>137 (94-210)</td>
<td>135 (94-210)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Door-to-balloon time (min)*</td>
<td>40 (27-63)</td>
<td>41 (27-64)</td>
<td>37 (26-55)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ischemic time (min)</td>
<td>220 (160-340)</td>
<td>185 (139-264)</td>
<td>180 (134-254)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Postprocedural TIMI 3 flow</td>
<td>1534 (89)</td>
<td>2756 (88)</td>
<td>1619 (88)</td>
<td>0.723</td>
</tr>
</tbody>
</table>

Values are mean ± standard deviation, n (%), or median (interquartile range). TIMI, Thrombolysis In Myocardial Infarction

*Door time reflects time of arrival at the PCI-capable center.
Circadian variation in infarct size in ST-elevation myocardial infarction

representing a relative reduction of 28%. Thus, circadian variation in ischemic time resembled the circadian pattern in infarct size with regard to time of peak risk, but not nadir risk (Figure 2). Postprocedural TIMI flow was similar across symptom onset time groups.

Subgroups
In univariable analysis, both prior myocardial infarction (–24%; 95%CI –31, –16; P<0.001) and prior PCI (–22%; 95%CI –30, –13; P<0.001) were associated with smaller infarct size (Table 1). The strongest predictor of infarct size appeared to be preprocedural TIMI 0 flow (+131%; 95%CI +119, +144; P<0.001). To test if the pattern of circadian variation in infarct size was different in subgroups, interaction terms between the baseline characteristics and symptom onset time (on a continuous scale) were entered into the regression model with infarct size as dependent variable (Table 1). This analysis demonstrated that circadian variation in infarct size was only different in patients with prior myocardial infarction (PInteraction <0.001; Figure 3A) and prior PCI (PInteraction =0.006; Figure 3B). In those subgroups of patients, infarct size followed a remarkable inverse pattern

### Table 3. Independent predictors of infarct size

<table>
<thead>
<tr>
<th>Model</th>
<th>Adjusted for baseline characteristics†</th>
<th>Estimate (95% CI)</th>
<th>P</th>
<th>PInteraction</th>
</tr>
</thead>
<tbody>
<tr>
<td>A:</td>
<td>adjusted for baseline characteristics†</td>
<td>Symptom onset time</td>
<td>–</td>
<td>0.004</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Prior myocardial infarction</td>
<td>–17% (–29; –4.7)</td>
<td>0.009</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Prior PCI</td>
<td>–23% (–34; –11)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>B:</td>
<td>adjusted for ischemic time</td>
<td>Symptom onset time</td>
<td>–</td>
<td>0.015</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ischemic time (per doubling)</td>
<td>+13% (+8.4; +18)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>C:</td>
<td>adjusted for baseline characteristics† and ischemic time</td>
<td>Symptom onset time</td>
<td>–</td>
<td>0.014</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Prior myocardial infarction</td>
<td>–19% (–30; –6.0)</td>
<td>0.005</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Prior PCI</td>
<td>–21% (–32; –8.6)</td>
<td>0.002</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ischemic time (per doubling)</td>
<td>+11% (+6.0; +16)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>D:</td>
<td>adjusted for baseline characteristics†, ischemic time, and hemodynamic status on admission</td>
<td>Symptom onset time</td>
<td>–</td>
<td>0.007</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Prior myocardial infarction</td>
<td>–19% (–30; –5.8)</td>
<td>0.006</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Prior PCI</td>
<td>–21% (–31; –8.0)</td>
<td>0.002</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ischemic time (per doubling)</td>
<td>+10% (+5.3; +15)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Systolic blood pressure &lt;90 mmHg</td>
<td>+40% (+18; +67)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Heart rate &gt;100 bpm</td>
<td>+20% (+6.9; +35)</td>
<td>0.002</td>
</tr>
</tbody>
</table>

CI, confidence interval; PCI, percutaneous coronary intervention

*P value for interaction with symptom onset time; †All variables listed in Table 1, accounting for the interactions with prior myocardial infarction and prior percutaneous coronary intervention
with smaller infarct size for symptom onset at night and larger infarct size during the day and evening. Circadian variation in infarct size did not differ by center ($P_{\text{interaction}} = 0.379$).

**Multivariable analysis**

To test whether circadian variation in infarct size persisted after adjustment for potential confounders, multivariable analysis was performed (Table 3). The association between symptom onset time and infarct size persisted after adjustment for baseline characteristics ($P = 0.004$; $P_{\text{interaction}} = 0.003$ with prior myocardial infarction; $P_{\text{interaction}} = 0.397$ with prior PCI; Model A). Although ischemic time was a strong independent predictor of infarct size (+11% per doubling; 95%CI +6.0, +16; $P < 0.001$), symptom onset time remained associated with infarct size after adjustment for baseline characteristics and ischemic time ($P = 0.014$; $P_{\text{interaction}} = 0.003$ with prior myocardial infarction; $P_{\text{interaction}} = 0.602$ with prior PCI; Model C). Addition of systolic blood pressure and heart rate to the model did not mitigate the association between symptom onset time and infarct size either (Model D). Of note, the interaction between symptom onset time and prior PCI did not persist in the multivariable models. Sensitivity analyses yielded similar results.

**Clinical outcome**

Absolute mortality was 279 patients at 30 days and 449 patients at 1 year. Thirty-day mortality was 2.9% in patients with symptom onset at night, 4.3% in patients with symptom onset during the daytime, and 4.9% in patients with symptom onset during the evening. This relation was statistically significant on a continuous scale ($P = 0.028$; Figure 4A). At 1-year follow-up, mortality rates were 5.3% for symptom onset at night, 7.1% for symptom onset during the daytime, and 7.0% for symptom onset during the evening. This represented a non-significant circadian variation ($P = 0.081$; Figure 4B). Infarct size was closely associated with both 30-day mortality (hazard ratio 1.29 per doubling of peak CK; 95%CI 1.19-1.39; $P < 0.001$) as well as 1-year mortality (hazard ratio 1.14 per doubling of peak CK; 95%CI 1.08-1.21; $P < 0.001$). However, the predictive value of infarct size as a single variable was only modest with regard to 30-day mortality (c-statistic 0.624; 95%CI 0.584-0.664) and 1-year mortality (c-statistic 0.575; 95%CI 0.543-0.606).
Figure 3. Differing patterns of circadian variation in infarct size. Circadian variation in infarct size was significantly different in patients with prior myocardial infarction (A) and prior PCI (B). The dashed lines represent the 95% confidence interval.

DISCUSSION

We analyzed the clinical impact and independent association between symptom onset time and enzymatic infarct size in consecutive STEMI patients undergoing primary PCI at 2 high-volume centers. To the best of our knowledge, our study is larger than all prior studies on this topic combined and is the first to report on subgroups and clinical outcome beyond 30 days. We found substantial circadian variation in infarct size that persisted after adjustment for baseline characteristics, ischemic time, and even hemodynamic parameters on admission. Infarct size was largest in patients with symptom onset at night and smallest during the morning. A different circadian pattern was seen in patients with prior myocardial infarction. These patients had smaller infarct size at night and larger infarct size during the daytime and evening. Despite its association with infarct size, symptom onset time was not a significant predictor of 1-year mortality.
The circadian pattern with largest infarct size at night and smallest infarct size in the morning we observed is similar to that reported in the studies by Reiter and Fournier. In the study by Suárez-Barrientos, however, a biphasic pattern was reported with smallest infarct size around midnight and 15:00. Arroyo and co-workers reported on larger infarct size between 00:00 and 12:00 as compared with 12:00-24:00. Ammirati et al. failed to confirm circadian variation in their population. These studies have been criticized on a number of points, including single center design, dichotomization or use of a simple sine function to model circadian variation, lack of multivariable adjustment for both baseline characteristics and ischemic time, use of extensive exclusion criteria, and inclusion of patients treated with PCI as well as thrombolysis. Our study design allowed us to overcome these limitations by using a large multicenter registry of patients routinely treated with primary PCI and application of minimal exclusion criteria. Adjustment for baseline characteristics and ischemic time is important in the context of circadian variation in infarct size, since baseline characteristics are also subjected to circadian variation. Prehospital delay, in-hospital delay, and total ischemic time are all known to exhibit circadian variation with the longest delays usually occurring at night. This will impact infarct size, as prior prospective and retrospective studies have clearly linked ischemic time to enzymatic infarct size as well as infarct size measured by magnetic resonance imaging and single-photon emission computed tomography (SPECT). In our study, the circadian variation in infarct size persisted after adjustment for baseline characteristics and ischemic time. This finding lends support to the hypothesis of circadian dependence of endogenous myocardial tolerance to ischemia/reperfusion injury. In addition to the central circadian clock located in
Circadian variation in infarct size in ST-elevation myocardial infarction

Part 1 – Symptom onset

the suprachiasmatic nucleus of the hypothalamus, peripheral molecular clocks have been identified in numerous tissues including the human heart. These peripheral circadian clocks are synchronized by the central circadian clock and are thought to be implicated in circadian regulation of cellular function. Indeed, approximately 8% of cardiac gene expression was found to be subjected to circadian variation in a key animal study. Although it is likely that endogenous circadian clocks help to match physiological and metabolic processes with the differing requirements during the day- and nighttime, evidence is emerging that they may also play a role in disease pathogenesis. In a rodent model of myocardial infarction, it was shown that infarct size was 3.5 times greater if induced at the sleep-to-wake transition as compared with the wake-to-sleep transition. This pattern was not seen in mice that were genetically modified to lack the cardiomyocyte circadian clock. Two proteins that have been implicated in mitochondrial permeability and cell death in response to stress (such as ischemia/reperfusion injury) were identified as possible molecular mediators: glycogen synthase kinase-3β (GSK-3β) and v-akt murine thymoma viral oncogene (Akt). Patients with a history of myocardial infarction had smaller infarct size, possibly due to prior loss of myocardium or pre-existing collateral circulation. Interestingly, an inverse pattern of circadian variation in infarct size was observed in these patients. A possible explanation for the different circadian pattern in infarct size is that patients with prior coronary artery disease are more likely to use beta-blockers and aspirin. Both of these classes of drugs are known to potentially alter circadian variation in the onset of myocardial infarction and may also impact the circadian variation in infarct size.

An alternative explanation is that the endogenous circadian variation in myocardial ischemic tolerance is altered in patients with prior coronary artery disease. This hypothesis is supported by the observation that ischemia alters myocardial molecular circadian clock function in a rat model. Although we found clear circadian variation in infarct size, symptom onset time did not significantly predict 1-year mortality. We did find circadian variation in 30-day mortality, but the pattern differed from the circadian variation in infarct size with lower mortality during the night and higher mortality during the morning and evening. A similar mortality pattern has been noted in another recent study. Previously, our group presented an in-depth analysis of these circadian mortality patterns. At night, myocardial infarction is a relatively infrequent event since sympathetic tone is lower, resulting in lower levels of circulating catecholamines and a
lower blood pressure and heart rate. In addition, thrombogenicity and cortisol levels are lower during the night. These factors may favorably impact mortality in patients that do experience myocardial infarction at night despite their larger infarct size. In this regard, it is important to highlight our finding that infarct size as a single variable provides only modest discriminatory capacity in predicting early and intermediate death. Therefore, it may well be that the 19% circadian variation in infarct size we observed in our study is too subtle to translate into a similar circadian mortality pattern (also considering the low mortality rates). With a hazardous period at night and a beneficial period during the morning, circadian variation in infarct size seems to be “out of phase” with the previously mentioned circadian variation in hemodynamic, hormonal, and thrombogenic factors, thereby further obscuring its impact on mortality. Finally, survivor bias may also play a role as unstable high-risk patients with symptom onset during the day may have a better chance of reaching the hospital and undergoing primary PCI in the first place.

**Limitations**

Several limitations of our study should be considered. Inherent to our study design, we cannot fully exclude the possibility of residual confounding by unmeasured factors such as operator skills and fatigue and variations in staffing levels of physicians and nurses. However, epicardial reperfusion as measured by postprocedural TIMI flow was similar throughout the day. No data were available on medical treatment of patients. While we were able to report on ischemic time and time of arrival at the PCI-capable center was available in most patients, unavailability of time of first medical contact limited optimal discrimination between patient delay and system delay. Similarly, no specific data were available on the race of the included patients, although we expect the vast majority to be of the Caucasian race. Furthermore, we used peak CK to measure infarct size. This approach is less accurate than measurement of infarct size using imaging modalities such as SPECT. Nonetheless, peak CK is a well-validated measure of infarct size that has shown to outperform many other biochemical measures of infarct size in a study that used SPECT-determined infarct size as the gold standard. Moreover, peak CK has also been used in most of the previous studies that have reported on circadian variation in infarct size, thus facilitating direct comparison.

**Conclusions**

In the present observational multicenter study in consecutive STEMI patients undergoing primary PCI, we found substantial circadian variation in infarct...
size that was independent of baseline characteristics and ischemic time. An inverse pattern was seen in patients with prior myocardial infarction. Our study strengthens the emerging concept of circadian dependence of myocardial tolerance to ischemia/reperfusion injury, although further confirmation in different ethnic groups and in studies that use imaging modalities to measure infarct size is warranted. Further elucidation of the molecular mechanisms underlying this phenomenon may help to identify potential therapeutic targets to alter this pattern and reduce ischemia/reperfusion injury in patients with STEMI.
REFERENCES


