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Circadian Rhythms in Patients With ST-Elevation Myocardial Infarction

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Background—Circadian rhythms with regard to time of symptom onset for patients with acute myocardial infarction have been observed, although their relationship to outcomes has been debated. We evaluated these rhythms in patients with ST-elevation myocardial infarction as a function of the 24-hour circadian cycle.

Methods and Results—The relationship between onset of symptoms during the 24-hour circadian cycle and prehospital delays from symptom onset to hospital arrival, timeliness of reperfusion, and in-hospital death was assessed in 2143 patients with ST-elevation myocardial infarction presenting from 2004–2008 at 1 of 3 tertiary-care healthcare ST-elevation myocardial infarction systems. There was a significant association between time of onset and the circadian cycle, with the greatest percentage (39%) of patients experiencing onset between 8 AM and 3 PM ($P<0.001$). Time of onset was associated with prehospital delay and timeliness of reperfusion. Patients with onset from 12 AM to 5:59 AM had median prehospital delays of 121 minutes versus 70 minutes from 12 PM to 5:59 PM ($P<0.001$). Patients with onset time from 12 AM to 5:59 AM had median door-to-balloon times of 75 minutes versus 60 minutes from 6 AM to 11:59 AM ($P<0.001$). Using multivariable modeling to control for baseline patient characteristics, prehospital delay, and timeliness of reperfusion, there was no significant association between time of symptom onset with in-hospital death.

Conclusions—Patients with ST-elevation myocardial infarction exhibit significant circadian patterns in symptom onset, prehospital delay, and timeliness of reperfusion. Patients who develop symptoms from 12 AM to 5:59 AM present with longer prehospital delays and have longer door-to-balloon times. After multivariable adjustment, there was no significant association between circadian patterns of time of onset and in-hospital death. (*Circ Cardiovasc Qual Outcomes*. 2010;3:382-389.)

Key Words: circadian rhythm ■ myocardial infarction ■ reperfusion injury

The effect of circadian rhythm on acute myocardial infarction has been the subject of considerable scientific interest and controversy.^{1–8} Some authors have identified an early to midmorning peak in mortality rates among patients with acute myocardial infarction, whereas others have identified different patterns.^{1–8} The distribution of when patients experience onset of symptoms as well as outcomes of care as a function of circadian rhythm have not been evaluated in a contemporary cohort of patients undergoing reperfusion therapy.

Multiple biological factors have been postulated as contributing to these circadian rhythms, including cyclic patterns in heart rate⁹; QT interval dispersion^{10–12}; hemostasis^{13–15}; platelet aggregation^{13,16}; lipoprotein levels^{17,18}; hormonal levels²; and sympathetic tone, particularly on awakening.¹⁹ In addition, early morning hours often represent the nadir levels of once-a-day morning dosing of cardioprotective medica-

tions. Furthermore, there are extrinsic environmental factors that also exhibit circadian patterns, such as patient perception of symptoms, willingness to go to the hospital, and choice and timeliness of reperfusion therapies during regular versus off hours. Both biological and environmental factors likely contribute to symptom onset and outcomes in acute myocardial infarction.

To assess circadian patterns in symptom onset and outcomes in acute myocardial infarction in contemporary practice, we collated and analyzed data from 3 tertiary-care healthcare systems, each of which had an organized system of care for patients with ST-elevation myocardial infarction (STEMI): Mayo Clinic (Rochester, Minn), Prairie Cardiovascular Consultants (Springfield, Ill), and Central Minnesota Heart Center (St Cloud, Minn). We sought to evaluate how variations in the onset of symptoms, prehospital delay, timeliness of reperfusion therapy, and in-hospital death relate as a function of the 24-hour circadian cycle.

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WHAT IS KNOWN

- Circadian rhythms have been identified in multiple physiological processes that may affect cardiovascular diseases, yet the association of these with acute myocardial infarction onset, treatment, and outcomes remains the subject of interest and controversy.

WHAT THE STUDY ADDS

- Patients with ST-elevated myocardial infarction have significant circadian patterns in symptom onset, prehospital delay, and timeliness of reperfusion.
- Patients who develop symptoms between 12 AM and 5:59 AM present with longer prehospital delays and have longer door-to-balloon times.
- After adjusting for differences in patient characteristics and treatment, there is no independent association between the timing of symptom onset and inpatient mortality.

Methods

STEMI Systems of Care

Details about the Mayo Clinic STEMI system have been published previously.²⁰ The system includes 28 regional community hospitals up to 150 miles away from a central hub (Saint Mary's Hospital [Rochester, Minn]). Patients presenting to Saint Mary's Hospital with STEMI were treated with primary percutaneous coronary intervention (PCI); those presenting within 3 hours to regional hospitals were treated with full-dose fibrinolytic therapy unless there were contraindications. Regional patients were immediately transferred to Saint Mary's Hospital and underwent rescue PCI if they had failed to reperfuse after fibrinolytic therapy or an early pharmacoinvasive strategy for those who appeared to have successfully reperfused with fibrinolytic therapy. Patients presenting to regional hospitals >3 hours after symptoms were transferred to Saint Mary's Hospital for primary PCI. Additionally, patients who had onset of symptoms <3 hours and with either a contraindication to fibrinolytic therapy or a considered high clinical risk because of cardiogenic shock or incessant ventricular arrhythmias were transferred to Saint Mary's Hospital for primary PCI. Consecutive patients (n=674) with STEMI from May 17, 2004, to December 31, 2007, were included in this analysis.

Details about the Prairie Cardiovascular Consultants STEMI system have been published previously.²¹ The system includes 6 regional community hospitals up to 88 miles away from 2 tertiary receiving hospitals. Patients presenting to the 2 tertiary hospitals were treated with primary PCI. For patients presenting to the regional hospitals, reperfusion strategy was based on the risk of hemorrhage and the availability of rapid interhospital transport. Patients at low risk for hemorrhage received full-dose fibrinolysis when rapid interhospital transport was not available. Patients treated with full-dose fibrinolytic therapy were immediately transferred to a receiving hospital for assessment and rescue PCI, if indicated. When rapid interhospital transport was available, patients were transferred for primary PCI. Patients with a contraindication to fibrinolytic therapy also were transferred for primary PCI. Consecutive patients with STEMI (n=597) from January 1, 2005, to December 31, 2007, were included in this analysis.

The Central Minnesota Heart Center STEMI system consists of 23 regional community hospitals up to 100 miles away from a central hub located in St Cloud, Minn. All patients presenting to Central Minnesota Heart Center or the regional hospitals were treated with primary PCI as the preferred reperfusion strategy. When there was an anticipated delay in interhospital transport due to inclement weather,

16 (1%) patients were treated with half-dose fibrinolytic therapy and then transferred for facilitated PCI. Consecutive patients (n=872) with STEMI from April 5, 2004, to January 13, 2008, were included in this analysis.

Data Collection

A trained research coordinator at each STEMI system prospectively collected and recorded the following time points while using the same data element definitions: (1) onset of symptoms; (2) arrival at the first hospital; (3) arrival at the tertiary hospital for those patients who required interhospital transfer; (4) time of drug administration for those treated with full-dose fibrinolytic therapy; and (5) time to first balloon inflation or use of another therapeutic interventional device, such as a stent or a thrombectomy catheter, for those treated with primary PCI. For the 16 patients treated with a facilitated PCI strategy, time to reperfusion was defined as first hospital door-to-balloon time. Demographic, clinical, and angiographic variables along with time metrics and in-hospital death also were collected. Because this analysis evaluated circadian rhythms, patients (n=163) in whom the time of symptom onset was not known were excluded.

Definitions

For bivariable descriptive analyses of baseline characteristics, the 24-hour clock was divided into 4 groups: group 1, 12 AM to 5:59 AM; group 2, 6 AM to 11:59 AM; group 3, 12 PM to 5:59 PM; group 4, 6 PM to 11:59 PM. The distribution of time of symptom onset, prehospital delay defined as the time from symptom onset to first hospital arrival, and in-hospital death from any cause were modeled as a function of circadian rhythm using a 24-hour clock as a continuous variable.

Statistical Analysis

Continuous variables are summarized as mean±SD, unless otherwise specified. Discrete variables are presented as frequency and percentages. Group differences were tested using 1-way ANOVA and Pearson χ^2 tests. Kaplan-Meier method was used to estimate distributions for time-to-event variables, such as time from symptom onset to first hospital arrival and time to reperfusion therapy. These statistics are summarized as median and interquartile range (Q1, Q3), with group differences tested by the log-rank test. $P<0.05$ was considered statistically significant.

The distribution of time of symptom onset over the 24-hour clock was tested against the null hypothesis of a uniform likelihood using the Rayleigh test.²² Sinusoidal functions were used to model prehospital delay times and in-hospital death as functions of the time of symptom onset. The 4 degrees of freedom sinusoid consisted of 1-period cosine, 1-period sine, 2-period cosine, and 2-period sine variables. Likelihood ratio tests were used to evaluate the statistical significance of symptom onset time.

Multiple-logistic mixed-effect regression models were used to investigate whether the association between time of symptom onset and in-hospital death could be explained by baseline patient clinical and hospital processes of care variables. A random site effect was included to account for intrasite correlation. The following variables were selected a priori on the basis of clinical relevance to the outcome of in-hospital death: prehospital delay from symptom onset to first hospital door, door-to-balloon time, door-to-needle time, age, sex, heart rate, systolic blood pressure, anterior myocardial infarction, diabetes, serum creatinine, cardiogenic shock, and congestive heart failure at presentation. Linear associations were assumed to avoid overfitting. All analyses were performed using statistical software (SAS version 9.1.3).

Results

The study population consisted of 2143 patients with STEMI and a known time of symptom onset. There were few significant differences in baseline demographic and clinical characteristics of the patient groups based on the time of symptom onset with the exceptions being age, heart rate,

Table 1. Patient Characteristics

Variable	12:00–5:59 (n=436)	6:00–11:59 (n=673)	12:00–5:59 (n=566)	6:00–11:59 (n=468)	<i>P</i>
Age, y	62.2±13.4	61.5±12.9	60.2±12.9	60.3±13.2	0.036
Male sex	307 (70)	513 (76)	434 (77)	350 (75)	0.10
Diabetes	72 (17)	97 (14)	78 (14)	82 (18)	0.29
Hypertension	250 (57)	389 (58)	307 (54)	256 (55)	0.52
Initial heart rate, bpm	75.8±19.8	74.0±18.7	77.4±19.4	78.6±19.2	<0.001
Initial SBP, mm Hg	133.9±32.8	134.8±31.3	135.5±31.3	136.7±28.5	0.60
Creatinine, mg/dL	1.2±0.9	1.1±0.4	1.1±0.3	1.1±0.6	0.51
Peripheral vascular disease	17 (5)	29 (6)	25 (6)	32 (9)	0.11
History of stroke	27 (9)	28 (6)	21 (6)	21 (7)	0.27
CHF status					0.020
Never	339 (91)	546 (95)	453 (95)	375 (92)	
Previous	3 (1)	2 (0)	8 (2)	9 (2)	
Current	31 (8)	27 (5)	15 (3)	23 (6)	
Prior MI	69 (16)	130 (19)	93 (16)	84 (18)	0.41
Prior PCI	74 (18)	126 (20)	99 (19)	77 (17)	0.76
Location of MI					0.75
Anterior	152 (35)	227 (34)	184 (33)	159 (34)	
Lateral	36 (8)	50 (8)	49 (9)	47 (10)	
Inferior	242 (56)	387 (58)	331 (59)	256 (55)	
Cardiogenic shock	36 (8)	45 (7)	41 (7)	28 (6)	0.59
Hyperlipidemia	237 (59)	386 (62)	351 (67)	277 (64)	0.12
Smoking status					0.034
Never	146 (35)	244 (38)	179 (33)	143 (32)	
Former	87 (21)	146 (23)	116 (21)	90 (20)	
Current	186 (44)	253 (39)	247 (46)	215 (48)	
Body mass index, kg/m ²	29.3±5.7	29.3±6.0	29.3±6.1	29.1±5.9	0.93
Ejection fraction, %	47.3±12.6	48.3±12.4	49.8±12.6	47.5±12.3	0.042
Median (Q1, Q3) prehospital delay from symptom onset to first hospital door, min	121 (60–290)	82 (49–157)	70 (41–150)	83 (44–180)	0.001

Data are presented as mean±SD or no. (%), unless otherwise indicated. CHF indicates congestive heart failure; MI, myocardial infarction; and SBP, systolic blood pressure.

congestive heart failure, smoking status, and ejection fraction (Table 1). Patients in group 3 were younger (60.2±12.9 years) compared with those in group 1 (62.2±13.4 years; $P=0.036$). In addition, there were significant differences in history of congestive heart failure, smoking status, and ejection fraction. The distribution of time of symptom onset as a function of the 24-hour clock is shown in Figure 1. There was a significant association between the time of day and likelihood of the onset of symptoms ($P<0.001$). The most common time of symptom onset occurred from 8 AM to 3 PM, during which time 39% of patients experienced onset of symptoms.

There was a significant relationship between time of symptom onset and the prehospital delay from symptom onset to first hospital arrival ($P<0.001$) (Figure 2 and Table 1). Patients in group 1 had a median time of 121 minutes (Q1, Q3, 60 to 290 minutes) before presenting to the emergency department compared with patients in group 3 who had a prehospital delay of 70 minutes (Q1, Q3, 41 to 150 minutes).

Ten percent of patients received fibrinolytic therapy, whereas 90% were treated with primary PCI either at the tertiary hospital or after having been transferred from a regional hospital (Table 2). The median door-to-needle time was 29 minutes (Q1, Q3, 16 to 35 minutes), median door-to-balloon time for patients presenting directly to a PCI center was 67 minutes (Q1, Q3, 54 to 91 minutes), and median door-to-balloon time for patients who were transferred to a PCI center was 117 minutes (Q1, Q3, 99 to 143 minutes). There were significant differences as a function of the circadian clock in door-to-balloon times for patients who presented directly to a PCI center (nontransferred patients) and underwent primary PCI (Table 3). Patients in group 2 had a median door-to-balloon time of 60 minutes compared to patients in group 4 and group 1 in whom the median door-to-balloon time was 75 minutes ($P<0.001$). Patients who were transferred to a PCI center for primary PCI had similar door-to-balloon times regardless of time of symptom onset, although these times were longer when compared to

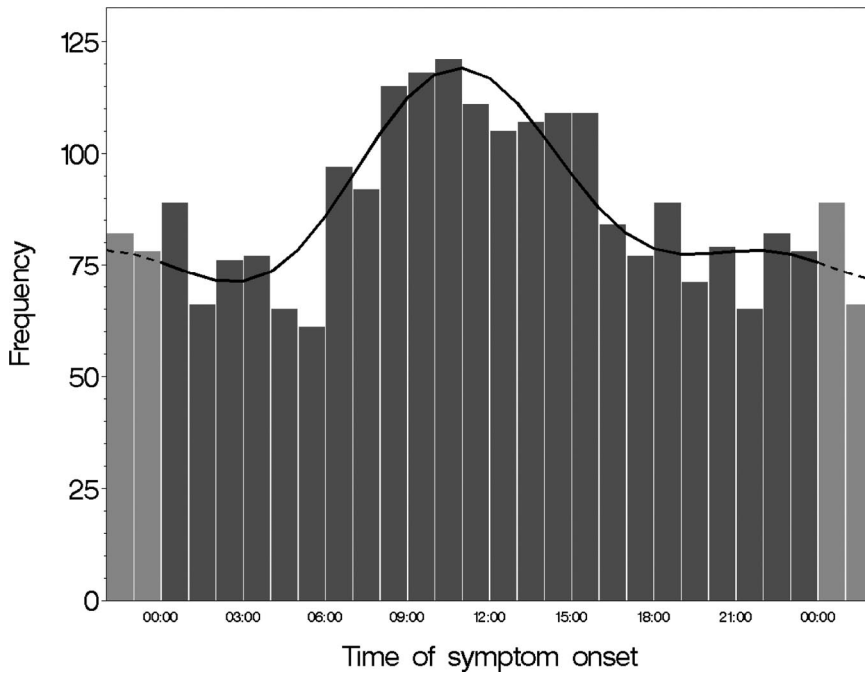


Figure 1. Frequency of STEMI incidents by hour of symptom onset. The line is a sinusoidal smoothing function indicating the average circadian trends. The dark bars represent a single 24-hour period. The plot indicates that STEMI were more frequent during the late morning and early afternoon hours.

patients presenting directly to a PCI center presumably because of the time taken for transfer.

In-Hospital Death

There were 63 (2.9%) in-hospital deaths. In-hospital mortality was modeled as a function of symptom onset time using a 4 degree-of-freedom sinusoidal function with a random site effect to account for intrasite correlations. This model indicated a significant association ($P=0.037$) with estimated mortality risk, ranging from 1.21% with a symptom onset time of 9:43 AM to 4.55% at 2:42 AM (Figure 3). Multivariable regression models were used to adjust for baseline risk

conferred by prehospital delay time, door-to-balloon time, door-to-needle time, age, sex, heart rate, systolic blood pressure, anterior myocardial infarction, diabetes mellitus, serum creatinine, cardiogenic shock, and congestive heart failure at presentation. After adjusting for these variables, the association between time of symptom onset and in-hospital mortality was mitigated and no longer significant ($P=0.26$) (Figure 3). Variables significantly associated with in-hospital death in the model were age ($P=0.049$) and cardiogenic shock ($P=0.017$) (Table 4). Heart rate also was nearly significantly associated ($P=0.055$) with death. To investigate which of these risk factors could be a true confounder for

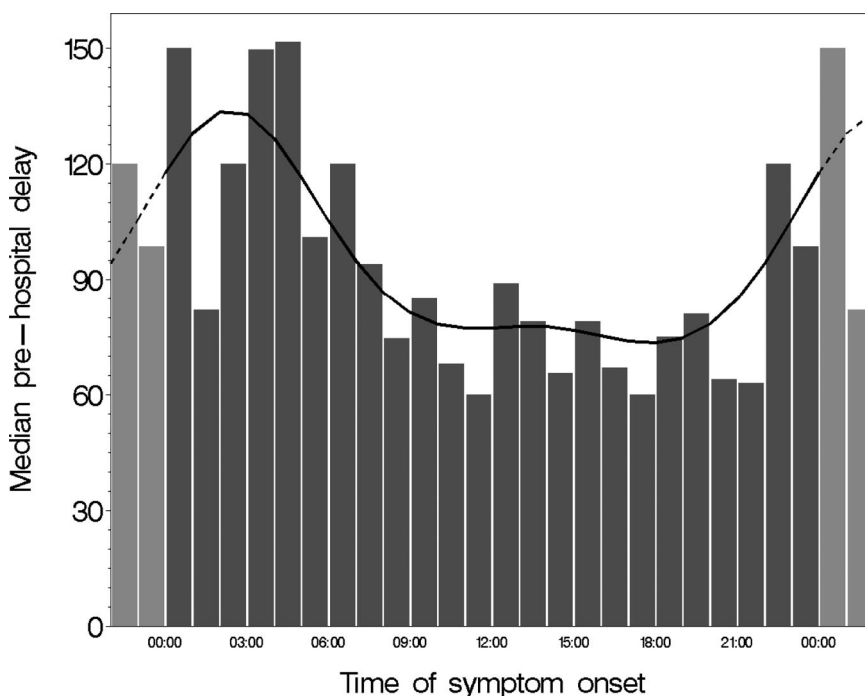


Figure 2. Median prehospital delay time (minutes) by hour of symptom onset. The line is a sinusoidal smoothing function. The plot indicates that the longest delays tended to occur between 2400 and 0459 hours.

Table 2. Reperfusion Therapy Received

Variable	Value
Type of treatment	
Primary PCI	898 (42)
Facilitated PCI	16 (1)
Transferred for PCI	1015 (47)
Fibrinolytics	214 (10)
Door to needle, min	29 (16–35)
Nontransferred patients door to balloon, min	67 (54–91)
Transferred patients door to balloon, min	117 (99–143)

Data are presented as no. (%) or median (Q1, Q3). N=2143.

relationship of time of symptom onset and in-hospital death, we adjusted for the association between time symptom onset and in-hospital death with each factor separately. Two of these risk factors, heart rate and cardiogenic shock, were adequate confounders in that adjusting for them alone produced a nonsignificant association ($P=0.066$ and 0.078 , respectively) between time of symptom onset and in-hospital death. Adjusting for all 3 of these results, the P value was 0.20 for the association between time of symptom onset and in-hospital mortality. We also investigated a model for circadian effect of symptom onset adjusted by modifiable covariates, namely prehospital delay, time to balloon, and time to needle. This model retained the significant circadian pattern of mortality risk by symptom onset time ($P=0.044$).

Discussion

The present study of patients presenting with STEMI to 3 regional systems identified patterns of acute myocardial infarction based on a 24-hour clock. The first main finding was a significant circadian rhythm of symptom onset that most commonly occurred from 8 AM to 3 PM (39%). Second, there is an association between symptom onset time and duration of prehospital delay, and patients with symptom onset between 12 AM and 6 AM tended to wait longer than patients with symptom onset at other times of the day. These circadian rhythm patterns for symptom onset time and prehospital delay were remarkably similar across the 3 systems. All 3 sites had post-12 AM peaks in risk. Third, although choice of reperfusion strategy at the 3 STEMI centers did not vary according to time of symptom onset, there were varia-

tions in median door-to-balloon times for nontransferred patients depending on the time of symptom onset. Finally, after multivariable adjustment, there was no association between symptom onset time and in-hospital death. The highest risk of mortality ($\approx 4\%$) occurred in patients with symptom onset between 1 AM and 4 AM and between 4 PM and 6 PM. This association, however, was not significant after adjusting for clinical risk factors, suggesting that the risk of mortality truly is related to these other variables and not to the specific time of presentation.

Circadian patterns of myocardial infarction have been the subject of considerable study and controversy.^{23,24} In the Physicians Health Study,²³ a randomized, double-blind, placebo-controlled trial of alternate-day aspirin administration by 22 071 male physicians from the United States, there were 342 cases of nonfatal myocardial infarction during the 5-year follow-up. In the patients who were not randomized to aspirin, there was a bimodal pattern of circadian variation, with the primary peak occurring between 4 AM and 10 AM and a secondary, but smaller peak, in the evening. Nearly 25% of the infarctions occurred during a 3-hour high-risk period within 3 hours after awakening. Similarly, during the same time frame, Pepine²⁵ found the peak in the circadian variation of acute myocardial infarction between 6 AM and 12 PM. Leiza et al³ evaluated 41 244 infarctions in a Spanish multicenter study of both patients with and without STEMI, using a series of tests based on a multiple sinusoidal cosiner analysis to study circadian rhythm. They found a circadian pattern in all subgroups. Using the variable of time of pain onset as the initiating index event, there was a morning peak at 10:10 AM. A similar finding was identified in a smaller study of 200 Indian patients in whom 50% of infarctions occurred between 4 AM and 10 AM.²⁶

Not all studies have been concordant. In a more recent series, Goldberg et al²⁷ evaluated a longitudinal study of 3837 residents of Worcester, Massachusetts, hospitalized for acute myocardial infarction between 1986 and 1997. Of these patients, 1755 were found to have a Q-wave myocardial infarction. In this study, there was no marked difference in the timing of hospital evaluation frequency during which the patients presented. Twenty-seven percent presented from 6 AM to 12 PM, 24% from 12 PM to 6 PM, 26% from 6 PM to 12 AM, and 23% from 12 AM to 6 AM.

Table 3. Reperfusion Therapy Received

Variable	12:00–5:59 (n=436)	6:00–11:59 (n=673)	12:00–5:59 (n=566)	6:00–11:59 (n=468)	P
Type of treatment,					0.35
Primary PCI	169 (39)	298 (44)	223 (39)	208 (44)	
Facilitated PCI	3 (1)	3 (0)	4 (1)	6 (1)	
Transferred for PCI	222 (51)	304 (45)	283 (50)	206 (44)	
Fibrinolytics	42 (10)	68 (10)	56 (10)	48 (10)	
Door to needle, min	29 (22–35)	25 (19–33)	24 (17–31)	29 (16–35)	0.98
Nontransferred patients door to balloon, min	75 (61–101)	60 (49–81)	64 (53–83)	75 (59–112)	0.006
Transferred patients door to balloon, min	119 (99–147)	118 (99–146)	114 (98–133)	119 (99–143)	0.71

Data are presented as no. (%) or median (Q1, Q2).

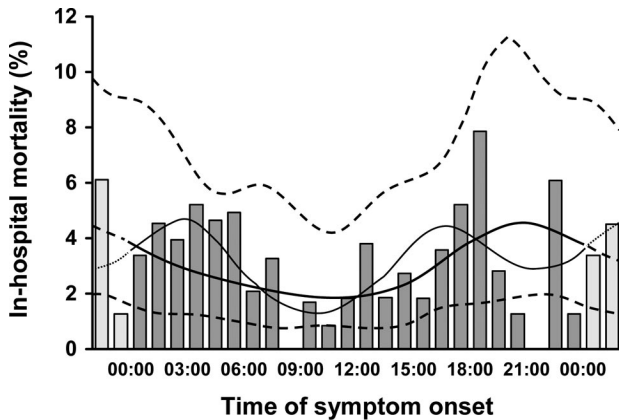


Figure 3. In-hospital death percentage by hour of symptom onset before (black line) and after (blue line) multivariable adjustment. The dashed blue lines represent 95% CIs for the risk-adjusted circadian pattern. The plot indicates that before multivariable adjustment, the lowest risk of in-hospital death occurred in STEMI with onset times between 0600 and 1159 hours.

The field is complicated by several issues. Smolensky et al⁹ performed a population-based epidemiology and clinical case study. Although they identified a temporal pattern with a single morning peak between 6 AM and 12 PM, there were several factors that the authors believed confounded the results. The authors postulated that the day-night pattern is at least partly dependent on the endogenous circadian rhythm that is synchronized by the daily routine of sleep. However, approximately 20% of the working population is involved in night- and rotating shift employment. Therefore, the authors concluded that the time-of-day studies are not likely to accurately represent the actual chronorisk of vulnerable individuals.

Potential putative mechanisms of a circadian rhythm also have been the focus of considerable study. These have included several broad groups: changes in physiological substances such as cortisol, melatonin, lipoproteins, and adhesion molecules; circadian rhythm in hemostatic parameters; and changes in physiological behavior, such as T-wave potentials, heart rate, and blood pressure, among others.^{9–19,24,28} Several of these mechanisms may affect treatment outcomes. Specifically, changes in hemostatic parameters and adhesion molecules may affect treatment with either fibrinolytic therapy or PCI. A more hypercoagulable state may render the patient more resistant to fibrinolytic therapy. In addition, circadian rhythms in blood pressure may affect afterload in the face of an acute ischemic event. Finally, variability in inflammation factors might affect plaque vulnerability.

There is another possibility that requires consideration that is harder to quantitate but has been studied and relates to the potential for circadian rhythm in the efficacy and timeliness of care provided by the medical team.^{29–33} Some studies have identified that patients undergoing PCI during off hours have worse outcomes than patients treated at other times. Glaser et al³⁰ studied potential factors associated with poorer prognosis for patients undergoing primary PCI during off hours. They evaluated clinical, angiographic, and procedural characteris-

Table 4. Multivariable Logistic Regression Model for In-Hospital Death

Variable	Odds Ratio	95% CI	P
Time of symptom onset*	0.26
Age, per decade	1.68	1.01–2.81	0.049
Male sex	0.91	0.22–3.72	0.80
Cardiogenic shock	14.2	3.09–65.5	0.017
Heart rate, per 20 bpm	1.64	0.97–2.76	0.055
Systolic blood pressure, per 30 mm Hg	0.70	0.35–1.41	0.16
Serum creatinine, per 0.5 mg/dL	1.17	0.89–1.54	0.13
Diabetes mellitus	1.57	0.34–7.20	0.33
CHF at presentation	0.55	0.06–5.46	0.38
Time to balloon, per 30 min	1.02	0.92–1.14	0.47
Time to needle, per 10 min	0.82	0.37–1.85	0.41
Delay (onset to ED) time, per 60 min	1.01	0.87–1.17	0.77
Anterior MI	1.07	0.29–3.96	0.85

CHF indicates congestive heart failure; ED, emergency department; and MI, myocardial infarction.

*Four degrees of freedom function. See Figure 3 for a depiction of the estimated circadian pattern.

tics in 685 patients undergoing primary PCI during either routine hours or off hours. In the 2 groups, the primary end points assessed were in-hospital death, myocardial infarction, and target vessel revascularization, and the authors found that patients presenting during off hours were generally sicker with more shock and had more multivessel coronary artery disease. They also found that when the PCI was performed during the night, there were more procedural complications, including coronary dissection, which was the case even though baseline lesion classification was similar during routine and off hours. From a clinical standpoint, the in-hospital mortality, myocardial infarction, and repeat target vessel revascularization rates were increased by 2.7-fold in patients treated with primary PCI during off hours. Whether this finding relates to operator and team fatigue; small changes in awareness, diagnosis, and treatment of complications; delays in reperfusion therapy; the fact that typically less-experienced physicians are present at least in teaching hospitals during off hours; and the known observed difference in platelet function or thrombotic state is unclear. Differentiating the variable contribution of all these variables is very complex. All 3 centers have well-organized systems of care based on established protocols to optimize timeliness of reperfusion therapy and care of patients with STEMI. Accordingly, these results in terms of circadian rhythm on in-hospital mortality may not be germane for all institutions.

In addition, our study documents that fixed variables, including age, heart rate, and cardiogenic shock, were important and, indeed, the most closely associated with in-hospital mortality. Such fixed variables cannot be modified, but it is possible that by minimizing door-to-balloon time or symptom onset-to-hospital presentation may mitigate some of the adverse effects of these variables. Of interest, although the time from symptom onset to first hospital door presentation was longer in patients in group 1, the circadian patterns in time of symptom onset were significantly associated with

in-hospital death. This finding may be the result of several factors. First, it may be related to significant survivor bias, with patients either not surviving to hospital or not being considered a candidate for catheterization. A second possibility relates to the fact that in our series, the differences in door-to-balloon time were only 15 minutes for nontransferred patients with STEMI and were nonexistent for transferred patients with STEMI. Third, a confounding factor is the fact that the time interval from symptom onset to balloon inflation is only an estimate of the time from when the artery became occluded to when it was reperfused. Symptom onset is only a guide to when the acute event started. Many patients with STEMI may progress intermittently from partial to complete occlusion and then back to partial occlusion in the very early stages of acute infarction. Finally, of course, are the small numbers of patients studied (ie, 2143, 63 deaths). This factor does not preclude that an association between symptom onset and in-hospital mortality exists and our CI for in-hospital death is very wide.

Limitations

There are several limitations to this analysis. We only have data on patients with STEMI who presented to the hospital; data on those who did not present to the hospital, who died at home, or who died during transport to the hospital were not available for analysis. Hence, there is a survival bias that could have confounded our results. Additionally, patient ability to precisely recall the time of symptom onset may be variable. Furthermore, our analysis of in-hospital death is affected by low statistical power, as there were only 63 events. This lack of power was evident in the multivariable model.

Conclusions

Patients with STEMI exhibit significant circadian rhythms. The most common time of onset is between 8 AM and 3 PM (39% of patients). Patients who develop symptoms between 12 AM and 6 AM waited longer before seeking medical care and have longer door-to-balloon times. Using a 24-hour continuous clock, there was no significant association between time of symptom onset and in-hospital mortality after adjusting for clinical risk factors.

Disclosures

None.

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