Circadian variations of ischemic burden among patients with myocardial infarction undergoing primary percutaneous coronary intervention

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Background Several parameters of cardiovascular physiology and pathophysiology exhibit circadian rhythms. Recently, a relation between infarct size and the time of day at which it occurs has been suggested in experimental models of myocardial infarction. The aim of this study is to investigate whether circadian rhythms could cause differences in ischemic burden in patients with ST-elevation myocardial infarction (STEMI) undergoing primary percutaneous coronary intervention (PPCI).

Methods In 353 consecutive patients with STEMI treated by PPCI, time of symptom onset, peak creatine kinase (CK), and follow-up at 30 days were obtained. We divided 24 hours into 4 time groups based on time of symptom onset (00:00-05:59, 06:00-11:59, 12:00-17:59, and 18:00-23:59).

Results There was no difference between the groups regarding baseline patients and management's characteristics. At multivariable analysis, there was a statistically significant difference between peak CK levels among patients with symptom onset between 00:00 and 05:59 when compared with peak CK levels of patients with symptom onset in any other time group (mean increase 38.4%, $P < .05$). Thirty-day mortality for STEMI patients with symptom onset occurring between 00:00 and 05:59 was significantly higher than any other time group ($P < .05$).

Conclusion This study demonstrates an independent correlation between the infarct size of STEMI patients treated by PPCI and the time of the day at which symptoms occurred. These results suggest that time of the day should be a critical issue to look at when assessing prognosis of patients with myocardial infarction.

Background

In mammals, many physiologic mechanisms exhibit diurnal variations, and most of these rhythms are independent of environmental timing cues. These endogenous circadian rhythms are composed of intracellular timing mechanisms termed *circadian clocks*. The circadian clock is an evolutionarily conserved timekeeping system that coordinates the physiology of the organism with daily changes in the environment. The biological clock is composed of transcriptional-translational feedback loops. In mammals, the master clock is located in the suprachiasmatic nuclei, but most peripheral tissues contain circadian clocks.[1] These transcriptional modulators have been identified within the heart (cardiomyocytes, vascular smooth muscle cells, endothelial cells, and fibroblasts)[2-5] and have been shown to regulate apoptosis, contractile function, metabolism, and gene expression and therefore confer the selective advantage of anticipation, permitting the cell to respond appropriately to a stimulus at a given time of the day.[6] Recently, experimental studies have shown that cardiomyocyte circadian clock affects the response of the heart to various stresses including ischemia/reperfusion by modulating multiple cardioprotective signaling pathways.[6,7]

It is well known that onsets of adverse cardiac events, such as sudden cardiac death,[8] stroke,[9] and myocardial infarction increase from 6 AM.[10] The higher incidence of myocardial infarction during the latter part of the morning (6 AM to noon) can be explained by the

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combination of rise in arterial blood pressure, hormonal stimulation (β-adrenergic, cortisol),[11] hyperreactivity of platelets,[12] and shear stress resulting in atherosclerotic plaque disruption and thrombosis. If frequency of myocardial infarction is higher during the morning, severity of myocardial infarction in terms of infarct size could have a different time pattern. In fact, a circadian vulnerability variations to ischemia has just recently been suggested with controversial results.[13,14] Accordingly, we speculate that time of the day onset of myocardial infarction could affect ischemic burden in patients with ST-elevation myocardial infarction (STEMI) undergoing primary percutaneous coronary intervention (PPCI).

Method

Patient population

Between January 01, 2009, and December 31, 2010, 588 consecutive STEMI patients underwent a PPCI at the University Hospital of Lausanne, Switzerland. Among them, patients with symptom-to-first-medical-contact time >12 hours, patients for whom time of symptom onset was unknown, patients with unknown peak creatine kinase (CK) levels and patients with a previous treatment by fibrinolysis or addressed to surgery for coronary artery bypass graft (CABG) were excluded. A total of 353 patients were finally included (Figure 1). We divided 24 hours into 4 time groups based on time of symptom onset (00:00-05:59, 06:00-11:59, 12:00-17:59, and 18:00-23:59). Laboratory, clinical, hemodynamic, angiographic, and demographic data were collected from the local database. Blood sampling for CK was performed at baseline (admission) and every 4 hours post-PCI until peak CK was reached.

Clinical follow-up

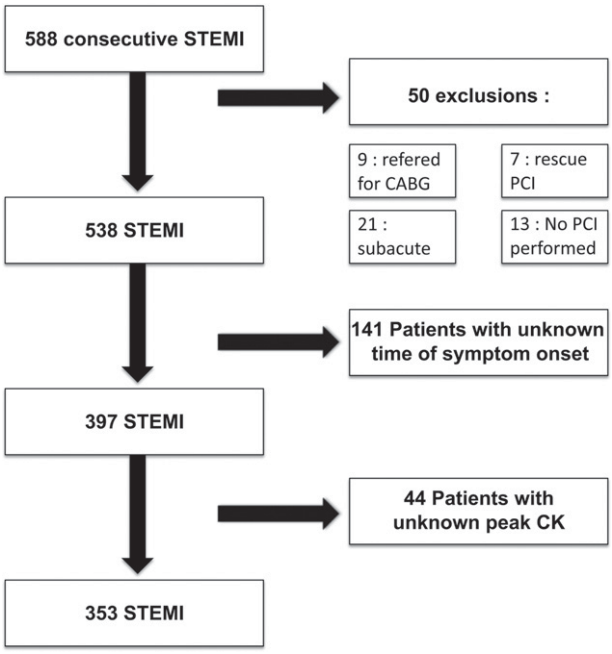
Patients were sent a written questionnaire to report their clinical events. When needed, patients and/or their general practitioners were contacted by telephone for additional information.

Statistical analysis

Expecting in the time group 00:00 to 05:59 a frequency of myocardial infarction onset of 20% and assuming in this group peak CK levels 40% higher than in all other time groups (06:00-23:59), a total of 322 patients was needed to detect the expected difference with an estimated power of 80% at a 2-side α of .05.

Statistical analysis was carried out using SPSS 15.0 software (SPSS, Inc, Chicago, IL), and significance was defined as $P < .05$. Continuous variables are expressed as mean ± SD. Categorical variables are reported as frequencies and percentages. Student *t* test or analysis of variance was used to compare continuous variables, as appropriate. Comparisons between categorical variables were evaluated using Pearson χ^2 test. To analyze the distribution of events over the 24-hour clock, we tested a sinusoidal function that modeled the distribution of events against a null hypothesis of a uniform likelihood. For multivariate analysis, a multiple linear regression analysis with peak CK levels as a continuous dependent variable was used. We included in the multivariate analysis the comparison of time group 00:00 to 05 :59 versus all other time groups (06:00-23:59) as a dichotomous variable. Major demographic characteristics were also included in the multivariate model. Kaplan-Meier curves for survival were constructed and compared between the 2 groups (first time group compared with all other time groups) with the log-rank test. $P < .05$ was considered statistically significant.

Figure 1



Study flow chart.

This study complied with the Declaration of Helsinki regarding investigations in humans and was approved by the Institutional Ethics Committee at the University Hospital of Lausanne, Switzerland. The authors are solely responsible for the design and conduct of this study, all study analyses, and drafting and editing of the manuscript. No extramural funding was used to support this work.

Results

Baseline clinical characteristics

Table I summarizes baseline clinical characteristics. No difference was found among the 4 time groups, except for the variable "prior PCI." Of note, there was no difference in myocardial infarction localization between the time groups.

Management characteristics

Table II summarizes baseline management characteristics. There was no difference among the 4 time groups in terms of procedure performance. Symptom-to-PCI hospital time or admission-to-needle time was similar between time groups. Of note, no difference in procedure duration, thrombolysis in myocardial infarction (TIMI) flow score at

Table I. Patients' clinical and angiographic characteristics

Group variable	00:00-05:59 (n = 62)	06:00-11:59 (n = 109)	12:00-17:59 (n = 112)	18:00-23:59 (n = 70)	*P*
Age (y), mean ± SD	64.02 ± 12.76	67.55 ± 12.1	66.38 ± 12.53	64.61 ± 13.43	.251
Male sex	51 (82%)	81 (74%)	80 (71%)	45 (64%)	.133
Diabetes	13 (21%)	28 (26%)	19 (17%)	9 (13%)	.16
Hypertension	29 (47%)	53 (49%)	63 (56%)	41 (59%)	.371
Smoking	36 (58%)	60 (55%)	55 (49%)	36 (51%)	.666
Obesity	18 (29%)	28 (26%)	29 (26%)	10 (14%)	.182
Cholesterol	29 (47%)	64 (59%)	51 (46%)	32 (46%)	.174
Aspirin	7 (15%)	17 (19%)	15 (15%)	14 (22%)	.6291
Clopidogrel	3(6%)	7(8%)	4(4%)	4(6%)	.7536
Statin	5 (10%)	14 (16%)	18 (18%)	16 (25%)	.2021
β-Blockers	5 (10%)	11 (12%)	12 (12%)	9 (14%)	.9422
ACE inhibitors/ARB	14 (29%)	32 (36%)	29 (29%)	21 (33%)	.7807
Initial heart rate (beat/min), mean ± SD	73.26 ± 16.94	72.6 ± 14.61	77.68 ± 16.39	76.42 ± 14.68	.1729
SBP (mm Hg), mean ± SD	127.6 ± 25.87	130.3 ± 21.15	128.7 ± 21.45	120.5 ± 22.34	.0778
DBP (mm Hg ± SD)	77.18 ± 14.74	75.23 ± 12.91	79.03 ± 12.72	73.75 ± 14.12	.1201
Location of MI					
Inferior	29 (47%)	45 (41%)	43 (38%)	38 (54%)	
Anterior	26 (42%)	52 (48%)	59 (53%)	22 (31%)	
Lateral	7 (11%)	9 (8%)	9 (8%)	9 (13%)	
Prior MI	0 (0%)	6 (6%)	7 (6%)	7 (10%)	.1
Prior PCI	2 (3%)	15 (14%)	5 (4%)	7 (10%)	.031
Ejection fraction (%), mean ± SD	46.48 ± 11.64	46.46 ± 11.9	48.91 ± 10.94	48.57 ± 11.17	.6833

ACE, Angiotensin-converting enzyme; *ARB*, angiotensin II receptor blockers; *SBP*, systolic blood pressure; *DBP*, diastolic blood pressure; *MI*, myocardial infarction.

Table II. Management characteristics

Group variable	00:00-05:59 (n = 62)	06:00-11:59 (n = 109)	12:00-17:59 (n = 112)	18:00-23:59 (n = 70)	*P*
Symptom-to-PCI hospital time (min), median ± SD	189 ± 181.1	162 ± 303.6	154.5 ± 159.3	152.5 ± 219.3	.4156
Admission-to-needle time (min), median ± SD	59.72 ± 28.3	61.63 ± 40.04	60.14 ± 42.09	69.15 ± 48.21	.4994
TIMI score at end of PCI, mean ± SD	2.750 ± 0.5853	2.736 ± 0.6836	2.686 ± 0.7872	2.838 ± 0.5534	.7792
Rentrop grade, mean ± (SD)	0.57 ± 0.73	0.51 ± 0.76	0.46 ± 0.63	0.45 ± 0.74	.7063
No. of stent, mean ± SD	1.208 ± 0.4104	1.2 ± 0.4577	1.112 ± 0.3176	1.228 ± 0.4233	.288
Size of the stent (mm), mean ± SD					
Length of the stent	24.29 ± 9.876	27.26 ± 13.27	26.11 ± 12.89	24.85 ± 8.003	.4924
Diameter of the stent	3.044 ± 0.5036	3.113 ± 0.5063	2.984 ± 0.6502	3.102 ± 0.6076	.4897
Procedure (PCI) duration (min), mean ± SD	67.92 ± 24.17	65.16 ± 27.93	67.76 ± 23.17	62.78 ± 26.79	.6479

the end of the procedure, or stent characteristics was observed between the different time groups.

Frequency distribution of STEMI symptoms onset

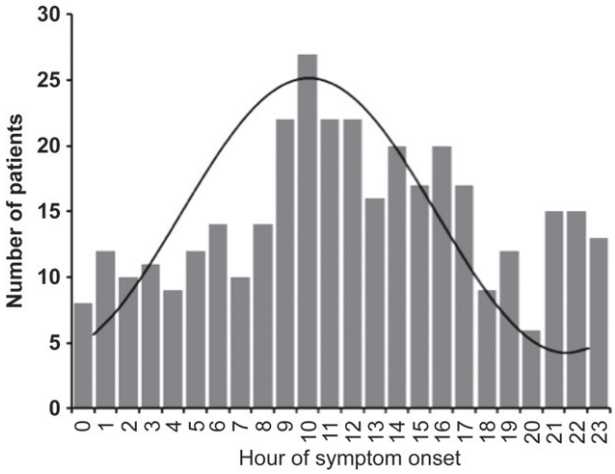
The frequency of myocardial infarction onset was higher between 08:00 and 14.59 (45.3% of patients) compared with the rest of the day (15:00-7:59). The modelized sinus function fitted better than a null hypothesis of a uniform likelihood ($P < .001$) (Figure 2). Comparing the 4 time groups, frequency of myocardial infarction was lower in time group 00:00 to 05:59 (17.56%) when compared with other time groups (30.88% for time group 06:00-11:59, 31.73% for time group 12:00-17:59, and 19.83% for time group 18:00-23:59).

Peak CK and time groups

There was a significant relationship between time of symptom onset and peak CK levels. Creatine kinase levels among patients with symptom onset between 0:00 and 05:59 were significantly higher than in the 3 other groups of patients with symptom onset at any other time of the day. Mean CK levels among patients with symptom onset between 00:00 and 05:59 were 3484 ± 3467 versus 2507 ± 2142 versus 2533 ± 2214 versus 2508 ± 2057 for patients with symptom onset between 06:00 and 11:59, 12:00 and 17:59, and 18:00 and 23:59, respectively ($P < .05$) (Figure 3A).

To exclude bias caused by "off-hours" duty, a similar analysis was performed in patients presenting during the

Figure 2



Frequency distribution of myocardial infarction onset during a 24-hour period. A statistically significant percentage was found in the time frame of 08:00 to 15:00($P < .05$).

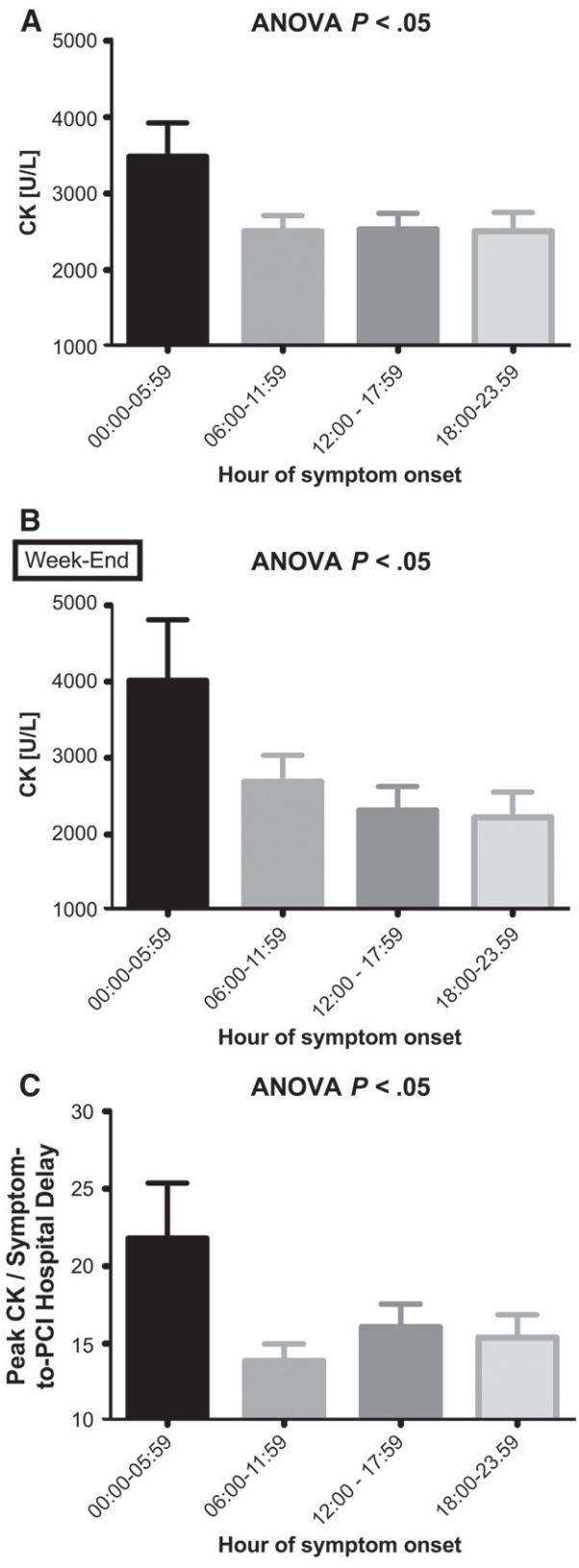
weekend. There was a statistically significant difference between CK levels among patients with symptom onset between 00:00 and 05:59 when compared with CK levels of patients with symptom onset in any other time group (4013 ± 3382 vs 2687 ± 2229 [06:00 and 11:59] vs 2309 ± 2017 [12:00 and 17:59] vs 2226 ± 1423 [18:00 and 23:59], $P < .05$) (Figure 3B).

Because "symptom-to-PCI hospital time" is a variable of utmost importance in terms of infarct size, we calculated the ratio (peak CK/symptom-to-PCI hospital time in minutes) for every patient of each group. There was a statistically significant difference between mean peak CK/symptom-to-PCI hospital time in minutes among patients with symptom onset between 00:00 and 05:59 when compared with patients with symptom onset in any other time group (21.79 ± 28.16 vs 13.88 ± 11.20 [06:00 and 11:59] vs 16.06 ± 14.83 [12:00 and 17:59] vs 15.39 ± 11.60 [18:00 and 23:59], $P < .05$) (Figure 3C).

Multivariable analysis

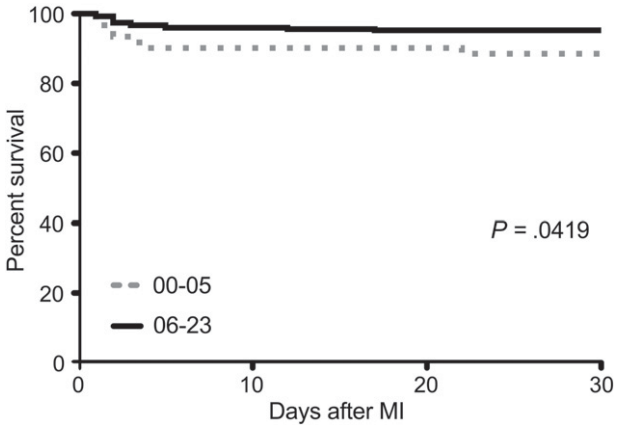
Given the significant higher CK levels in time group 0:00 to 05:59 than any other time group of the day, we performed a multiple-logistic mixed-effect regression

Figure 3



Mean peak CK levels distribution in the different time groups. A statistically significant difference of mean peak CK levels was observed between the time groups 00:00 to 05:59 compared with any other time groups of the day ($P < .05$) (A). Similar difference was observed either during "off-hours" duty ($P < .05$) (B) or when peak CK level was balanced to "symptom-to-PCI hospital times" ($P < .05$) (C).

Figure 4



Kaplan-Meier curves showing percent survival free from death in the time group 00:00 to 05:59 and in the other time group.

model. This difference remained significant after multivariable analysis (regression coefficient 2.41, 95% CI 153.54-1513.20, log-rank $P = .016$) and was not explicable by age, gender, hypertension, diabetes, cholesterol, smoking habit, obesity, myocardial infarction localization, previous myocardial infarction, or previous PCI.

Clinical follow-up

Follow-up at 30 days was obtained in 94.9% of the population. There was no significant difference in the in-hospital mortality rate among the 4 time groups. We observed 16 in-hospital deaths (4.53%): 6 deaths (9.68%) occurred in the time group 00:00 to 05:59, 4 (3.67%) in the time group 06:00 to 11:59, 5 (4.46%) in the time group 12:00 to 17:59, and 1 (1.43%) in the time group 18:00 to 23:59 ($P = .1363$). However, there was a significant difference in the mortality rate at 30 days among the 4 time groups. We observed 20 deaths at 30 days (5.97%): 7 (11.48%) deaths occurred in the time group 0:00 to 05:59, 5 (4.95%) for the time group 06:00 to 11:59, 6 (5.66%) for the time group 12:00 to 17:59, and 2 (2.99%) for the time group 18:00 to 23:59. The Kaplan-Meier percentage survival estimates at 30 days were 88.53% in the time group 00:00 to 05:59 and 95.26% in the other time group ($P < .05$) (Figure 4).

Discussion

In this study, conducted in 353 consecutive patients with STEMI undergoing PPCI, we observed a circadian variation in peak CK after myocardial infarction, a surrogate of myocardial infarct size. Infarct size was higher in patients with symptom onset during the period between 00:00 and 05:59, and this was independent of baseline clinical or management variables. In addition, we observed a higher mortality rate at 30 days among the group of patients with symptom onset between 00:00 and 05:59.

Knowing the time of the day is a key issue for any organism, allowing it to react appropriately to all sorts of stress. Indeed, the demands placed on an organism fluctuate dramatically over the course of the day, and anticipation regarding these demands gives a selective advantage, allowing the organism to react before the stimuli occur. Cellular mechanisms exist in the cardiovascular system, like in every eukaryote cell, that orchestrate oscillation of tissue function during a 24-hour period. For instance, experimental studies have shown that cardiac redox status and fatty acid metabolism,[6,15] but also myocardial contractile function, are regulated in a circadian manner.[16] It is therefore tempting to wonder whether ischemic stress would have a different impact on the myocardium over a 24-hour period. Recent studies have shown a profound effect of time of the day on ischemic burden in mouse models of myocardial infarction.[7,17] In addition, these results were blunted in mouse models, genetically modified at the level of the circadian clock mechanism.[7,17] Evidence of such regulation mechanism in humans is sparse and controversial.[13,14] Holmes et al[13] assessed the circadian variation of symptom onset and in-hospital mortality in 2,143 patients with STEMI. The authors found a significant association between time of symptom onset and circadian cycle, with the greatest percentage of patients with symptom onset between 08:00 and 15:00. Our results are in line with the results from Holmes et al. In the present study, we found a significant percentage of patients with symptom onset between 08:00 and 15:00 (45.3% vs 39% in Holmes' study). If symptom onset arises more frequently between 08:00 and 15:00, ischemic burden caused by vascular obstruction might have a different variation over a 24-hour period. This issue has been assessed in the study of Holmes et al, where the authors found a nonsignificant trend of higher in-hospital mortality between 00:00 and 05:59 and also between 18:00 and 23:59 after multivariable adjustment. Indeed, Holmes et al found a higher prehospital delay time in the time group 00:00 to 05:59 (121 minutes vs 70-83 minutes for the other time groups), which creates an inherent bias although these variables were included in the statistical analysis. To limit such hurdle, we limit the study to one single center during a limited period to keep homogeneous management characteristics. In addition, our population was restricted to patients having STEMI and treated by PPCI. This diverges from the study of Holmes et al, where >10% of patients received systemic thrombolysis. Accordingly, these different management characteristics observed in the study of Holmes et al might have blunted a potentially significant higher in-hospital mortality. On the other hand, we did not find

either difference in terms of in-hospital mortality. Indeed, we found a difference in mortality rate only at 30 days.

The study recently published from Suarez-Barrientos et al[14] assessed peak CK and troponin level as surrogate of infarct size in 811 patients with STEMI. The authors found a significant higher infarct size in the time group 06:00 to 11:59 and 18:00 to 23:59 even after multivariable adjustment. Our results are different in terms of time at which the myocardium has maximal vulnerability to ischemia. We found higher peak CK in the time group 00:00 to 05:59 compared with any time group. Of note, Suarez-Barrientos et al observed a significant higher incidence of anterior wall myocardial infarction in the time group of 06:00 to 11:59 and a significant lower rate of PPCI in this same time group. These latter variables are indeed of utmost importance in terms of infarct size. In our study, the rate of anterior wall infarction was similar among all time groups as well as PPCI procedure duration, stent characteristics, and TIMI flow at the end of the procedure. In addition, we found a higher 30-day mortality in the time group of 00:00 to 05:59 putting forward this period of symptom onset critical for patients with STEMI. We certainly cannot rule out a regional effect where a wake-up time shift would explain the differences between the study of Suarez-Barrientos et al and the present study.

Limitations

The number of patients included remains relatively small, but our STEMI system of care allowed us to obtain 4 homogeneous groups in terms of clinical characteristics, management, and delays. In addition, peak CK is only a surrogate of infarct size, and magnetic resonance imaging with late gadolinium enhancement may have given additional infarct size information. Of note, no statistical difference in left ventricular ejection fraction was observed among the 4 time groups at admission, and we do not have echocardiography at follow-up for all patients.

Conclusions

The present study shows circadian variations in infarct size and in 30-day mortality in patients with STEMI treated by PPCI after multivariable adjustment. These results highlight the influence of the time of day on the pathophysiology of myocardial infarction and suggest that myocardium has higher vulnerability to ischemia during the period of 00:00 to 05:59. Accordingly, the time of day should be a critical issue to look at when assessing the prognosis after STEMI.

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