Novel imaging aspects in the management of patients with acute coronary syndromes

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Time of symptom onset and value of myocardial blush and infarct size on prognosis in patients with ST-Elevation Myocardial Infarction

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Abstract

In patients with ST-segment elevation myocardial infarction (STEMI) the time of onset of ischemia has been associated with myocardial infarction (MI) size. Myocardial blush grade (MBG) reflects myocardial response to ischemia/reperfusion injury, which may differ according to time of day. The aim of our study was to explore the 24-hour variation in MBG and MI size in relation to outcomes in STEMI patients. A retrospective multicenter analysis of 6970 STEMI patients was performed. Time of onset of STEMI was divided into four 6-hour periods. STEMI patients have a significant 24-hour pattern in onset of symptoms, with peak onset around 09:00 hour. Ischemic time was longest and MI size, estimated by peak creatine kinase concentration, was largest in patients with STEMI onset between 00:00 and 06:00 hour. Both MBG and MI size were independently associated with mortality. Time of onset of STEMI was not independently associated with mortality when corrected for baseline and procedural factors. Interestingly, patients presenting with low MBG between 00:00 and 06:00 had a better prognosis compared to other groups. In conclusion, patients with symptom onset between 00:00 and 06:00 hour have longer ischemic time and consequently larger MI size. However, this does not translate into a higher mortality in this group. In addition, patients with failed reperfusion presenting in the early morning hours have better prognosis, suggesting a 24-hour pattern in myocardial protection.

Introduction

Cardiovascular physiological and biological factors exhibit circadian rhythms, which influence cardiovascular diseases [1,2,3]. The onset of acute coronary events, such as acute myocardial infarction (MI), sudden cardiac death and stent thrombosis, has a profound peak incidence in the morning hours [4,5,6,7]. Circadian variations in intrinsic factors such as adrenergic activity and thrombogenicity, have been proposed as important contributing factors of this time-of-day dependence [8,9].

In ST-elevation myocardial infarction (STEMI) patients, MI size reflects the amount of myocardial injury. Restoring myocardial blood flow, by means of primary percutaneous coronary intervention (PCI), positively influences the myocardial response to injury. Recent studies show a significant association of time of symptom onset with MI size, demonstrating larger MI size in the early morning hours, consequently resulting in a reduction of left ventricular function and increased incidence of heart failure [10,11,12]. The time-of-day dependent variation of MI size implies also a circadian variation in (intrinsic) vulnerability of the myocardium to ischemia [10,12].

Myocardial blush grade (MBG) represents an angiographic measurement of microvascular (capillary) perfusion. It reflects myocardial response to ischemic injury and reperfusion and is associated with both short and long term outcomes after acute MI [13,14]. A time-of-day variation to ischemic injury may therefore be reflected in a circadian variation of MBG.

The aim of our study was to evaluate if the time of symptom onset influences the MBG and MI size in relation to outcomes in a cohort of STEMI patients. We hypothesize that there is a time of symptom onset dependent relation of MBG to MI size resulting in differences in outcomes.

Materials and methods

Study population

We performed retrospective analysis of consecutive patients admitted with STEMI to two large PCI centers (University Medical Center Groningen, Groningen and Isala Clinics, Zwolle) in the Netherlands. Patients who presented in the period from January 2004 to December 2010 were included. The study was approved by the local ethics committee and conformed to the ethical standards outlined by Portaluppi et al. [15].

Uniform ambulance protocols involving all patients with symptoms suspect for STEMI are used in both hospitals. All patients were transported to the catheterization laboratory, and acute coronary angiography and subsequent primary PCI were performed as part of the routine treatment for all STEMI patients. The strategy of intervention (e.g. balloon dilatation, thrombus aspiration, stent placement) was left

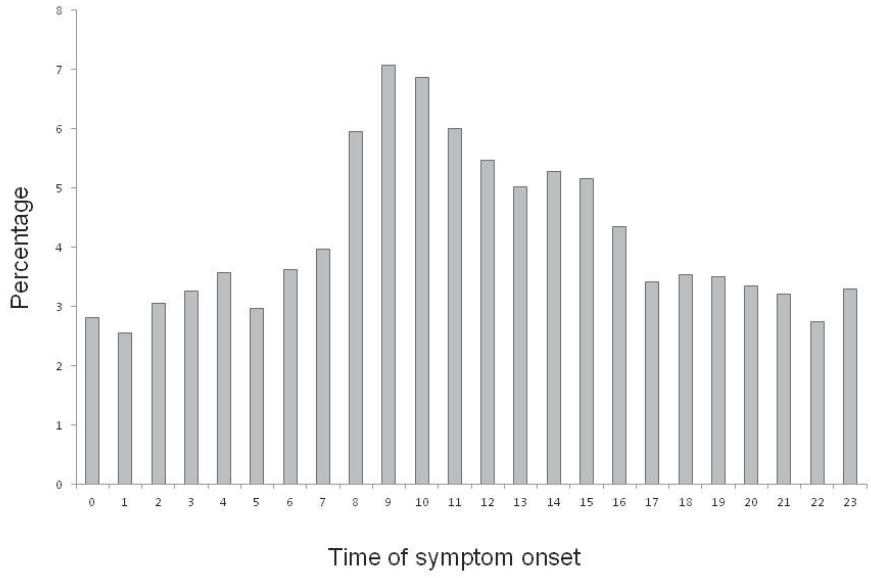


Figure 1. Percentages of patients with time of symptom onset per hour group - Percentage of patients per hour group. 0 = 00:00 – 01:00 hour; 1= 01:00 – 02:00 hour; 2 = 02:00 – 03:00; etc.

to the operator's discretion. This protocol is in accordance with the guidelines of the European Society of Cardiology, American College of Cardiology and the American Heart Association [16,17].

STEMI was defined as the presence of chest pain suggestive of myocardial ischemia with ECG signs compatible with acute MI (ST-segment elevation ≥2mm in V_2-V_3 and ≥1mm in all other leads) [18]. All patients received pretreatment with acetylsalicylic acid (500mg intravenously), heparin (5000IU), and clopidogrel (300 or 600mg orally, according to at that time valid guidelines) during transportation to the hospital, or these drugs were administered at the emergency ward in case of patient's self-referral.

All patients of whom time of symptom onset was known and who were treated by PCI within 12 hours after symptom onset, as stated in international guidelines [16,17], were included in the analyses.

Data collection

Patient characteristics were recorded on admission in either case record forms or a computer-based database. The primary independent variable was time of symptom onset, which is defined as the self reported symptom onset time. To gain insight in the 24-hour pattern of complaints of the patients, 1-hour intervals were selected to perform figurative analysis (Figure 1). Subsequently, patients were divided into four

groups according to the time of symptom onset: Group 1: 00:00–06:00 hour; group 2: 06:00–12:00 hour; group 3: 12:00–18:00 hour; and group 4: 18:00–00:00 hour. This is in accordance with recent literature [10,12,19].

Pre-hospital delay was defined as the time form onset of chest pain to the time of arrival at the hospital (door time point). Door to balloon time was defined as the time from arrival at the hospital to the restoration of epicedial blood flow by first intervention (stenting, balloon dilatation of thrombus aspiration) during primary PCI. Ischemic time was defined as the time from onset of chest pain to the restoration of epicardial blood flow by first intervention during primary PCI. Vital signs (systolic and diastolic blood pressure and heart rate) were collected at arrival in the catheterization laboratory. Epicardial reperfusion was assessed according to the Thrombolysis In Myocardial Infarction (TIMI) flow grading system before and after PCI [20]. Microvascular reperfusion was assessed by MBG as follows (14): 0=no myocardial blush, or contrast density; 1=minimal myocardial blush; 2=moderate myocardial blush but less than that obtained during angiography of a contralateral or ipsilateral non-infarct-related coronary artery; and 3=normal myocardial blush comparable to that obtained during angiography of a contralateral or ipsilateral non-infarct-related coronary artery. Procedural success was defined as TIMI flow 3 with MBG 2 to 3 after PCI [21]. MI size was estimated by peak levels of serum creatine kinase (CK) and myocardial-band of CK (CKMB). CK and CKMB measurements were collected in all patients following a standardized protocol at admission and 3, 6, 12 and 24 hours after primary PCI. Marker levels of CK and CKMB were determined as a UV assay and immunologic UV assay (Mega, Merck, Darmstadt, Germany) from January 2004 till March 2006 and thereafter as a UV assay and an immunologic UV assay (Modular P, Roche, Mannheim, Germany) in Groningen and as a UV assay and an immunologic UV assay (Modular P, Roche, Mannheim, Germany) in Zwolle. Clinical follow-up data were collected from hospital records, telephone contact (with either the general practitioner or the patient) and through coupling of municipal mortality records. Reinfarction was defined as the onset of symptoms of ischemia combined with new ST-segment elevations or an increase of serum CK of CKMB to at least twice the upper limit of the normal range. Major adverse cardiac event was defined as death, reinfarction or target vessel revascularization (either by PCI or coronary artery bypass grafting).

Statistical analysis

Normally distributed continuous variables are presented as mean±SD, unless otherwise specified. Continuous variables with skewed distribution are presented as

medians with interquartile range (Q1 and Q3). Categorical variables are presented as numbers and percentages. Group differences were tested using Kruskal-Wallis, ANOVA, log- rank and Pearson χ^2 tests where appropriate.

The distribution of time of symptom onset over 24 hours was tested against the null hypothesis of a uniform distribution with the Rayleigh test [22]. Multivariable Cox regression analysis was fitted to analyze the predictive value of MI size and MBG on all-cause mortality. Baseline and procedural variables: time of symptom onset, age, gender, history of diabetes, systolic blood pressure, heart rate and ischemic time were selected for both models beforehand. Time of symptom onset was modeled using sinusoidal functions. The four-degree of freedom sinusoidal function consisted of 1-period sine, 1-period cosine, 2-period sine and 2-period cosine variables [19]. The likelihood ratio test was used to evaluate the statistical significance of time of symptom onset. Ischemic time and CK were first transformed logarithmically, to account for its skewed distribution. Retransformation of parameter and 95% confidence intervals into meaningful units was performed in the final model. The Kaplan-Meier method was used for survival analyses for groups categorized in low/high MBG (MBG 0/1 vs. MBG 2/3) and above/below median peak CK levels. Group differences were tested using the logrank test. Logistic regression analysis was fitted to calculate odds ratios for each group stratified by high/low MBG and above/below median peak CK levels. The group with lowest mortality was used as a reference category. The bonferroni method was used to adjust *p* values for multiple testing. Statistical significance was defined as *p* value of <0.05. Statistical analyses were performed using STATA version 11 (College Station, TX).

Results

From January 2004 until December 2010, a total of 7850 patients with STEMI treated with primary PCI were included: 3360 in Groningen and 4490 in Zwolle. Time of onset of complaints was unknown in 282 patients, and 598 of the remaining patients had time from symptom onset to first intervention of >12 hours. Therefore, 6970 patients were included in the final analyses. MBG was available in 82% of these patients.

There was a significant 24-hour variation in onset of STEMI symptoms with peak onset at 09:00 (Figure 1), as estimated by Rayleigh test (p<0.001).

Baseline characteristics are shown according to the 6-hour intervals as described in the methods section. The characteristics were comparable between the different time groups except for age, gender, body mass index, heart rate, family history of heart diseases, and smoking status (Table 1).

There was a significant difference between the groups in pre-hospital delay,

Table 1. Baseline characteristics

Variable	00:00 - 5:59	6:00 - 11:59	12:00 - 17:59	18:00 - 23:59	P-value
N =	1269	2335	1998	1368	
Demographics					
Age (years)	62.8±12.6	64.0±12.6	63.2±12.6	62.2±12.9	<0.001
Sex (female)	30.1 (383)	26.9 (628)	25.9 (518)	28.4 (388)	0.046
Body mass index (kg/m2)	26.4 [24.4-29.3]	26.3 [24.2-28.9]	26.2 [24.2-29.0]	26.6 [24.5-29.4]	0.022
Heart rate	75.1±18.0	74.8±17.6	76.4±18.8	78.3±19.8	<0.001
Systolic blood pressure	130.5±26.1	129.7±25.7	129.1±26.3	130.8±27.3	0.288
Diastolic blood pressure	77.2±16.1	77.3±15.8	76.4±15.8	77.9±16.8	0.090
Heart rate >100 bpm	8.0 (91)	6.6 (137)	8.8 (158)	11.3 (137)	<0.001
Systolic blood pressure <90 mmHg	3.4 (39)	4.3 (90)	4.8 (86)	5.7 (69)	0.060
Medical history					
History of hypertension	39.1 (480)	34.9 (786)	35.5 (681)	35.5 (463)	0.085
History of diabetes	12.8 (161)	11.5 (265)	10.1 (198)	11.3 (154)	0.120
Hypercholesterolemia	25.2 (293)	24.6 (533)	22.5 (403)	24.1 (302)	0.288
Smoker	49.0 (592)	41.0 (900)	46.3 (867)	48.8 (634)	<0.001
Family history	46.2 (548)	40.9 (895)	41.4 (777)	43.1 (553)	0.021
History of MI	9.2 (115)	9.3 (214)	9.6 (187)	8.8 (119)	0.913
History of PCI	7.5 (95)	8.7 (201)	8.6 (172)	7.7 (105)	0.502
History of CABG	3.1 (38)	3.1 (72)	2.7 (53)	2.1 (28)	0.255
Time variables					
Ischemic time (minutes)	224 [160-370]	197 [147-282]	177 [132-250]	180 [135-255]	<0.001
Pre hospital delay (minutes)	173 [110-300]	150 [102-238]	130 [90-195]	137 [95-210]	<0.001
Door to balloon (minutes)	40 [27-61]	43 [27-65]	40 [27-61]	36 [26-53]	<0.001
Laboratory values					
CK maximum (mg/L)	1540 [616-3268]	1300 [531-2886]	1285 [568-2750]	1305 [571-2923]	0.004
CKMB maximum (mg/L)	197 [84-360]	170 [73-322]	162 [76-311]	171 [77-315]	0.002
Angiographic characteristics					
Anterior infarction	46.6 (585)	43.7 (1004)	41.2 (810)	42.6 (576)	0.021
1 vessel disease	43.7 (551)	46.5 (1073)	46.0 (910)	47.1 (639)	0.320
Stent placement	86.9 (1099)	86.8 (2006)	87.1 (1725)	86.9 (1180)	0.995
Thrombus aspiration	37.2 (467)	37.5 (862)	39.3 (774)	37.7 (509)	0.569
TIMI flow pre-PCI					0.025
0	58.5 (734)	54.1 (1247)	55.1 (1089)	51.1 (693)	
1	8.4 (105)	9.7 (224)	9.4 (186)	8.9 (121)	
2	16.0 (201)	16.0 (369)	16.5 (327)	18.3 (248)	
3	17.1 (215)	20.1 (464)	19.0 (375)	21.6 (293)	
TIMI flow post-PCI					0.322
0	0.8 (10)	1.4 (33)	1.5 (29)	0.8 (11)	
1	1.2 (15)	1.6 (37)	1.0 (20)	1.0 (14)	
2	9.4 (118)	8.7 (201)	9.4 (186)	9.6 (130)	
3	88.6 (1111)	88.2 (2032)	88.1 (1738)	88.6 (1201)	
Myocardial Blush Grade					0.036
0	4.2 (44)	5.3 (99)	5.1 (83)	5.4 (63)	
1	19.7 (206)	16.1 (299)	15.0 (244)	14.4 (169)	
2	35.3 (369)	37.0 (685)	37.5 (611)	35.4 (415)	
3	40.7 (425)	41.6 (770)	42.5 (692)	44.8 (526)	
Myocardial Blush Grade 2/3	62.6 (794)	62.3 (1455)	65.2 (1303)	68.8 (941)	0.058
Successful PCI	73.6 (768)	75.9 (1406)	77.4 (1261)	77.8 (913)	0.067
Outcomes					
30 day mortality	2.8 (36)	3.9 (92)	4.5 (90)	5.6 (76)	0.005
1 year MACE	14.7 (187)	16.3 (381)	15.8 (317)	16.3 (222)	0.637
1 year mortality	5.2 (66)	6.9 (161)	7.0 (140)	7.4 (101)	0.111

The data are mean±SD, median [IQR] or percentages (numbers). Bpm = beats per minute; CABG = coronary artery bypass graft; CK = creatine kinase; CKMB = myocardial band of creatine kinase; IQR = interquartile range; LAD = left anterior descending artery; LCx = left circumflex artery; MACE = major adverse cardiovascular event; MI = myocardial infarction; mmHg = millimeter of mercury; PCI = percutaneous coronary intervention; RCA = right coronary artery; SD = standard deviation; TIMI = Thrombolysis In Myocardial Infarction.

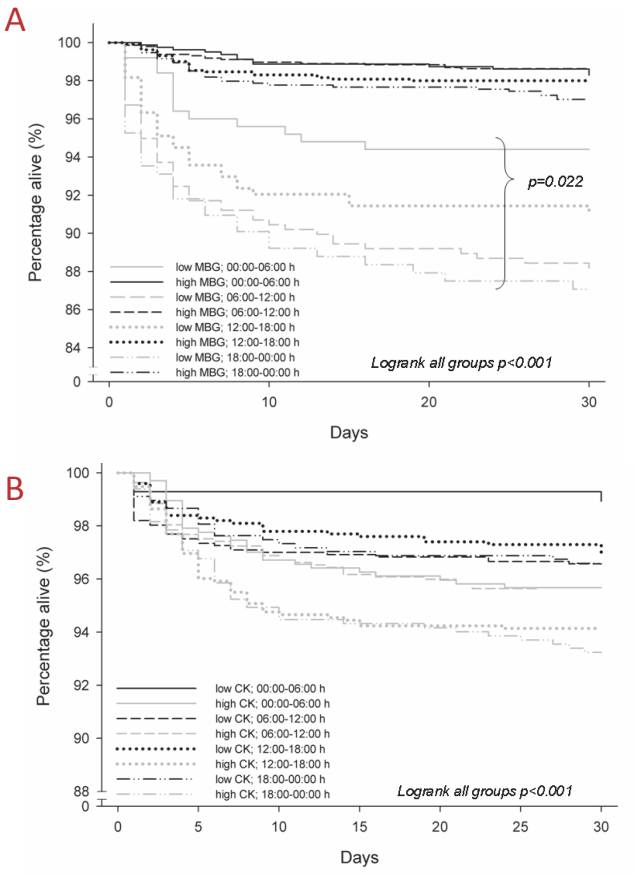
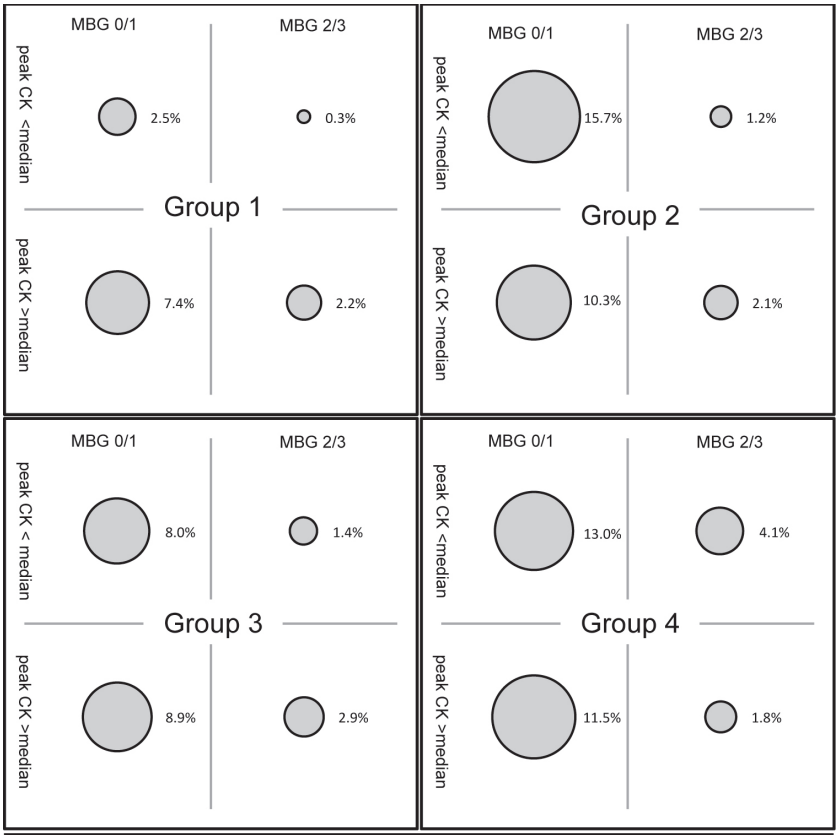


Figure 2(a). Thirty-day survival rates of high and low MBG per group - Thirty-day survival rates of MBG (MBG 2/3) and low MBG (MBG 0/1) per group of symptom onset time. (b) **Thirty-day survival rates of above and below median CK levels per group -** Thirty-day survival rates of low CK (below median CK) and high CK (above median CK) levels per group of symptom onset time. h=hour.

ischemic time and door-to-balloon times. Most strikingly, patients in group 1 encountered longer pre-hospital delay and consequently also longer ischemic time. Angiographic characteristics were comparable between the groups except for anterior infarction and TIMI flow pre-PCI. Procedural success was not different between the groups. Achievement of MBG 2/3 was not significantly different between the groups, although there was a trend toward higher grades in group 4. MI size differed significantly between the groups, with highest median CK and CKMB values in group 1.

Follow-up was available for all patients. The 30-day mortality rate was significantly different between the groups, with lowest in the group 1. However, in multivariable Cox regression analysis time of symptom onset, modeled with four degrees of freedom function, was neither associated with 30-day mortality nor 1-year mortality (Table 2). Both MI size and MBG were independent predictors of 30-day and 1-year mortality. Survival analyses were performed for each group categorized into low MBG (MBG 0/1) and high MBG (MBG 2/3), and for each group categorized into below and above median CK level. The categories with high MBG had all a favorable survival,



Group		OR (95% CI)	p-value
1	MBG0/1 CK<median	9.584 (0.858 – 107.031)	0.996
	MBG0/1 CK>median	29.512 (3.805 – 229.034)	0.018
	MBG2/3 CK<median	*Reference*	
	MBG2/3 CK>median	8.408 (1.060 – 66.685)	0.658
2	MBG0/1 CK<median	68.575 (9.123 – 515.457)	0.001
	MBG0/1 CK>median	42.451 (5.721 – 314.797)	0.004
	MBG2/3 CK<median	2.936 (0.352 – 24.279)	1.000
	MBG2/3 CK>median	7.875 (1.031 – 60.127)	0.699
3	MBG0/1 CK<median	32.243 (4.038 – 257.440)	0.016
	MBG0/1 CK>median	36.098 (4.782 – 272.505)	0.008
	MBG2/3 CK<median	5.356 (0.683 – 41.999)	1.000
	MBG2/3 CK>median	11.083 (1.469 – 83.635)	0.295
4	MBG0/1 CK<median	48.130 (6.001 – 385.997)	0.004
	MBG0/1 CK>median	55.205 (7.316 – 416.552)	0.002
	MBG2/3 CK<median	6.682 (0.843 – 52.974)	1.000
	MBG2/3 CK>median	15.921 (2.108 – 120.234)	0.109

Figure 3. Bubble-plot of percentage 30-day mortality per group categorized by myocardial blush grade (0/1 vs. 2/3) and CK levels (below vs. above median) - 30-day mortality is presented per category of blush (0/1 vs. 2/3) and peak CK levels (below vs. above median) for each time of symptom onset group. The size of the bubble presents the percentage of deaths per category, relative to the largest percentage of all categories. The accompanying table shows logistic regression analysis of all groups, with the group with lowest mortality serving as a reference category. P-values are corrected for multiple testing, using bonferroni correction.

Table 2. Cox-regression analysis of 30-day and 1-year mortality

	30-day mortality		1-year mortality	
	HR (95% CI)	P- value	HR (95% CI)	P- value
Time of symptom onset*	..	0.7303	..	0.8169
Age	1.06 (1.05 - 1.08)	<0.001	1.07 (1.06 - 1.08)	<0.001
Gender	0.90 (0.63 - 1.28)	0.551	0.96 (0.74 - 1.24)	0.733
History of diabetes	1.24 (0.82 - 1.88)	0.307	1.70 (1.27 - 2.27)	<0.001
Systolic blood pressure <90 mmHG	8.27 (5.85- 11.70)	<0.001	5.51 (4.07 - 7.47)	<0.001
Heart rate >100 bpm	3.39 (2.39 - 4.81)	<0.001	2.91 (2.19 - 3.86)	<0.001
Peak CK	1.45 (1.07 - 1.95)	0.015	1.29 (1.03 - 1.61)	0.029
Ischemic time	1.06 (0.70 - 1.60)	0.796	1.12 (0.81 - 1.58)	0.479
MBG	0.54 (0.45 - 0.63)	<0.001	0.62 (0.55 - 0.71)	<0.001

* Four degrees of freedom function. P-value of likelihood ratio test is given.
Bpm = beats per minute; CK = creatine kinase; MBG = myocardial blush grade; mmHg = millimeter of mercury.

which did not differ between the groups according to the time of day. However, there was a significant difference in the survival of the groups categorized into low MBG. Patients presenting with start of symptoms between 00:00 and 06:00 (group 1) had a significantly improved outcome when compared to the patients within the other groups (logrank: $p<0.022$; Figure 2a). When categorized according to below or above median CK levels, survival was significantly different between the groups with favorable survival in patients with symptom onset time 00:00 – 06:00 and below median CK levels (logrank $p<0.001$; Figure 2b). To gain further insight into the relationship of MBG and MI size on 30-day mortality during the day, these variables were plotted in a bubble-plot for each group (Figure 3). The percentage of deaths per category (based on high/low MBG and above/below median CK levels) showed a distinct pattern of distribution between the groups. Specifically, favorable outcomes were noted in group 1 patients presenting with low MBG and below median CK levels.

Discussion

The findings of this study can be summarized as follows: (1) we confirm in our combined registry of STEMI patients that there is a significant 24-hour pattern in the onset of symptoms, with a peak of onset at 09:00 hour; (2) patients with onset of symptoms between 00:00 and 06:00 hour have a longer ischemic times and accordingly larger enzymatic MI sizes; (3) procedural success is comparable throughout 24-hours; (4) despite the longer ischemic time and bigger MI size, this did not translate into higher 30-day and 1-year mortality in patients with onset between 00:00 and06:00 hour. In contrast, mortality was lowest in this group, which is an unexpected finding; and (5) patients with low MBG presenting in the early morning hours have better prognosis,

suggesting a 24-hour pattern in relation of MBG and MI size with outcome.

Several previous studies described a circadian variation in the incidence of acute MI and sudden cardiac death. A peak with onset of symptoms in the morning between 06:00 and noon is well established [10,12,19,23,24,25]. A meta-analysis containing 30 studies showed that 31.6% of acute MI onset is observed in this morning period [26]. The circadian rhythm of symptom onset has been ascribed to diurnal variations in autonomic nervous activity, fluctuations in platelet and coagulation activity, and catecholamine levels [27,28,29,30]. It has been reported that pharmacological treatment alters circadian rhythm, especially beta-blockers, aspirin and calcium blockers [3,5,30,31]. Additionally, the schedule of ingestion of medication may influence a patients risk for cardiovascular events. Unfortunately, we lacked data on maintenance medication in our cohort.

In our study, ischemic time was significantly different between the groups with longest ischemic times in the 00:00 – 06:00 hour group (p<0.001). The direct transport to a catheterization laboratory for primary PCI, and thereby circumventing other hospitals or the emergency departments, reduces time from the first medical contact to coronary intervention [32]. With a standardization of this protocol similar response and transportation times can be reached 24 hours a day. Unfortunately we lack data on the times between the STEMI diagnosis and arrival of the ambulance at the hospital. However, prehospital triage and transport to the PCI center is uniform around the clock, and thus we can assume that the longer ischemic times in the 00:00 – 06:00 hour group are mainly due to longer patient related delay. Patients with symptom onset between 00:00 and 06:00 hour wait longer before they contact medical services. This is in accordance with the results of Holmes et al. [19]. To some extent the prehospital delay during the night could be affected by slower response times of emergency medical services personal. Indeed in a retrospective study analyzing 568 calls for medical help because of out-of-hospital cardiac arrest it was observed that the response times were slowest during the night and fastest during the afternoon [33]. However, door-to-balloon times and angiographical success of the primary PCI did not differ according to the time of day in our study, suggesting stable performance of healthcare professionals.

It has been questioned whether the quality of treatment with PCI is equal during normal duty hours and off duty hours. Several studies have assessed in-hospital, medium and long-term outcomes for PCI therapy during on-hours compared to off-hours. Distinct longer delay times during off-hours are found in most of these studies, but there are conflicting results in terms of angiographic and clinical outcomes for patients treated during off-hours [34,35,36,37,38,39,40,41,42,43,44,45]. These conflicting results may be due to presentation of sicker patients and less successful PCI procedures during

off-hours [46]. However, a recent study by Noman et al. did not find any differences [40]. In our study, procedural success rates showed no significant differences between the groups, although there was a trend towards lower success rates in group 1.

A circadian pattern is also seen in the effectiveness of treatment of acute STEMI. Although primary PCI is a more effective strategy in STEMI patients than thrombolytic therapy [47], both treatment methods show circadian patterns in effectiveness. Thrombolytic therapy shows lower reperfusion rates in the early morning hours probably due to circadian fluctuation of endogenous hemostasis and thrombolytic activity [48,49]. Intrinsic mechanisms may influence myocardial perfusion after primary PCI as well. MBG was significantly lower in patients undergoing primary PCI during the night hours (00:00-08:00) (38). Recently it was observed that in STEMI patients treated with primary PCI epicardial and microvascular patency was more impaired when infarction started in the period between 18:00 and 05:59 hour. Corrected TIMI frame count and ST-segment resolution were used as measures of epicardial and microvascular patency (50). In our study there was no significant difference in the achievement of post PCI TIMI flow 3 and MBG 2/3 between groups, although there was a trend towards a higher proportion of MBG 2/3 in group 4. When analyzed in the two time groups according to Suzuki et al. there was no significant difference either (data not shown).

In our study, infarct size was significantly larger in the 00:00 – 06:00 hour group. This may be attributed to a longer ischemic time and a higher incidence of anterior MI in this group [51]. However, other factors may potentially also play important roles in the circadian variation of infarct sizes [11,12]. Durgan et al. showed in a mice model that there is an association between time of day and tolerance of the heart to ischemia/reperfusion, resulting in larger infarct size injury at the sleep-wake transition, and reduced left ventricular function 1 month later [52]. The time of day variation was lost when the mice were genetically ablated for the cardiomyocyte circadian clock. When translated to humans, MI size and left ventricular function were found to be dependent on time of occlusion of the epicardial vessel, suggesting a time-dependent variation in the tolerance to ischemia/reperfusion [11,12]. However, these studies were small and monocentric and a larger multicenter analysis could not confirm these findings [53].

In our study population, the crude 30-day mortality was lower in group 1, which seems contradictory, especially since this group is associated with large MI sizes and therefore one would expect impaired prognosis. Importantly, this finding is consistent when analyzed separately per hospital (data not shown). Nevertheless, when adjusted for other parameters, the group variable was not associated with mortality.

Interestingly, mortality was lowest in group 1 patients with low MBG compared to the other time groups. These patients might represent a group of patients who have a higher tolerance for ischemia compared to others.

Of note, obstructive sleep apnea is associated with an increased incidence of acute MI between 00:00 and 12:00 hour [54,55]. Hypoxic periods are common in sleep apnea patients, which may result in a better tolerance to myocardial ischemia.

Recent other studies showed no differences in outcomes in terms of in-hospital mortality between different time groups [12,19]. However, Fournier et al. reported a significant higher mortality at 30-days in patients with symptom onset between 00:00 and 06:00 hour compared to the rest of the 24-hour period [10].

As shown in Figure 3, the percentages of deaths per MBG and peak CK category are different amongst the groups and therefore the association of MBG and peak CK levels with 30-day mortality might be different during the day. This is an interesting finding that warrants further study into the relationship of CK, as a reflection of myocardial injury, with MBG, as a reflection of microvascular perfusion after mechanical treatment, on outcome.

Several aspects have to be taken into account when interpreting our results in light of other articles. The inclusion criteria between the studies are somewhat different: Reiter et al. included only patients with ischemic times <6 hours and TIMI flow grade 0 before PCI, whereas Suarez-Barrientos et al. excluded all patients with previous MI [11,12]. On the other hand, Ammirati et al. analyzed their cohort applying the exclusion criteria of both aforementioned studies [53].

Survivor bias, meaning that in our study less high-risk patients were reaching the hospital before deceasing during the 00:00–06:00 hour period, may be of importance for our findings. From studies in cardiac arrest patients, it is known that return of spontaneous circulation and survival are lower in in-hospital and out-of-hospital cardiac arrest patients during night hours [56,57]. In addition, 30-day survival rates are significantly lower in patients with out-of-hospital cardiac arrest at night [57].

This analysis has several limitations. First, the parameter time of symptom onset relies on patient's retrospection and is therefore susceptible to recall bias. Second, no information was available on the patient chronotype nor on employment on night or shift work schedules, which is suggested to influence the clock time of acute MI onset [58]. Third, only patients that presented to the hospital and received primary PCI were included in the analysis; patients not reaching the hospital alive or not receiving primary PCI were therefore not included and could have been a confounder to our results. Fourth, information on medical treatment as well as time of ingestion of medication is lacking in our data; this may be of influence on circadian rhythms and

as such to our findings.

Conclusions

STEMI patients have a significant 24-hour pattern in onset of symptoms, with peak onset at 09:00 hour. MI size and MBG but not time of symptom onset are associated with 30-day and 1-year all cause mortality. The relation of MBG and MI-size with mortality differs throughout the day. Patients with failed reperfusion presenting in the early morning hours have better prognosis, suggesting a 24-hour pattern in relation of myocardial perfusion and infarct size with outcome.

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