Clinical Research in Cardiology
https://doi.org/10.1007/s00392-017-1189-8

ORIGINAL PAPER

Circadian dependence of manual thrombus aspiration benefit in patients with ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention

Stephane Fournier[1] · Olivier Muller[1] · Umberto Benedetto[2] · Marco Roffi[3] · Thomas Pilgrim[4] · Franz R. Eberli[5] · Hans Rickli[6] · Dragana Radovanovic[7] · Paul Erne[8] · Stéphane Cook[9] · Stéphane Noble[3] · Rachel Fesselet[1] · Andrea Zuffi[1] · Sophie Degrauwe[1] · PierGiorgio Masci[1] · Stephan Windecker[4] · Eric Eeckhout[1] · Juan F. Iglesias[1] · on behalf on the AMIS Plus Investigators

Received: 6 July 2017 / Accepted: 27 November 2017

Abstract

Background The clinical benefit of manual thrombus aspiration (TA) during primary percutaneous coronary intervention (PPCI) in patients with ST-segment elevation myocardial infarction (STEMI) remains uncertain. This study assessed the impact of circadian rhythms on the effectiveness of manual TA.

Methods and results We conducted an observational study of patients enrolled in the Acute Myocardial Infarction in Switzerland Plus registry. STEMI patients undergoing PPCI with (TA group) or without (PCI-alone group) manual TA were divided based on time-of-day symptom onset: group 1 (00:00–05:59), group 2 (06:00–11:59), group 3 (12:00–17:59) and group 4 (18:00–23:59). The primary endpoint was circadian variation of myocardial infarction (MI) size. The secondary endpoint was in-hospital all-cause mortality. Between 2009 and 2014, 3648 patients underwent PPCI (TA, 49%). After propensity-score matching, 2860 patients were included. Minimal myocardial Injury was observed in groups 2 and 3 (peak creatine kinase level group 1, 2723 ± 148 U/l; group 2, 2493 ± 105 U/l; group 3, 2550 ± 106 U/l; group 4, 2952 ± 144 U/l; $p = 0.044$) in the TA group, whereas no time-of-day dependence was found in PCI-alone group. After periodic sinusoidal regression analysis, a circadian relationship between time-of-day symptom onset and MI size was demonstrated in the TA group ($p < 0.001$). In-hospital all-cause mortality was 3.4% in the TA group and 4.3% in the PCI-alone group ($p = 0.20$).

Conclusions In this large registry of STEMI patients, manual TA did not reduce in-hospital all-cause mortality. Nonetheless, there was a circadian dependence of TA effectiveness with greatest myocardial salvage for patients with symptom onset between 06:00 and 17:59.

Keywords Circadian rhythms · Primary percutaneous coronary intervention · Manual thrombus aspiration · Myocardial infarct size

✉ Juan F. Iglesias
Juan.Fernando.Iglesias@gmail.com

[1] Department of Cardiology, Lausanne University Hospital, Rue du Bugnon 46, 1011 Lausanne, Switzerland

[2] Bristol Heart Institute, University of Bristol, Bristol, UK

[3] Division of Cardiology, University Hospital, Geneva, Switzerland

[4] Department of Cardiology, Bern University Hospital, Bern, Switzerland

[5] Department of Cardiology, Triemli Hospital, Zurich, Switzerland

[6] Division of Cardiology, Kantonsspital St. Gallen, St. Gallen, Switzerland

[7] AMIS Plus Data Center, University of Zurich, Zurich, Switzerland

[8] Laboratory of Signal Transduction, Department of Biomedicine, Basel University Hospital, Basel, Switzerland

[9] Department of Cardiology, University Hospital, Fribourg, Switzerland

Published online: 08 December 2017

Abbreviations

ACS	Acute coronary syndrome
AMIS	Acute myocardial infarction in Switzerland
CK	Creatine kinase
I/R	Ischemia/reperfusion
MI	Myocardial infarction
PCI	Percutaneous coronary intervention
PPCI	Primary percutaneous coronary intervention
STEMI	ST-segment elevation myocardial infarction
TA	Thrombus aspiration
TIMI	Thrombolysis In myocardial infarction

Introduction

Primary percutaneous coronary intervention (PPCI) is the most effective reperfusion strategy for patients with acute ST-segment elevation myocardial infarction (STEMI) [1]. Distal thrombus embolization resulting in microvascular obstruction and failure to restore optimal microvascular perfusion remains a major limitation of PPCI and has been associated with increased mortality [2].

Manual thrombus aspiration (TA) during PPCI has been introduced with the intent to reduce thrombus burden, prevent distal embolization and increase microvascular perfusion [3, 4]. However, the clinical benefit of routine manual TA during PPCI remains uncertain owing to conflicting results of randomized clinical trials. The single-center randomized Thrombus Aspiration during Percutaneous Coronary Intervention in Acute Myocardial Infarction Study (TAPAS) demonstrated improved myocardial reperfusion and a nearly 50% reduction in 1-year mortality among STEMI patients undergoing manual TA compared with PPCI alone [5, 6]. Conversely, two recent large-scale multicenter randomized trials, the Thrombus Aspiration During ST-Segment Elevation Myocardial Infarction (TASTE) trial [7, 8] and the Trial of Routine Aspiration Thrombectomy with PCI vs. PCI Alone in Patients with STEMI (TOTAL) [9], as well as subsequent meta-analyses [10, 11] have consistently shown that manual TA did not reduce all-cause mortality and adverse clinical outcomes when compared with PPCI alone. Accordingly, current European Society of Cardiology and American College of Cardiology/American Heart Association guidelines do not recommend the routine use of manual TA during PPCI for STEMI. However, the optimal selection of patient subgroups who might derive benefit from manual TA during PPCI remains a matter of debate and the use of TA in patients with STEMI is heterogenous between hospital [12].

Circadian rhythms have been shown to exert a critical influence on the pathogenesis of STEMI [13]. Multiple large-scale registry-based studies demonstrated a time-of-day-dependent variation of MI size among STEMI patients undergoing PPCI with larger infarct size and increased in-hospital mortality around midnight, irrespective of the total ischemic time [14–17]. Furthermore, previous studies have shown substantial circadian variation in the efficacy of reperfusion strategies such as fibrinolysis and PCI among patients with STEMI, with the lowest reperfusion success and impaired clinical outcomes during the early morning hours [18, 19]. These data suggest a circadian dependence of myocardial tolerance to the ischemia/reperfusion (I/R) injury during STEMI. We aimed to assess the impact of circadian rhythms on the clinical benefit of manual TA in a large real-world cohort of STEMI patients undergoing PPCI.

Methods

Study design

We conducted a retrospective analysis of patients included in Acute Myocardial Infarction in Switzerland (AMIS) Plus, a large, nationwide, multicenter registry of patients admitted with acute coronary syndrome (ACS) to hospitals in Switzerland. AMIS Plus was founded in 1997 by the Swiss Societies of Cardiology, Internal Medicine and Intensive Care Medicine with the aim to understand the transfer, use and practicability of knowledge gained from randomized trials, and to generate data for the planning of subsequent prospective randomized studies. From 106 hospitals treating ACS in Switzerland, 82 hospitals temporarily or continuously enrolled patients and AMIS Plus registry. The design of the registry has been described previously [20].

AMIS Plus collects prospectively 230 items on a computer-based database including medical history, comorbidities, cardiovascular risk factors, clinical presentation, out-of-hospital management, early in-hospital management, reperfusion therapy, hospital course, diagnostic tests used or planned, length of stay, discharge medication and discharge destination, immediate drug treatment and discharge medication. Participating centers provide blinded data for each patient through standardized internet-based or paper-based questionnaires and are strongly encouraged to enroll all patients fulfilling the inclusion criteria to avoid selection bias. Hospital data are provided and completed by the treating physician or a trained study nurse. All data are checked for completeness, plausibility and consistency by the AMIS Plus Data Center in the Epidemiology, Biostatistics and Prevention Institute at the University of Zurich.

Study population

We examined an observational cohort of patients with STEMI who underwent PPCI within 12 h of symptom onset from January 2008 to December 2014 and were included in the AMIS Plus registry. STEMI was defined by symptoms

of ischemia and at least 1-mm new (or presumed new) persistent ST-segment elevation in two or more contiguous limb leads or at least 2-mm in two or more contiguous precordial leads, or new (or presumed new) left bundle branch block. Manual TA was performed at the discretion of the operator using one of the approved aspiration devices and followed by conventional PCI to the culprit lesion. No mechanical aspiration devices were included in this analysis. Epicardial reperfusion was assessed using the Thrombolysis in Myocardial Infarction (TIMI) flow grading system before and after PPCI. Patients were divided into two groups based on the use of manual TA before PCI (TA group) or PCI only (PCI-alone group). The TA group included all patients in whom manual TA was attempted. Patients were further divided into four time groups based on the time-of-day symptom onset, in line with recent literature [16, 17]: group 1 (00:00–05:59), group 2 (06:00–11:59), group 3 (12:00–17:59) and group 4 (18:00–23:59).

Study endpoints

The primary endpoint was circadian variation of final MI size, as determined by peak CK release during the hospital period. The secondary endpoint was all-cause mortality during the hospital period.

Statistical analysis

The results are presented as percentages for categorical variables and analyzed using the Chi square test or the Fisher's exact test as appropriate. Continuous normally distributed variables are expressed as means ± standard deviation (SD) and compared using the two-tailed Student's *t* test. Continuous non-normally distributed variables are expressed as median and interquartile ranges and analyzed using the Mann–Whitney *U* test. According to previously published methodology [15], peak CK level was plotted against time-of-day symptom onset expressed over a 24-h interval and to determine whether the relationship between MI size and time-of-day symptom onset follows a circadian pattern, a periodic sinusoidal regression analysis was performed using the equation $f(t) = a + b \times \sin(2p \times (t - c)/24)$, where '*a*' represents the rhythm mean value, '*b*' indicates the amplitude of this sine function, and '*c*' indicates its origin. A 24-h period for circadian rhythm was assumed. A circadian rhythm was deemed to be present if the amplitude of the fitted curve was significantly different from 0 using the Wald test. Propensity-score matching analysis was performed to adjust for all demographic and procedural variables between TA and PCI-alone groups (Table 1). Greedy matching in the form of nearest neighbor matching within a caliper of ± 0.05 on the propensity score was employed and randomly matched one patient in the TA group to one patient in the PCI-alone group. Ischemic time was used a continuous variable; all variables were added as linear term and no interaction was used. SPSS software (version 24.0.0, SPSS Inc., Chicago, Illinois, USA) was used for all statistical analyses.

Ethical considerations

The study protocol complies with the Declaration of Helsinki regarding investigations on humans and was approved the Swiss board for data security and all regional ethics commissions.

Results

From 1st January 2008 to 31st December 2014, a total of 4154 patients with STEMI from 51 Swiss hospitals were prospectively enrolled in the AMIS Plus registry. 3648 STEMI patients underwent PPCI within 12 h of symptom onset and were included for analysis. Of these, 1800 patients (49%) underwent manual TA before PCI and 1848 patients (51%) were treated with PCI only (Fig. 1).

Study population

The baseline characteristics of the study population are listed in Table 1. Overall, patients in the TA group were younger, more likely male, had lower rates of hypertension and previous coronary artery bypass grafting, and had shorter reperfusion delays compared with patients undergoing PCI only. Rates of cardiogenic shock and anterior MI were not statistically different between the two groups. Patients in the TA group were less likely to receive aspirin or a $P2Y_{12}$ receptor antagonist, compared with patients in the PCI-alone group. There were higher rates of glycoprotein IIb/IIIa inhibitors use in the TA group than in the PCI-alone group. Procedural success rates, defined as rates of post-procedural TIMI flow grade 3, were significantly lower in patients undergoing manual TA compared with those treated with PCI only.

Propensity-score matching analysis was performed to adjust for all demographic and procedural variables between TA and PCI-alone groups, producing a cohort of 2860 patients (1430 patients in TA and PCI-alone groups) (Fig. 1). After propensity-score matching, baseline demographics and procedural characteristics were well balanced between the two propensity-matched cohorts (Table 1).

Circadian patterns of myocardial infarction incidence and myocardial infarct size

A 24-h variation in MI onset time was observed in the overall STEMI population. The peak incidence of MI symptom onset was observed between 08:00 and 14:59 ($n = 1300$,

Table 1 Baseline clinical, angiographic and procedural characteristics

	Overall population			Propensity-score matched population		
	Thrombus aspiration group	PCI-alone group		Thrombus aspiration group	PCI-alone group	
	$n = 1800$	$n = 1848$	p value	$n = 1430$	$n = 1430$	p value
Age (years)	60 (52, 70)	64 (54, 74)	< 0.001	60 (52, 71)	62 (53, 71)	0.085
Male sex	1440 (80.0)	1391 (75.3)	0.001	1124 (78,6)	1116 (78,0)	0.751
Ischemic delay (minutes)	185 (131, 279)	195 (137, 307)	0.007	183 (128, 275)	190 (135, 289)	0.284
Body mass index (kg/m^2)	26.5 (24.2, 29.4)	26.4 (24.2, 29.4)	0.615	26.4 (24.2, 29.4)	26.5 (24.2, 29.4)	0.864
Dyslipidemia	931 (56.7)	897 (54.8)	0.290	795 (55.6)	779 (54.5)	0.573
Hypertension	890 (47.4)	988 (52.6)	0.002	742 (51.9)	755 (52.8)	0.653
Diabetes mellitus	238 (13.5)	270 (15.4)	0.113	204 (14.3)	215 (15.0)	0.597
Smoking status			0.464			0.545
Active smokers	782 (46.9)	743 (45.6)		604 (42.2)	621 (43.4)	
Non smokers	887 (53.1)	887 (54.4)		826 (57.8)	809 (56.6)	
Previous myocardial infarction	195 (11.0)	233 (13.1)	0.064	157 (11.0)	165 (11.5)	0.679
Previous PCI	222 (12.6)	229 (12.8)	0.807	184 (12.9)	181 (12.7)	0.911
Previous CABG	33 (1.9)	52 (2.9)	0.041	34 (2.4)	35 (2.4)	1.000
Killip class			0.986			0.490
I	1545 (86.5)	1587 (86.2)		1237 (86.5)	1240 (86.7)	
II	111 (6.2)	118 (6.4)		92 (6.4)	83 (5.8)	
III	27 (1.5)	30 (1.6)		21 (1.5)	20 (1.4)	
IV	103 (5.8)	106 (5.8)		77 (5.4)	90 (6.3)	
Anterior myocardial infarction	730 (40.6)	795 (43.1)	0.131	570 (39.9)	608 (42.5)	0.160
Drug therapy at admission						
Aspirin	106 (5.9)	147 (8.0)	0.014	330 (23.1)	355 (24.8)	0.293
$P2Y_{12}$ inhibitor	368 (22.7)	439 (26.7)	0.008	93 (6.5)	106 (7.4)	0.378
Oral anticoagulation	55 (3.4)	50 (3.1)	0.606	64 (4.5)	61 (4.3)	0.855
Immediate drug therapy						
Aspirin	1759 (98.0)	1817 (98.3)	0.461	1399 (97.8)	1408 (98.5)	0.267
$P2Y_{12}$ inhibitor	1728 (96.0)	1805 (97.7)	0.004	1378 (96.4)	1394 (97.5)	0.104
Glycoprotein IIb/IIIa antagonist	726 (40.3)	359 (19.4)	< 0.001	384 (26.9)	345 (24.1)	0.103
Unfractioned heparin	1560 (86.9)	1503 (81.6)	< 0.001	1212 (84.8)	1206 (84.3)	0.796
Low-molecular-weight heparin	377 (21.0)	435 (23.8)	0.048	328 (22.9)	315 (22.0)	0.591
Bivalirudin	53 (3.0)	36 (2.0)	0.053	42 (2.9)	35 (2.4)	0.488
Number of diseased vessels						
1	908 (50.4)	770 (41.7)	< 0.001	708 (49.5)	691 (48,3)	0.55
2	519 (28.8)	579 (31.3)	0.1	406 (28.4)	448 (31,3)	0.094
3	302 (16.8)	486 (26.3)	< 0.001	278 (19.4)	278 (19,4)	1
Infarct-related artery						
Left main coronary artery	20 (1.1)	48 (2.6)	0.001	19 (1.3)	17 (1,2)	0.867
Left anterior descending artery	788 (43.8)	900 (48.7)	0.003	615 (43.0)	654 (45,7)	0.153
Right coronary artery	808 (44.9)	781 (42.3)	0.11	642 (44.9)	616 (43,1)	0.346
Left circumflex artery	272 (15.1)	394 (21.3)	< 0.001	241 (16.9)	250 (17,5)	0.692
TIMI flow grade after PPCI			0.007			0.321
0	8 (0.5)	23 (1.6)		20 (1.4)	6 (0,4)	
1	16 (1)	10 (0.7)		14 (1.0)	18 (1,3)	
2	75 (4.7)	52 (3.5)		74 (5.2)	86 (6,0)	
3	1487 (93.8)	1394 (94.3)		1322 (92.4)	1320 (92,3)	

Ischemic delay: symptom onset-to-PPCI time. Values are expressed as mean (± SD) or number (percentage)

IQR interquartile range, *CABG* coronary artery bypass grafting, *MI* myocardial infarction, *PPCI* primary percutaneous coronary intervention, *TIMI* thrombolysis in myocardial infarction

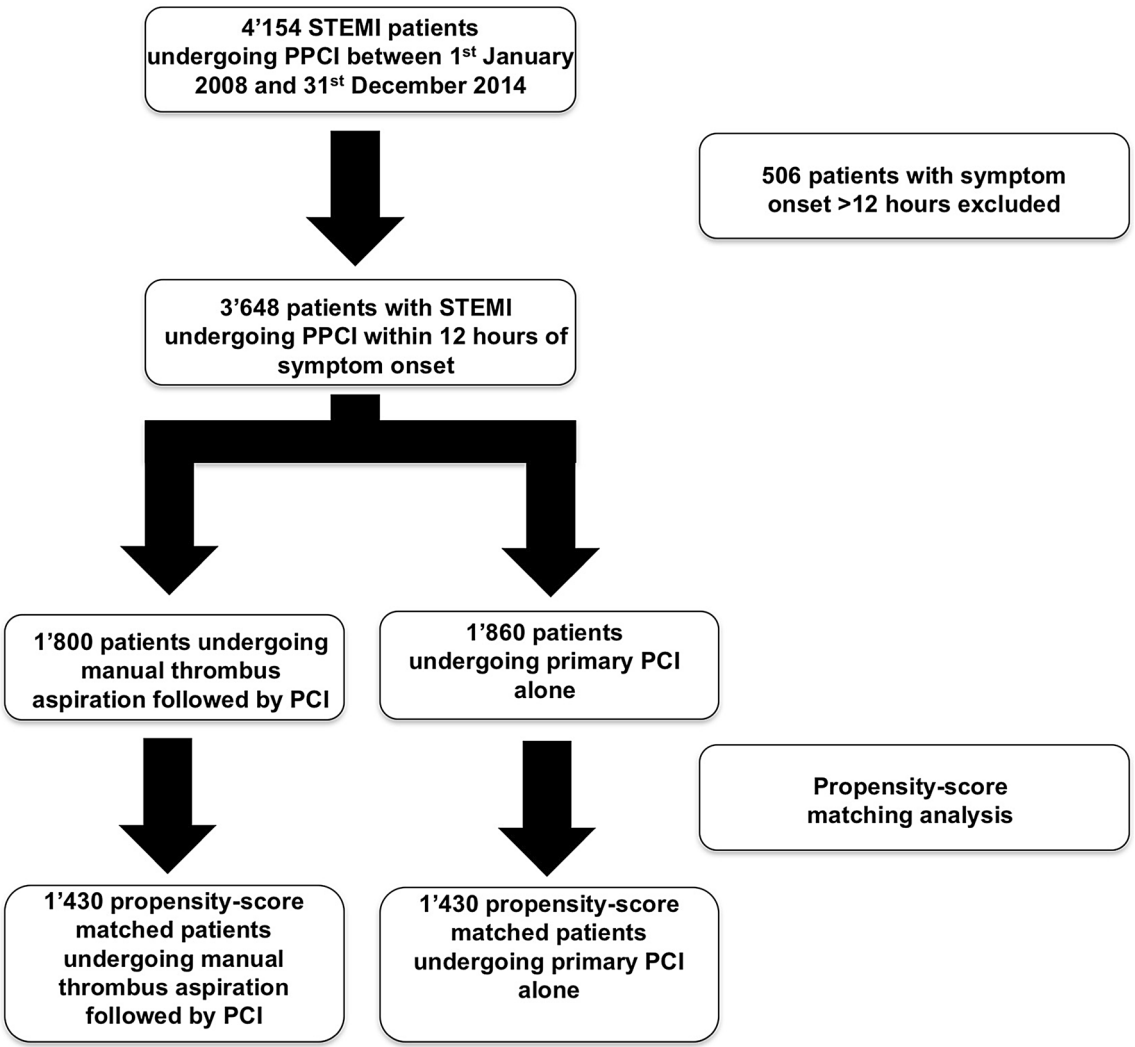

Fig. 1 Study flow chart. *PPCI* primary percutaneous coronary intervention, *STEMI* ST-segment elevation myocardial infarction

45.5%), whereas the lowest incidence occurred between 19:00 and 04:59 ($n = 857$, 30%). When the incidence of STEMI was plotted against time-of-day symptom onset, the distribution fitted a sinusoidal function that fulfilled criteria for a significant circadian pattern ($p < 0.001$) (Fig. 2). A significant circadian variation in MI size, as determined by peak CK release, was also demonstrated in the overall study population following PPCI. The distribution showed a sinusoidal function matching criteria for a significant circadian dependence between MI size and time-of-day symptom onset ($p < 0.001$) (Fig. 2). In the overall population, the largest MI size was observed between 18:00 and 23:59, whereas the smallest MI size occurred in the 06:00–11:59 interval.

In-hospital primary and secondary outcomes

Patients undergoing manual TA during PPCI demonstrated a larger final MI size during hospital admission when compared to patients treated with PCI only (peak CK level 2636 ± 61 vs. 1893 ± 59 U/L; $p < 0.001$). In the TA group, the largest myocardial injury was observed when symptom onset occurred between 18:00 and 23:59 (group 1, 2723 ± 148 U/l; group 2, 2493 ± 105 U/l; group 3, 2550 ± 106 U/l; group 4, 2952 ± 144 U/l; $p = 0.044$ for trend). The distribution displayed a sinusoidal function matching criteria for a significant circadian dependence between MI size and time-of-day symptom onset for patients undergoing manual TA ($p < 0.001$). The amplitude of the sinusoidal curve was 344 U/l (Fig. 3). Notably, there was significantly greater benefit of manual TA with respect to myocardial salvage among patients with symptom onset between 06:00 and 17:59 with a 15% reduction in mean MI size when compared to patients undergoing TA in the 18:00–05:59 interval (mean difference, groups 2 + 3 vs. groups 1 + 4, 391 U/l; $p = 0.01$). In addition, proportion of TIMI flow 3 was significantly higher in groups 2 + 3 vs.

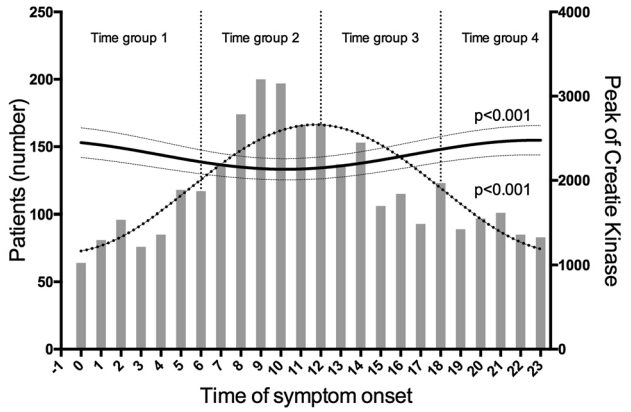

Fig. 2 Circadian variation of myocardial infarction incidence and myocardial infarct size. Histograms represent the relationship between MI incidence (left *y*-axis) and time-of-day symptom onset (*x*-axis) in the overall population. Bar charts display number of patients with symptom onset and demonstrate a lower MI incidence during the night hours and a peak MI incidence between 08:00 and 14:59 ($p < 0.001$). Solid line represents the fitted sinusoidal curve of peak CK level (right *y*-axis) plotted against time-of-day symptom onset (*x*-axis), demonstrating largest MI size in patients with symptom onset between 22:00 and 02:00 ($p < 0.001$). Dashed lines represent 95% confidence interval. *CK* creatine kinase, *MI* myocardial infarction

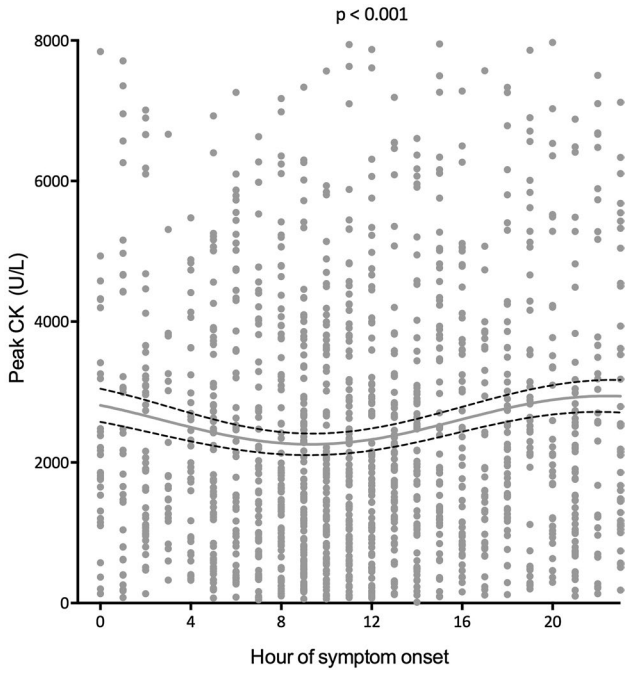

Fig. 3 Circadian dependence of myocardial infarct size on time-of-day symptom onset in patients undergoing manual thrombus aspiration. Solid line represents myocardial infarct size, assessed by peak creatine kinase level (*y*-axis) plotted against time-of-day symptom onset (*x*-axis), demonstrating a sinusoidal curve that fulfills criteria for a significant circadian pattern ($p < 0.001$). Dashed lines represent 95% confidence interval

groups 1 + 4 in the TA group (852 = 93.4% vs 468, 90.3%, respectively, $p = 0.036$).

Contrariwise, there was no significant circadian relationship between MI size and time-of-day symptom onset in patients treated with PCI only (group 1, 2044 ± 124 U/l; group 2, 1756 ± 93 U/l; group 3, 1850 ± 128 U/l; group 4, 2024 ± 136 U/l; $p = 0.239$ for trend). In the PCI-alone group, proportion of TIMI flow 3 was comparable in groups 2 + 3 vs. groups 1 + 4 (537 = 92.6% vs 785 = 92.4%, respectively, $p = 0.870$).

All-cause in-hospital death was not statistically different between TA and PCI-alone groups (3.4 vs. 4.3%, respectively; hazard ratio 1.28; 95% confidence interval 0.87–1.89; $p = 0.20$).

Discussion

The major findings of the present study from a large, prospective, nationwide cohort of unselected patients undergoing PPCI for STEMI can be summarized as follows: (1) MI size demonstrates a circadian dependence on time-of-day symptom onset with the largest MI size in patients with symptom onset between 18:00 and 23:59; (2) manual TA during PPCI does not reduce in-hospital all-cause mortality compared with PCI alone; and (3) the effectiveness of manual TA during PPCI varies according to the time-of-day symptom onset, with the largest myocardial salvage in patients with symptom onset between 06:00 and 17:59.

To the best of our knowledge, this is the first study suggesting the influence of circadian patterns on the clinical benefit of manual TA during PPCI. These findings provide important insights to understand the circadian pathophysiology of STEMI and might contribute to the appropriate selection of STEMI patients that may derive benefit from the selected use of manual TA during PPCI.

Circadian variation in acute myocardial infarction incidence and myocardial infarct size

Consistent with the results of previous studies [16, 17, 21], our findings demonstrate a circadian variation of STEMI onset time with a peak incidence in the early morning period at the sleep-to-wake transition confirming the critical influence of circadian rhythms on MI pathophysiology. The circadian pattern of MI incidence has been traditionally attributed to time-of-day-dependent fluctuations of noncardiac factors, such as increased sympathetic activity [22], increased platelet aggregability [23], decreased endogenous fibrinolytic activity [23], and increased cortisol levels [24] during the early morning hours. Beyond the existence of circadian patterns of MI incidence, we observed a circadian dependence of MI size on the time of myocardial ischemia

onset with the largest myocardial injury among patients with symptom onset between 22:00 and 02:00. These findings are in line with the results of numerous previous studies [14–17] and support the hypothesis of a circadian dependence of endogenous myocardial tolerance to I/R injury.

Circadian variation in manual thrombus aspiration effectiveness

In this large, real-world nationwide registry of STEMI patients undergoing PPCI, routine manual TA as compared with PCI alone did not reduce the risk of in-hospital all-cause death. These findings are consistent with the results of two recent large-scale randomized clinical trials [8, 9] and subsequent meta-analyses [10, 11].

The potential influence of time-of-day symptom onset and circadian rhythms on the clinical benefit of manual TA has not been reported previously. Based on the data from our large nationwide registry, we demonstrate for the first time a circadian relationship between the effectiveness of manual TA and time of STEMI onset. The largest myocardial salvage was demonstrated in patients with STEMI onset between 06:00 and 17:59, suggesting a potential benefit of manual TA when performed during the day time. The exact mechanism underlying the circadian dependence of manual TA effectiveness cannot be directly derived from our study. However, our current knowledge concerning the role of human circadian rhythms in the pathogenesis of cardiovascular disease advocates for different possible explanations.

First, time-of-day-dependent variations in blood viscosity, coronary blood flow, plasma cortisol and catecholamine levels, platelet aggregation and activation, coagulation factors and endogenous thrombolytic activity have been reported [23, 25, 26]. Platelet aggregation in response to epinephrine, adenosine diphosphate and thrombin is heightened during early morning hours [23, 25]. Similarly, plasma fibrinogen levels increase between 06:00 and 12:00, whereas antithrombin levels decline [23]. Time-of-day-dependent fluctuations in tissue-type plasminogen activator inhibition may also contribute to both increased prothrombotic state during the early morning period and enhanced natural fibrinolytic activity during the evening hours [27]. These circadian patterns in platelet behavior and thrombotic propensity that result in 24-h fluctuations of the physiological balance between prothrombotic and fibrinolytic factors may potentially explain time-of-day-dependent variations in the effectiveness of manual TA.

A 24-h-dependent variation in the efficacy of pharmacological and mechanical myocardial reperfusion strategies has been described among patients with STEMI. Thrombolytic therapy has been associated with lowest reperfusion rates in early morning and late evening hours and highest efficacy when administered between noon and midnight [18, 19]. Time of the thrombolytic therapy has also been shown as an independent factor with major impact on successful reperfusion and dose adjustment of thrombolytic agents according to the time of day has been suggested [28]. This circadian resistance to thrombolysis has been explained by time-of-day-dependent fluctuations in endogenous prothrombotic and fibrinolytic activities [18, 19]. Both plasminogen activator inhibitor-1 (PAI-1) [18] and platelet surface activation markers [26] have been shown to display a circadian pattern with highest PAI-1 levels and increased platelet aggregability in early morning hours, which coincides with the morning peak of thrombus formation and platelet aggregation [23, 25]. Similarly, a significant circadian variation with respect to microvascular perfusion, MI size and clinical outcomes has been reported for STEMI patients undergoing PPCI [29]. After correction for baseline confounding factors, PPCI performed between 04:00 and 08:00 was associated with increased 1-year mortality, whereas patients treated between 08:00 and 16:00 showed improved myocardial perfusion and reduced long-term mortality rates. These findings tend to support the hypothesis of circadian variations in myocardial tolerance to ischemia, which may potentially extent to myocardial salvaging interventions.

Second, there is growing evidence from preclinical studies suggesting a circadian variation in myocardial tolerance to I/R injury. Time-of-day-dependent variations in cardiomyocyte circadian clock genes expression that modulate myocardial I/R tolerance throughout the 24-h cycle have been observed in animal models. In a murine model, hearts undergoing prolonged myocardial ischemia at sleep-to-wake transition exhibited a 3.5-fold increase in MI size compared with those at wake-to-sleep transition [30]. Interestingly, the time-of-day-dependent variation in infarct size was abolished after deletion of the cardiomyocyte circadian clock gene [30]. A similar circadian dependence of MI size on coronary artery occlusion onset time has been described in humans. STEMI patients referred for PPCI experienced maximal myocardial injury when infarction started in early morning hours and reperfusion occurred near to sleep-to-wake transition, suggesting a comparable time-dependent mechanism of myocardial protection in the human heart [15]. Furthermore, STEMI patients with failed myocardial reperfusion after PPCI presenting in early morning hours have demonstrated greater tolerance to myocardial ischemia resulting in reduced 30-day mortality rates, compared with those presenting between 06:00 and midnight [31]. These observations combined with our findings highlight a time-of-day-dependent variation in myocardial tolerance to I/R injury, which may be relevant to clinical trials examining the efficacy of myocardial salvaging interventions during PPCI. Despite the precise mechanism remains unclear,

a strong relationship between cascades mediating in I/R injury and those regulated by cardiomyocyte circadian clock genes has been recently suggested [13].

Study limitations

Our data must be interpreted in view of several limitations. First, our study includes all limitations of a large nationwide registry, such as potential bias and unmeasured confounders associated with nonrandomized studies. In addition, we cannot exclude the possibility of underreporting of clinical outcomes. Despite the large size of our study population, our cohort may not have the power to detect differences in rates of in-hospital all-cause mortality related to the use of manual TA among subgroups of STEMI patients. Second, biomarkers (peak CK levels) were used as a surrogate of final MI size [32, 33] whereas recent non-invasive imaging modalities, such as cardiac magnetic resonance imaging (MRI) [34] and single-photon emission computed tomography (SPECT), provide nowadays greater sensitivity and specificity for determination of MI size. However, peak CK levels have been extensively used as a surrogate outcome to determine final MI size in numerous studies evaluating circadian rhythms in patients with STEMI [14–16]. Furthermore, previous studies have shown a strong relationship between peak CK levels and absolute MI size, as determined by MRI and SPECT, in STEMI patients undergoing PPCI [35]. Third, technical aspects such as the presence of bifurcation lesions [36–38], treatment of non-culprit lesion [39] or intravenous morphine administration [40] were not recorded. Finally, other confounders such as higher operator experience at day time may also play a role. However, it has been previously suggested that the procedure time, number of stents, stents length or diameter and use of contrast were similar between day and night in a study investigating the circadian variation of MI size in STEMI patients [17].

Conclusions

In a large, real-world contemporary cohort of patients undergoing PPCI for STEMI, routine manual TA did not reduce the risk of in-hospital all-cause death compared with PCI alone. We observed a circadian dependence of manual TA effectiveness with greatest myocardial salvage in patients with symptom onset during the daytime. These findings support the emerging concept of a circadian dependence of myocardial tolerance to the I/R injury. An adjustment of myocardial salvaging interventions based on time-of-day symptom onset may be warranted for patients with STEMI treated with PPCI.

Compliance with ethical standards

Conflict of interest The authors have no conflicts of interest to declare.

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