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Original Article

Impact of admission hours on each stage of care and total reperfusion delays in patients with ST elevation myocardial infarction

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Abstract: Background: ST segment elevation myocardial infarction (STEMI) is preferably treated by prompt primary percutaneous coronary intervention (pPCI). Delays in initial stages of care of STEMI patients admitted off versus routine hours are controversial. The aim of this study was to evaluate time periods in each stage of care of STEMI patients submitted to pPCI in a private tertiary hospital during on- *vs*. off-hours, and the adherence to current guidelines recommended times. Methods: consecutive STEMI patients admitted 2013-2019 who underwent pPCI were enrolled in this cohort study. Time periods were prospectively registered and other variables retrieved from electronic medical records. Primary outcomes were the time periods of each stage of care, since patient arrival in the emergency room (ER) until reperfusion of the culprit artery, performed during on-hours (weekdays, from 08:00 AM to 07:59 PM) or off-hours (all other days and time periods, or holidays). Results: 218 patients were included, 131 (60%) presented off-hours, with longer time periods between calling the catheterization laboratory staff until reperfusion, [55 min × 72 min; P < 0.001] and ER door-to-reperfusion [73 min × 98 min; P < 0.001]. Exploratory analysis by year suggested a decreasing reperfusion delay during on-hours admissions. In most years, total time for reperfusion exceeded the sixty minutes frame recommended in current North American guidelines, for both on- and off-hours admissions. Considering the ninety minutes recommendation of the European guideline, only on-hour admissions were in accordance during most years. Conclusions: STEMI patients, particularly when admitted off-hours, have lags in some stages of care, culminating in delayed myocardial reperfusion greater than recommended in current guidelines.

Keywords: Cardiac care, acute myocardial infarct, acute coronary syndrome, door-to-reperfusion time, PCI, STEMI, guidelines

Introduction

In centers enabled with catheterization laboratory (cath lab) 24 hours, 7 days a week all-year round, primary percutaneous coronary intervention (pPCI) is the preferable reperfusion therapy for patients with ST segment elevation myocardial infarction (STEMI) [1-3]. Electrocardiogram (ECG) is the cornerstone to guide the appropriate therapy [4]. Current guidelines recommend reperfusion delays - arrival in the emergency room (ER) until reperfusion of the culprit artery - no longer than 60 or 90 minutes [1, 5, 6]. Shorter times until reperfusion are associated with better outcomes [7, 8]. Total time between first medical assessment and reperfusion is a strong predictor of adverse outcomes [7, 9, 10], particularly mortality. In patients with STEMI and cardiogenic shock, every 10 minutes delay between first medical contact and reperfusion results in additional 3.3 deaths for every 100 patients treated with pPCI [11].

Among several factors that contribute to delays in reperfusion of STEMI patients, a poten-

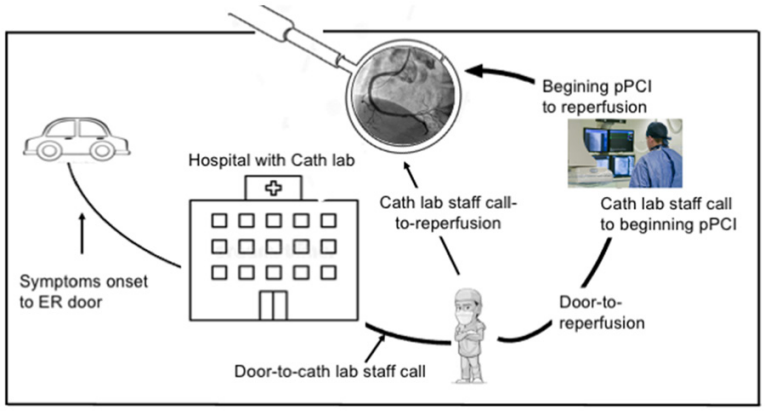

Figure 1. Stages of care for STEMI patients undergoing pPCI.

tial association between off-hours admissions in the ER and unfavorable clinical outcomes has been described [12-14]. Although patients' clinical characteristics are the main determinants of disease severity, initial medical care and ER treatment protocols play a major role determining clinical outcomes in STEMI cases [1, 15-17]. Therefore, assessing time periods and identifying delays in each stage of care of STEMI patients can help reduce treatment lags, resulting in improved survival. These time periods involve several marks of care: patient arrival in the ER, STEMI diagnosis, calling the cath lab staff, beginning of the procedure and coronary reperfusion. Detailed assessment of each of these time periods is the primary outcome, an innovative aspect of this study. Reperfusion delays in accordance to limits proposed by current guidelines are a key step to achieve ideal outcomes. Specific reperfusion delays were secondary outcomes, as well as in-hospital adverse clinical outcomes.

Materials and methods

Study design and patient population

This study was carried out in a private tertiary hospital in the largest city of southern Brazil. Men and women aged 18 years and over, admitted for the diagnosis of STEMI in the largest private hospital in southern Brazil, affiliated to Johns Hopkins Medicine International, were eligible. Electrocardiogram definitions of STEMI were in accordance with current guidelines and consisted, in summary, at least 1 mm ST segment elevation in two contiguous leads in the frontal plane or 2 mm in the horizontal plane, or typical ischemic chest pain in patients with new or presumably new left bundle branch block. Hospital records of all patients undergoing pPCI between January 2013 and July 2019 were reviewed, as well as records from the ER department and those obtained in the cath lab to determine eligibility. Nursing team standardized and prospectively recorded the time periods used in the study.

STEMI was considered the index event and a standardized and detailed review of the electronic medical records was carried out, extracting information regarding clinical presentation, pPCI procedure and in-hospital outcomes. In addition, for quality control purposes, printed and stored data from the pPCI reports and angiograms, as well as complementary exams were reviewed, including echocardiography and anesthetic records.

Primary and secondary outcomes

Primary outcomes were the time periods (in minutes) of each stage of care, categorized to on-hours (weekdays, from 08:00 AM to 07:59 PM) or off-hours (all other days and time periods, or holidays) (**Figure 1**):

- Door-to-cath lab staff call: time period between patient arrival in the ER until calling the cath lab staff (anesthetist, technician, nurse and interventional cardiologist). Among patients who presented a STEMI during an ongoing hospitalization, the time period between STEMI diagnosis until calling the cath lab staff was considered.

- Cath lab staff call-to-reperfusion: time period between calling the cath lab staff until reperfusion of the culprit coronary artery.

- Door-to-reperfusion: time period between patient arrival in the ER (or diagnosis, for patients already hospitalized) until reperfusion of the culprit coronary artery.

Assessment of door-to-reperfusion times within the guidelines recommended limits of 90 [5,

6] or 60 minutes [1], stratified by on- and off-hours, was considered a co-primary outcome.

Time periods related to patient and procedural delays were considered secondary outcomes:

- Time period between symptoms onset and patient arrival in the ER.

- Time period between calling the cath lab staff until beginning of the pPCI.

- Time period between beginning the PCI until reperfusion of the culprit coronary artery.

- Duration of the pPCI: from the beginning (arterial puncture) until the end (catheteres out) of the procedure.

In-hospital clinical outcomes occurring after the pPCI were also secondary outomes, independently adjudicated, and combined as a composite outcome: stent thrombosis, post-MI angina, heart failure (according to the New York Heart Association (NYHA classification), stroke and in-hospital death.

Clinical, demographic and angiographyc characteristics

Patient information retrieved from electronic records were: age; sex; cardiovascular risk factors: life-time smoking, previous medical diagnosis of hypertension, diabetes mellitus; previous myocardial infarction (MI); chronic renal failure; previous stroke; peripheral arterial disease, previous heart failure symptoms and the antiplatelet regimen used during hospitalization. An additional information was verified: primary payor - private health insurance plans or person's own funds (out-of-pocket).

Blood tests performed on admission were obtained, including serum creatinine, high-sensitivity troponin and hemoglobin. Information regarding killip class (categorized as IV or other), electrocardiogram on admission and echocardiogram performed after the pPCI were also obtained. Technical aspects of the pPCI procedure were assessed: vascular access (radial or femoral); pre dilation of the lesion (yes or no); culprit vessel (left main, left anterior descending artery or branches, left circumflex artery or branches, right coronary artery or branches, saphenous bypass grafts); diagnosis of multivessel disease (other severe coronary stenosis besides the culprit vessel); presence and number of bifurcations (none, one or two); thrombus aspiration (yes or no); use of drug-eluting stents (yes or no); stent post dilatation (yes or no); number and total length of stents used to treat the culprit vessel; stent diameter (mm); TIMI flow (Thrombolysis in Myocardial Infarction) at the end of the pPCI, categorized as 3 or less than 3; presence or absence of no reflow phenomenon (when anterograde flow was not restored after culprit lesion treatment). In addition, presence of residual lesions and treatment assessment of non-culprit lesions regarding number, total length and diameter of stents was carried out.

Statistical analysis and sample size calculation

The analysis was performed using the SPSS Software (SPSS Statistics for Windows, version 18.0; IBM corp., Armonk, NY, USA). Comparisons of means and standard deviations (SD) were obtained for normally distributed variables using t-test or chi-square test for categorical variables, described through percentages. The Mann-Whitney test was used to analyze the association between door-to-reperfusion during on-hours *vs.* off-hours, as well as other time periods, using median (interquartile interval). Temporal trends of the door-to-reperfusion time period was analyzed by year according to on- vs. off-hours. Multivariate analyzes were performed to control confounding factors using a Poisson regression with robust estimator to analyze the association of on- and off-hours with time to reperfusion recommended in the guidelines, controlling for age and sex. Data from all available sources were reviewed, resulting in no missing records.

The sample size was estimated by the door-to-reperfusion time period during off-hours admissions, which was expected to be at least 15 ± 20 min longer than during on-hours [12], with 80% power and 95% confidence interval (95% CI), using the EPIDAT (Xunta de Galícia, version 3.1, 2006, distributed by PAHO Pan-American Health Organization). It would be necessary to evaluate at least 180 consecutively STEMI patients to obtain 80% power, considering the P value < 0.05 as statistically significant. P value between 0.05 and 0.1 was considered to show a tendency towards association. In order to have statistical power for adjustment

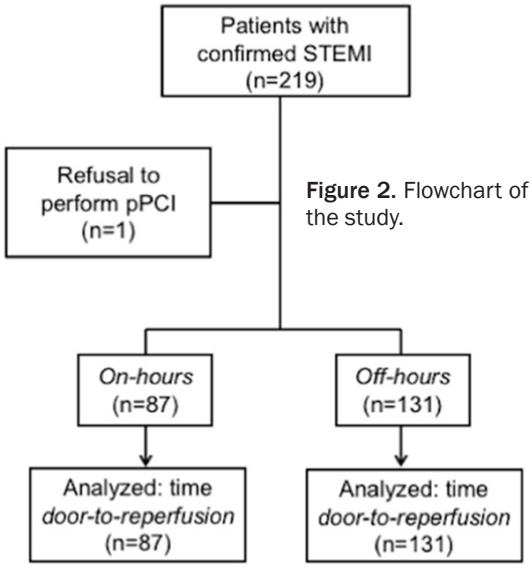

Figure 2. Flowchart of the study.

of potential confounding factors, all eligible patients were included.

Ethical aspects

Patients participate in the Ethics Committee of the institution that approved the study (Number: 3,439,184), which is accredited by the Office of Human Research Protections as an Institutional Review Board. It was in accordance with the Declaration of Helsinki and the Americas document of good practices of research. Concealment, privacy and anonymity of the collected data were maintained.

Results

During the study period, 219 STEMI patients underwent pPCI. The study flowchart shows that one patient was excluded for refusing to perform the PCI, totaling 218 patients included in the analyses (**Figure 2**).

The time of arrival of patients with STEMI in the ER peaked at 11 A.M., increasing from 9 A.M. to 5 P.M. during on-hours (81.6%). Most patients arrived in the ER on weekdays (63.3%) and few during holidays (3.7%) (**Table 1**). The majority of patients were male, aged 67.3 ± 13.3 years, and most reported lifetime smoking. High prevalence of hypertension and diabetes was observed and most patients did not have a history of MI. Patients with diabetes tended to be hospitalized during on-hours. The majority of patients were in sinus rhythm and 13.5% were in cardiogenic shock at admission. In approximately 94% of the patients, private health insurance plans were the primary payor (**Table 1**).

Co-primary and secondary outcomes according to time of arrival in the ER are shown in **Table 2**. Most patients held back their symptoms and retarded seeking medical attention by their own means, delaying prompt care. The average time between symptom onset and ECG diagnosis was 212.0 ± 176.4 minutes, and there were no marked differences between patients admitted during on- and off-hours Door-to-reperfusion delays were more pronouced in off-hours admissions [98 (77-129) *vs*. 73 (55-109) min; P < 0.001]. During off-hours, cath lab staff call-to-reperfusion was longer than on-hours [72 (55-84) *vs*. 55 (40-67) min; P < 0.001]. In addition, time periods between calling the cath lab staff until beginning of the pPCI and total duration of the procedure were also longer during off-hours. Door-to-cath lab staff call differences during on- and off-hours were also statistically significant.

Table 3 describes procedural characteristics showing that technical aspects did not differ between on- and off-hours admissions, except for the higher rate of stent post dilatation (66.3% *vs*. 80.2%) and greater number of stents implanted in the culprit vessel (1.2 ± 0.6 *vs*. 1.4 ± 0.7) during off-hours.

Figure 3 shows that from 2013 to 2019 there were downward trends in door-to-reperfusion and door-to-cath lab staff call time periods for on-hour admissions, while during off-hours there was an upward trend towards 2016 and a downward trend towards 2019.

Figure 4 presents a high proportion of pPCI procedures cases with reperfusion after 60 minutes and not exceeding 90 minutes, with statistically significant differences according to admission hours for most years. The relative risk (95% CI) for exceeding 60 min during off-hours was 1.33 (1.15-1.54; P < 0.001), which did not substantially change after controlling for age and sex. Similarly, having a reperfusion exceeding 90 min during off-hours accounted for a non-adjusted relative risk: 1.78 (1.27-2.50; P = 0.001) and adjusted relative risk 1.76 (1.25-2.47; P = 0.001).

Table 1. Characteristics of the population according to admission hours [Mean ± SD or n (%)]

	Total (n = 218)	*On-hours* (n = 87)	*Off-hours* (n = 131)	*P* value
Age (years)	67.3 ± 13.3	69.0 ± 12.6	66.3 ± 13.7	0.15
Male sex	152 (69.7)	56 (64.4)	96 (73.3)	0.16
Lifetime smoking	138 (63.3)	50 (57.5)	88 (67.2)	0.15
Hypertension	150 (68.8)	59 (67.8)	91 (69.5)	0.8
Diabetes mellitus	54 (24.8)	27 (31.0)	27 (20.6)	0.08
Previous MI	37 (17.0)	15 (17.2)	22 (16.8)	0.9
Previous stroke	13 (6.0)	6 (6.9)	7 (5.3)	0.6
Chronic kidney disease	24 (11.0)	12 (13.8)	12 (9.2)	0.3
Peripheral arterial disease	9 (4.1)	3 (3.4)	6 (4.6)	0.7
Heart failure	13 (6.0)	8 (9.2)	5 (3.8)	0.10
Antiplatelet therapy				0.8
AAS	217 (99.5)	87 (100.0)	130 (99.2)	1.0*
Clopidogrel	113 (51.8)	46 (52.9)	67 (51.1)	
Ticagrelor	105 (48.2)	41 (47.1)	64 (48.9)	
Killip IV	28 (13.5)	10 (12.5)	18 (14.1)	0.7
Sinus rhythm	205 (94.0)	81 (93.0)	124 (94.7)	0.9
Initial elevated troponin	166 (78.7)	71 (84.5)	95 (74.8)	0.09
Primary payor				0.7
Private health insurance plan	204 (93.6)	82 (94.3)	122 (93.1)	
Out-of-pocket	14 (6.4)	5 (5.7)	9 (6.9)	
Arrival in the emergency room				< 0.001*
Monday-Friday; 8:00 AM-7:59 PM	87 (39.9)	87 (100)	0	
Monday-Friday; 8:00 PM-7:59 AM	46 (21.1)	0	46 (35.1)	
Weekend	77 (35.3)	0	77 (58.8)	
Holiday	8 (3.7)	0	8 (6.1)	

*Fischer exact test.

Table 2. Time periods for each stage of patient care until reperfusion of the culprit coronary artery, according to admission hours

Time (in minutes, median; IQ interval)	*On-hours* (n = 87)	*Off-hours* (n = 131)	*P* value
Symtom onset to ECG diagnosis	225.8 ± 186.9	203.0 ± 169.2	0.4
Door-to-cath lab staff call	17 (8-41)	23 (13-48)	0.046
Cath lab staff call until beginning of the pPCI	33 (24-46)	46 (36-56)	< 0.001
Beginning of the pPCI until reperfusion	19 (14-29)	22 (14-34)	0.2
Door-to-reperfusion	73 (55-109)	98 (77-129)	< 0.001
Cath lab staff call-to-reperfusion	55 (40-67)	72 (55-84)	< 0.001
Duration of pPCI	58 (43-73)	73 (58-88)	0.003

Mann-Whitney test: median (interquartile interval; IQ). ECG: electrocardiogram; cath: catheterization; pPCI: primary percutaneous coronary intervention.

In-hospital length of stay was in average 5.9 ± 3.8 days. In-hospital mortality was 7.5% among patients admitted during on-hours and 12.5% in off-hours admissions (P = 0.3). Mortality among patients presenting with cardiogenic shock was 42.9% versus 6.6% in those without (P < 0.001). However, there was no statistically significant difference in cardiogenic shock prevalence according to admission hours (8.0% *vs.* 10.7% P = 0.5). The incidence of major ad-

Table 3. Procedural characteristics according to admission hours [n (%) or mean ± SD]

	On-hours (n = 87)	*Off-hours* (n = 131)	*P* value
Radial access	60 (69.8)	92 (70.8)	0.9
Lesion pre-dilatation	66 (76.7)	104 (79.4)	0.6
Culprit vessel			0.8
Left main	9 (10.5)	13 (9.9)	
Left anterior descending	34 (39.5)	47 (35.9)	
Left circumflex	15 (17.4)	22 (16.8)	
Right coronary	28 (32.6)	47 (35.9)	
Saphenous vein graft	0	2 (1.6)	
Multivessel disease	57 (66.3)	84 (64.1)	0.7
Bifurcation lesions			0.4
None	74 (85.1)	102 (77.9)	
One	11 (12.6)	26 (19.8)	
Two	2 (2.3)	3 (2.3)	
Thromboaspiration	19 (21.8)	21 (16.2)	0.3
Drug eluting stent	78 (98.7)	123 (96.9)	0.4
Stent post-dilatation	57 (66.3)	105 (80.2)	0.02
Stents in culprit vessel			
Total number of stents	1.2 ± 0.6	1.4 ± 0.7	0.02
Total lenght (mm)	18-38	20-41	0.10
Smaller diameter (mm)	2.5-3.5	2.5-3.0	0.6
Larger diameter (mm)	2.5-3.5	2.75-3.50	0.7
Final TIMI 3 flow	62 (72.9)	103 (78.6)	0.3
No reflow	8 (9.3)	6 (4.6)	0.14
Stents in other vessels*			
Total number of stents	1.8 ± 0.5	1.9 ± 0.4	0.3
Total lenght (mm)	18.0-62.25	27.75-75.75	0.15
Smaller diameter (mm)	2.31-2.75	2.25-3.50	0.7
Larger diameter (mm)	2.56-2.94	2.63-3.50	0.2
Residual lesions	52 (67.1)	80 (61.1)	0.4
Ejection fraction (%)**	45-65	45-62	0.15

*non-culprit vessels. **IQ: interquartile range, Mann-Whitney test.

verse clinical outcomes was 29.8%, without difference between on- and off-hours presentations for any of the individual endpoints (10.1% in-hospital mortality, 2.4% stroke, 6.0% heart failure, 10.7% angina recurrence, 0.5% stent thrombosis).

Discussion

The present study discriminated the time periods in each stage of care of STEMI patients admitted into one of the largest private hospitals from southern Brazil, assessing all possible sources of reperfusion delays from symptom onset until establishment of coronary flow in the culprit artery. We showed that compared to off-hours, on-hours admissions had shorter time periods between calling the cath lab staff until beginning the pPCI, as well as door-to- reperfusion delays. However, exploratory analysis by year allowed to discriminate door-to-cath lab staff call and door-to-reperfusion time periods, showing similar downward patterns for on-hour admissions, while for off-hour presentations there was a cyclical pattern.

The results of our study are in line with previous studies of Italian [18], German [19] and Chinese [20] centers, showing that presentations off routine hours were associated with longer total ischemic times, varying from 132 to 646 minutes, compared to on-hour presentations (124 to 461 minutes). On the other hand, by discriminating time periods of each stage, it was possible to target interventions to reduce reperfusion delays.

Among strategies that can reduce reperfusion delays, there are interventions from a hospital managerial perspective up to initiatives from public health system authorities. One simple strategy consists in directly referring chest pain patients to the ECG, with prompt interpretation by a physician [21]. In some developed countries [17, 19], ECG is carried out while the patient is being transported to the hospital, allowing early STEMI diagnosis and notification of the cath lab staff before patient arrival. In this case, they can be admitted directly in the cath lab, allowing reduction of time between first medical contact until reperfusion to 88 minutes, instead of 98 minutes observed in health systems that did not implement this approach [17]. Even though effective interventions would include public health policies for structuring the pre-hospital medical care, institutional protocols could be implemented to expedite ECG, execution and activation of the cath lab staff. Reductions in total ischemic times have prognostic implications and the effect on mortality is particularly rele-

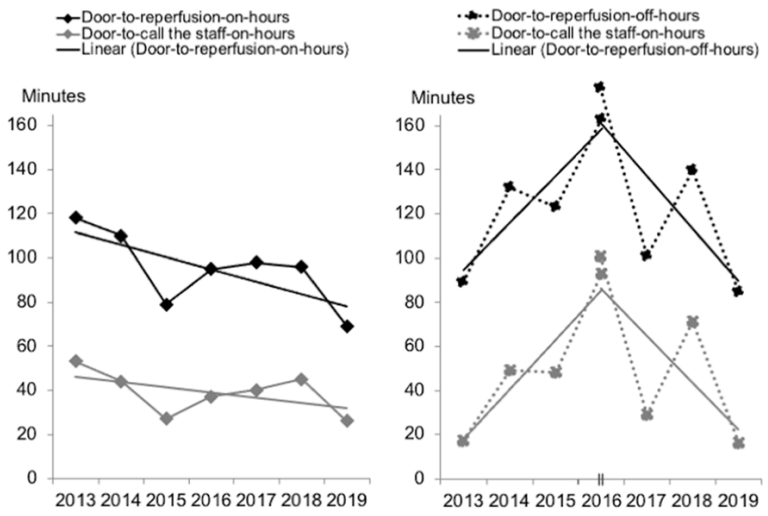

Figure 3. Temporal trend on time of door-to-reperfusion and door-to-cath lab staff call, during on- and off-hours.

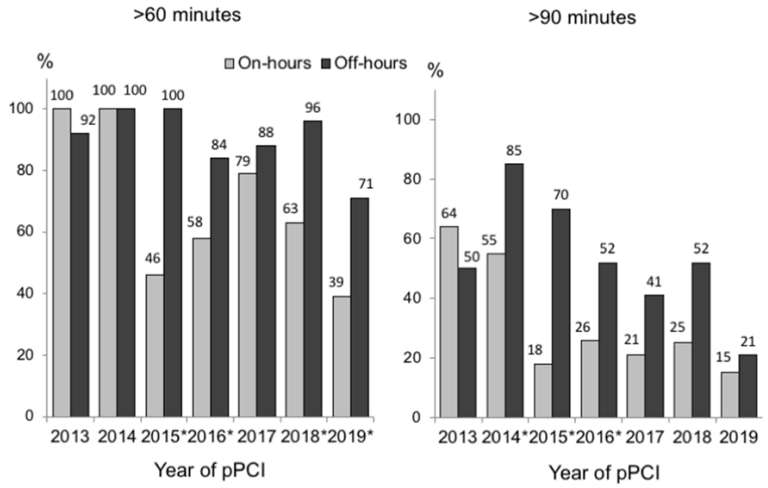

Figure 4. Percentage of pPCI by time of door-to-reperfusion over 60 and 90 minutes during on- and off-hours. *P < 0.05 or < 0.1 for year-to-year analysis. Analysis in the total sample: P < 0.001 for differences during on- and off-hours for total time > 60 and > 90 minutes.

vant [11]. Performing pPCI within 60 minutes of presentation clearly results in lower mortality rates compared to pPCI after 90 [22] or 120 minutes [8].

In the present study, there was no difference in mortality rates according to on- and off-hour admissions probably due to the limited sample size and short follow-up. Previous studies carried out in Brazil also did not detect a difference in mortality of STEMI patients admitted during routine versus off hours [12, 23]. Nevertheless, we found an elevated proportion of patients not receiving reperfusion in the time frame recommended by current guidelines [1, 5, 6]. Notwithstanding, patients with corresponding clinical characteristics received similar care, regarding technical aspects of the pPCI, during on- and off-hour presentations. Differences observed in rates of stent post-dilation of the culprit artery and greater number of stents implanted during off-hours suggest that there is no detrimental care in procedures being performed off-hours. In addition, systematic assessment of protocols in STEMI management and regular feedback appear to improve team performance and reduce mortality [24].

Inclusion of all confirmed STEMI patients treated at a large tertiary hospital during six and a half years allowed exploratory analyses by year, highlighting target actions to reduce total ischemic times. In addition, this study demonstrated that even in a large private institution, with an enabled cath lab 24 hours, 7 days a week, reperfusion delays are above recommended. In conclusion, patients with STEMI admitted to a private hospital during off-hours tend to have longer total ischemic times. Institutional measures and public policies to allow faster reperfusion of STEMI patients, especially during off-hours, should be sought.

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Disclosure of conflict of interest

None.

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