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INFLUENCE OF TOTAL ISCHEMIC TIME ON CLINICAL OUTCOMES IN PATIENTS WITH ST-SEGMENT ELEVATION MYOCARDIAL INFARCTION

<i>Aim</i>	To evaluate the effect of the total time of myocardial ischemia on results of the treatment of patients with ST segment elevation acute myocardial infarction (STEMI) who underwent percutaneous coronary interventions (PCI).
<i>Material and methods</i>	This study used data from a hospital register for PCI in STEMI from 2006 through 2017. 1649 patients were included. Group 1 consisted of 604 (36.6%) patients with a total time of myocardial ischemia not exceeding 180 min; group 2 included 531 (32.2%) patients with a duration of myocardial ischemia from 180 to 360 min; and group 3 included 514 (31.2%) patients with a duration of myocardial ischemia longer than 360 min.
<i>Results</i>	Mortality was lower in group 1 (2.3%) than in groups 2 and 3 (6.2 and 7.2%, respectively; $p_{1-2}=0.001$; $p_{1-3}<0.001$; $p_{2-3}=0.520$). The incidence of major cardiac complications («adverse cardiac events», MACE) was lower in group 1 (4.1%) than in groups 2 and 3 (7.3 and 9.5%, respectively, $p_{1-2}=0.020$; $p_{1-3}<0.001$; $p_{2-3}=0.200$). The incidence of no-reflow phenomenon was higher in group 3 (9.7%) than in groups 2 and 3 (4.5 and 5.3%, respectively ($p_{1-2}=0.539$; $p_{1-3}=0.001$; $p_{2-3}=0.005$). The major factors associated with the increased total time of myocardial ischemia >180 min were age (odd ratio, OR, 1.01 at 95% confidence interval, CI, 1.0 to 1.02; $p=0.044$), female gender (OR, 1.64 at 95% CI 1.26 to 2.13; $p<0.001$), chronic kidney disease (OR 1.82 at 95% CI 1.21 to 2.74; $p=0.004$). Performing prehospital thrombolysis was associated with a decrease in the total time of myocardial ischemia (OR 0.4 at 95% CI 0.31 to 0.51; $p<0.001$). A strong direct correlation was observed between the total time of myocardial ischemia and the time from the onset of pain syndrome to hospitalization ($r=0.759$; $p<0.001$).
<i>Conclusion</i>	The total time of myocardial ischemia >180 min was associated with increased mortality and development of MACE. The total time of myocardial ischemia >360 min was associated with increased incidence of the no-reflow phenomenon. The major predictors for the time of myocardial ischemia >180 min included age, female gender, and chronic kidney disease. The use of pharmacoinvasive strategy was associated with an increased number of patients with a total duration of myocardial ischemia <180 min. The contribution of the time of prehospital delay to the total time of myocardial ischemia was greater than the contribution of the «door-to-balloon» time. The time of prehospital delay showed a strong direct correlation with the total time of myocardial ischemia.
<i>Keywords</i>	Acute myocardial infarction; percutaneous coronary interventions; total time of myocardial ischemia
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Introduction

Primary percutaneous coronary intervention (PCI) is the preferred reperfusion method for acute ST-segment elevation myocardial infarction (STEMI) [1, 2]. The time from diagnosis to insertion of a coronary guidewire to the infarct-related coronary artery (CA) should not exceed 120 minutes. If primary PCI is impossible within the specified time interval, a pharmaco-invasive intervention is recommended. The pharmaco-invasive therapy includes prehospital thrombolysis followed by a PCI within 2 to 24 hours or an emergency life-saving PCI, if thrombolytic therapy (TLT) is ineffective.

During primary PCI, the door-balloon time is an important test parameter calculated as the time from the admission to the recanalization of the infarct-related artery. Recent years saw a significant decrease in the door-balloon time in most countries with well-developed STEMI patient care systems [3]. However, further reduction in the door-balloon time at a particular stage brings no reduction in mortality [4, 5]. Several researchers have observed that the total time of myocardial ischemia, i.e., the time from the pain onset to the reperfusion, might be a more accurate predictor of death risk in patients with STEMI [6, 7].

Objective

To investigate the effects of the total time of myocardial ischemia on the outcomes in STEMI patients treated with PCI.

Material and methods

The study used a hospital-based registry of STEMI patients who underwent PCI from 2006 to 2017. A total of 1,649 patients were included. The inclusion criteria were a long-term angina attack that began no more than 12 hours (up to 24 hours in case of persistent ischemia) before hospitalization, ST-segment elevation of ≥ 1 mm in two or more consecutive limb leads and/or ≥ 2 mm in the chest leads, PCI within ≤ 12 hours from the pain onset or up to 24 hours in the case of persistent ischemia.

All patients signed an informed consent form to be included in the study. The study complies with the ethical principles of the Declaration of Helsinki.

The patients were divided into three groups based on the total time of myocardial ischemia. Group 1 included patients with a total time of myocardial ischemia not exceeding 180 minutes ($n=604$), Group 2 – from 180 to 360 minutes ($n=531$), and Group 3 – more than 360 minutes ($n=514$).

In patients who underwent primary PCI, the total time of myocardial ischemia was calculated as the time from pain onset to the insertion of a coronary guidewire to the infarct-related artery [1]. In patients subjected to a pharmaco-invasive intervention, the total time of myocardial ischemia was defined as the time from pain onset to the administration of a thrombolytic drug. If TLT was ineffective or there were signs of reperfusion with preserved complete thrombosis of infarct-related artery on the coronary angiography, the total time of myocardial ischemia was calculated like for primary PCI.

The technical aspects of PCI were defined by an X-ray endovascular surgeon. All patients received standard anti-thrombotic therapy prior to PCI.

When the pharmaco-invasive intervention was performed, patients received TLT with a full dose of tenecteplase before hospitalization. The efficacy of TLT was assessed in 90 minutes. If there were ECG signs of ST-segment resolution of more than 50%, thrombolysis was regarded effective. In such a case, early conventional PCI was performed within 24 hours. In the case of ineffective TLT, emergency, life-saving PCI was performed.

Within the structure of the total time of myocardial ischemia the following measures were analyzed: the time from pain onset to hospital admission, the time from hospital admission to artery recanalization (door-balloon time), and the time from pain onset to the administration of a thrombolytic drug if TLT is used.

The immediate angiographic success of interventions was determined by the achievement of the TIMI 3 blood flow, myocardial blush grade (MBG) 3, the absence of occlusion of the large lateral branches (with a diameter of more than 2 mm), residual thrombi, and dissections. The no-reflow phenomenon was established, if blood flow was less than TIMI 3, or if TIMI 3 was achieved, but myocardial blush grade was less than 3.

The analysis of in-hospital outcomes of interventions included assessing mortality, the frequencies of recurrent MI, and stent thrombosis. We also analyzed the frequency of reaching the MACE (major adverse cardiac events) composite endpoint (mortality, recurrent MI, stent thrombosis). Before discharge, all patients underwent echocardiography and calculation of the left ventricular ejection fraction (LVEF) and measurement of LV myocardial asynergy.

Statistical processing of the findings was performed using the SPSS statistical software suite version 21.0 (SPSS Inc., USA). The distribution of quantitative variables was estimated by means of the Kolmogorov-Smirnov test. Since all quantitative variables had non-normal distribution, the data is expressed as the median (Me) and the interquartile range. The Kruskal-Wallis test was used to compare the three groups. The chi-square test and Fisher's exact test were used to compare categorical variables [22]. For multiple comparisons using the Bonferroni correction, the differences were statistically significant with the two-sided value $p < 0.017$, in other cases with the two-sided value $p < 0.05$. A single-variate model of binary logistic regression was used to determine the optimal intervals to analyze the total time of myocardial ischemia. The mortality index was used as a dependent variable. Accordingly, the time frames selected were those with the lowest achieved statistical significance level in the univariate logistical regression model. Binary logistical regression was used to determine the independent predictors of the increased total time of myocardial ischemia. The total time of myocardial ischemia more than 180 minutes was a dependent binary variable. All indicators with the baseline inter-group differences or statistical trends were included in the binary logistic regression model. The correlation was determined using Pearson's linear correlation coefficients, in order to identify collinear factors. The factors were regarded as linearly correlated when correlation coefficients were more than 0.35. In such a case, the multivariate binary logistic regression model included a factor with a minimal level of significance as calculated in a univariate model of logistic regression for each variable individually. The Spearman's rank correlation factors were used to statistically investigate the correlation between the total

time of myocardial ischemia and the time from pain onset to hospitalization and hospitalization to revascularization.

Results

Group 1 included the largest number of patients – 604 (36.6%). Groups 2 and 3 included 531 (32.2%) and 514 (31.2%) patients, respectively. The analysis of clinical characteristics (Table 1) revealed that patients in groups with the shorter total time of myocardial ischemia were younger. There were more male patients in Group 1 than in

Group 2 and Group 3. There were no statistically significant differences between the groups compared in terms of body mass index, blood sugar, the frequency of cardiogenic shock at admission, history of revascularization, the frequency of coronary heart disease, MI, and history of arterial hypertension. Both prehospital and hospital time intervals were longer with a longer total time of myocardial ischemia in the groups analyzed. The analysis of angiographic characteristics showed no statistically significant differences in the localization of the infarct-related artery and the

Table 1. Baseline clinical characteristic of the patient groups

Parameter	Total time of myocardial ischemia			P
	Group 1, up to 180 min (n=604)	Group 2, from 180 to 360 min (n=531)	Group 3, more than 360 min (n=514)	
Age, years	57 [51; 65]	59.5 [52; 67]	61 [53; 71.3]	$p_{1-2}=0.007$; $p_{1-3}<0.001$; $p_{2-3}=0.004$
Male	489 (81.1)	367 (69)	354 (68.9)	$p_{1-2}<0.001$; $p_{1-3}<0.001$; $p_{2-3}=0.979$
Body mass index, kg/m ²	28 [25; 31]	28.6 [26; 32]	29 [26; 32]	$p_{1-2}=0.065$; $p_{1-3}=0.112$; $p_{2-3}=0.769$
History of diabetes mellitus	87 (14.4)	95 (17.9)	113 (22)	$p_{1-2}=0.116$; $p_{1-3}<0.001$; $p_{2-3}=0.095$
Blood plasma glucose level, mmol/L	7.7 [6.4; 9.4]	7.8 [6.4; 9.8]	7.6 [6.2; 9.5]	$p_{1-2}=0.764$; $p_{1-3}=0.350$; $p_{2-3}=0.327$
History of CHD	187 (31)	180 (33.8)	192 (37.4)	$p_{1-2}=0.310$; $p_{1-3}=0.026$; $p_{2-3}=0.235$
History of arterial hypertension	466 (77.3)	437 (82.1)	421 (81.9)	$p_{1-2}=0.043$; $p_{1-3}=0.057$; $p_{2-3}=0.921$
CKD	Stage I	6 (1)	8 (1.6)	$p_{1-2}=0.612$; $p_{1-3}=0.401$; $p_{2-3}=0.743$
	Stage II	16 (2.7)	31 (6.0)	$p_{1-2}=0.719$; $p_{1-3}=0.005$; $p_{2-3}=0.018$
	Stage IIIa	6 (1.0)	23 (4.5)	$p_{1-2}=0.058$; $p_{1-3}<0.001$; $p_{2-3}=0.072$
	Stage IIIb	5 (0.8)	11 (2.1)	$p_{1-2}=0.122$; $p_{1-3}=0.066$; $p_{2-3}=0.764$
	Stage IV	1 (0.2)	2 (0.4)	$p_{1-2}=0.472$; $p_{1-3}=0.401$; $p_{2-3}=0.241$
	Stage V	–	1 (0.2)	$p_{1-3}=0.460$; $p_{2-3}=0.491$
History of MI	107 (17.7)	74 (13.9)	95 (18.5)	$p_{1-2}=0.078$; $p_{1-3}=0.749$; $p_{2-3}=0.045$
History of revascularization	70 (11.6)	46 (8.6)	48 (9.3)	$p_{1-2}=0.100$; $p_{1-3}=0.219$; $p_{2-3}=0.696$
Cardiogenic shock at admission to hospital	21 (3.5)	19 (3.6)	20 (3.9)	$p_{1-2}=0.687$; $p_{1-3}=0.607$; $p_{2-3}=0.912$
Time from pain onset to hospitalization, min	85 [60; 110]	155 [120; 215]	360 [295.5; 600]	$p_{1-2}<0.001$; $p_{1-3}<0.001$; $p_{2-3}<0.001$
Time from hospitalization to PCI, min	60 [45; 90]	75 [55; 120]	95 [65; 229]	$p_{1-2}<0.001$; $p_{1-3}<0.001$; $p_{2-3}<0.001$
Time from pain onset to thrombolytic therapy, min	75 [55; 120]	180 [92.5; 239.5]	240 [71.3; 446.3]	$p_{1-2}<0.001$; $p_{1-3}<0.001$; $p_{2-3}=0.485$
Total time of myocardial ischemia, min	125 [95; 150]	239.5 [205; 280.8]	727.5 [463.8; 1500]	$p_{1-2}<0.001$; $p_{1-3}<0.001$; $p_{2-3}<0.001$
Infarct-related artery localization				
LCA trunk	6 (1)	5 (0.9)	8 (1.6)	$p_{1-2}=0.932$; $p_{1-3}=0.401$; $p_{2-3}=0.374$
LAD	281 (46.6)	233 (44)	232 (45.1)	$p_{1-2}=0.458$; $p_{1-3}=0.664$; $p_{2-3}=0.770$
LCX	65 (10.8)	76 (14.4)	61 (11.9)	$p_{1-2}=0.068$; $p_{1-3}=0.567$; $p_{2-3}=0.232$
RCA	237 (39.3)	198 (37.4)	197 (38.3)	$p_{1-2}=0.442$; $p_{1-3}=0.696$; $p_{2-3}=0.717$
Second-order arteries	22 (3.6)	25 (4.7)	27 (5.3)	$p_{1-2}=0.365$; $p_{1-3}=0.192$; $p_{2-3}=0.696$
Multi-vessel coronary disease	151 (25)	148 (28)	141 (27.4)	$p_{1-2}=0.264$; $p_{1-3}=0.365$; $p_{2-3}=0.844$
Infarct-related artery occlusion	313 (51.9)	362 (68.4)	365 (71)	$p_{1-2}<0.001$; $p_{1-3}<0.001$; $p_{2-3}=0.400$
Use of drug-eluting stents	240 (41.7)	203 (40.4)	200 (40.8)	$p_{1-2}=0.559$; $p_{1-3}=0.717$; $p_{2-3}=0.833$
Transradial access	389 (64.5)	349 (65.6)	399 (77.6)	$p_{1-2}=0.795$; $p_{1-3}<0.001$; $p_{2-3}<0.001$
Prehospital thrombolysis	177 (29.4)	81 (15.2)	58 (11.3)	$p_{1-2}<0.001$; $p_{1-3}<0.001$; $p_{2-3}=0.073$

The data is expressed as the absolute and relative numbers (n (%)) or the median and the interquartile range (Me [25th percentile; 75th percentile]). CHD, coronary heart disease; CKD, chronic kidney disease; MI, myocardial infarction; PCI, percutaneous coronary intervention; LCA, left coronary artery; LAD, left anterior descending artery; LCX, left circumflex artery; RCA, right coronary artery.

severity of coronary artery disease. Complete occlusion of the infarct-related artery was less common, and prehospital thrombolysis was more common in Group 1 than in Groups 2 and 3. Transradial access of PCI was used more often in Group 3, than in Groups 1 and 2.

The analysis of hospital outcomes (Table 2) revealed that immediate angiographic success was achieved more often in Group 1 than Group 3. At the same time, there were no statistically significant differences in the frequency of immediate angiographic success between Groups 1 and 2 and Groups 2 and 3. The no-reflow phenomenon was observed in Group 3 more often than in Groups 2 and 1. At the same time, there were no statistically significant differences in the frequency of the no-reflow phenomenon between Group 1 and Group 2. Mortality was lower in Group 1 than in Groups 2 and 3. There were no statistically significant differences in mortality between Group 2 and Group 3. There were no differences between the groups in the frequencies of stent thrombosis, MI recurrence, stroke, or complications at the puncture site. Major adverse cardiac events (MACE) developed in Group 1 more often than in Group 3. LVEF was higher in Group 1 than in Groups 1 and 2. The size of LV myocardial asynergy was statistically significantly smaller in Group 1 than in Group 3.

According to the results of binary logistic regression, the main factors associated with the increased total time of myocardial ischemia of more than 180 minutes were: age (odds ratio (OR) 1.01, 95% confidence interval (CI) 1.0–1.02; $p=0.044$); female sex (OR=1.64, 95% CI 1.26–2.13; $p<0.001$); and chronic kidney disease (OR=1.82, 95% CI 1.21–2.74; $p=0.004$). At the same time, prehospital thrombolysis was associated with the reduced total time of myocardial ischemia (OR 0.4, 95% CI 0.31–0.51; $p<0.001$).

The correlation analysis (Figure 1, A) showed that there was a strong direct relationship between the total time

of myocardial ischemia and the time from pain onset to hospital admission ($r=0.759$; $p<0.001$). There was also a weak correlation between the total time of myocardial ischemia and the door-balloon time (Figure 1, B; $r=0.264$; $p<0.001$).

Discussion

Our findings demonstrated the effects of the total time of myocardial ischemia on mortality in STEMI patients. They confirm the conclusions of several previous trials in which the total time of myocardial ischemia was also an important predictor of hospital and long-term mortality [6–11]. For example, in the Korean register of acute MI, the total time of myocardial ischemia (less than 180 minutes) remained the only independent predictor of the reduced 30-day mortality in the risk-adjusted groups (relative risk (RR) 0.78, 95% CI 0.62–0.99; $p=0.04$) [8]. Kaweck et al. [9] described a paradox when the reduced total time of myocardial ischemia did not affect mortality rates at the population level between 2006 and 2013. However, the increased total time of myocardial ischemia remained an independent predictor of annual mortality at the individual level (RR=1.024, 95% CI 1.015–1.034; $p<0.001$). It should be noted that despite a significant reduction in mortality with the total time of myocardial ischemia of less than 180 minutes, in our study there were no significant differences in this measure between the groups with the total myocardial ischemia time from 180 to 360 minutes and more than 360 minutes. Moreover, no statistically significant differences were observed between Group 2 and Group 3 in the primary hospital outcomes and LV performance. Thus, it is essential to perform revascularization as soon as possible after the pain onset.

We established a strong direct correlation between pre-hospital delay and the total time of myocardial ischemia. At the same time, the correlation between the door-balloon

Table 2. Hospital outcomes

Parameter	Total time of myocardial ischemia			p
	Group 1, up to 180 min	Group 2, from 180 to 360 min	Group 3, more than 360 min	
Immediate angiographic success	567 (94)	486 (91.4)	451 (87.7)	$p_{1-2}=0.049$; $p_{1-3}<0.001$; $p_{2-3}=0.071$
No-reflow phenomenon	27 (4.5)	28 (5.3)	50 (9.7)	$p_{1-2}=0.539$; $p_{1-3}=0.001$; $p_{2-3}=0.005$
Mortality	14 (2.3)	33 (6.2)	37 (7.2)	$p_{1-2}=0.001$; $p_{1-3}<0.001$; $p_{2-3}=0.520$
Stent thrombosis	4 (0.7)	8 (1.5)	10 (1.9)	$p_{1-2}=0.167$; $p_{1-3}=0.055$; $p_{2-3}=0.583$
Recurrent MI	10 (1.7)	6 (1.1)	10 (1.9)	$p_{1-2}=0.449$; $p_{1-3}=0.718$; $p_{2-3}=0.281$
MACE (death, MI recurrence, stent thrombosis)	25 (4.1)	39 (7.3)	49 (9.5)	$p_{1-2}=0.020$; $p_{1-3}<0.001$; $p_{2-3}=0.200$
Stroke	2 (0.3)	2 (0.4)	–	$p_{1-2}=0.900$; $p_{1-3}=0.191$; $p_{2-3}=0.164$
Complications at the puncture site	37 (6.1)	21 (3.9)	22 (4.3)	$p_{1-2}=0.161$; $p_{1-3}=0.207$; $p_{2-3}=0.902$
LVEF at discharge, %	48 [43; 52]	46 [42; 49]	46 [41; 51]	$p_{1-2}=0.002$; $p_{1-3}=0.016$; $p_{2-3}=0.762$
LV asynergy	25 [20; 40]	30 [20; 40]	30 [20; 40]	$p_{1-2}=0.047$; $p_{1-3}=0.015$; $p_{2-3}=0.664$

The data is expressed as the absolute and relative numbers (n (%)) or the median and the interquartile range (Me [25th percentile; 75th percentile]). MI, myocardial infarction; MACE, major adverse cardiac events; LVEF, left ventricular ejection fraction, LV, left ventricle.

time and the total time of myocardial ischemia was weak. Several previous studies questioned whether the total time of myocardial ischemia was a better predictor of mortality and MACE than the door-balloon time [12, 13]. Moreover, the reduced door-balloon time is associated with the decreased mortality and MACE rate with a shorter pre-hospital delay [6].

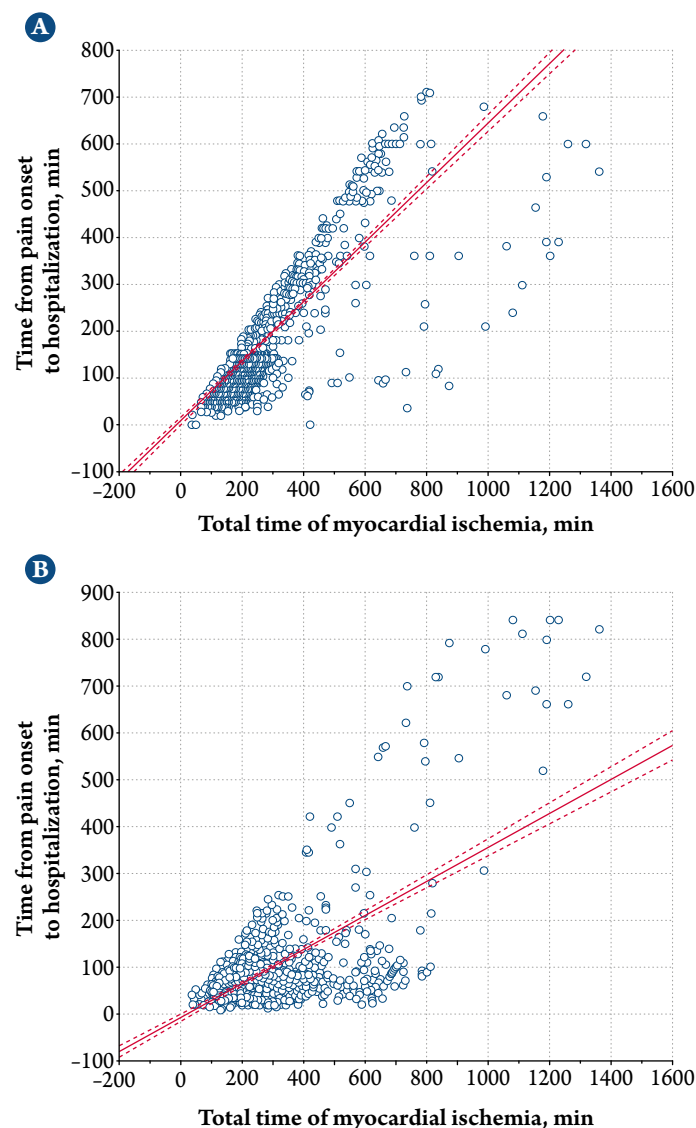
Several previous trials noted that the use of pharmacoinvasive therapy is associated with the decreased total time of myocardial ischemia [14–16], which is consistent with our findings. However, there are some contradictions. For example, in the case of pharmacoinvasive strategy, the time from pain onset to the administration of a thrombolytic drug is used in the trials to calculate the total time of myocardial ischemia [17]. The fact that a certain length of time is needed for artery recanalization, if thrombolysis is used, was not taken into account. It should be noted that several randomized trials evaluating the efficacy of the pharmacoinvasive therapy compared to the primary PCI did not analyze the total time of myocardial ischemia in detail [18, 19]. Moreover, the absence of statistically significant differences in the results of the trials makes the question of the actual reduction of the total time of myocardial ischemia when using the pharmacoinvasive intervention more controversial.

We determined that age and female sex are factors associated with the increased total time of myocardial ischemia. Finnegan et al. [20] established that most women consider MI a typical «male» disease, which leads to an underestimating of the personal risk and results in seeking treatment late. Moreover, women usually have atypical clinical symptoms. This can complicate timely diagnosis and results in the increased total time of myocardial ischemia [21]. It was previously noted that the delay before primary PCI increases with the older age of STEMI patients [22]. In some cases, this is due to the challenging timely diagnosis because of the common atypical symptoms in elderly patients [23].

Despite the obvious benefits of reducing the total time of myocardial ischemia, the target guidelines for achieving this time interval are not clearly defined. This is partially because the total time of myocardial ischemia is largely dependent on the delay caused by the patient's behavior during the onset of pain. It is a challenge to influence this indicator objectively. Previous activities aimed at informing the public about the behavior in the event of retrosternal pain were generally found to be ineffective [22, 24]. Projects aimed at educating patients were also ineffective in the long term [24]. The most promising approach is now considered implementing the targeted preventive measures in patients at high risk of late seeking treatment [22].

It is generally accepted that the total time of myocardial ischemia should not exceed 120 minutes [6]. However,

Figure 1. Correlational analysis of the total time of myocardial ischemia and the time from pain onset to hospital admission (A); the total time of myocardial ischemia, and the door-balloon time (B)



the statistically significant influence on mortality was determined in several studies only by the increased total time of myocardial ischemia of more than 180 minutes [8, 10]. According to the Australian Register, a total time of myocardial ischemia of more than 240 minutes was associated with the development of major adverse cardiac events (MACE) [11]. Thus, it is important that the effects of this parameter on the treatment outcomes for patients with STEMI be studied further.

It should be noted that our study has several limitations: specifically, the retrospective nature of the study and the inclusion of long-term patient data in the analysis. Therefore, some correlations may be irregular. For example, the overlapping of trends of the increased use of transradial access and the annual increase in the number of elderly patients is likely to cause an increased rate of using of transradial access

in patients with a longer total time of myocardial ischemia. Moreover, patients with longer myocardial ischemia may have been treated with TLT less frequently at the prehospital stage. This is likely to produce false-positive results in terms of its effects on reducing the total time of myocardial ischemia.

Conclusion

A total time of myocardial ischemia of more than 180 minutes is associated with increased mortality and frequency of major adverse cardiac events (MACE). A total time of myocardial ischemia of more than 360 minutes is associated with increased frequency of the no-reflow

phenomenon. The main predictors of increased myocardial ischemia time of more than 180 minutes are age, female sex, and chronic kidney disease. The use of pharmaco-invasive therapy is associated with an increased number of patients with a total time of myocardial ischemia of less than 180 minutes. The contribution of pre-hospital delay to the total time of myocardial ischemia is greater than that of the door-balloon time. Pre-hospital delay is strongly correlated with the total time of myocardial ischemia.

No conflict of interest is reported.

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