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Size of Acute Myocardial Infarction Correlates with Earlier Time of Initiation of Reperfusion Therapy with Cardiac Perfusion Scintigraphy: A National Single-Center Study

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Background: The aim of this study was to determine the correlation between the size of acute myocardial infarction (AMI) and the time of initiation of reperfusion therapy with cardiac perfusion scintigraphy.

Material/Methods: Overall, 80 patients with acute ST elevation myocardial infarction (STEMI) were examined. All patients were treated with primary percutaneous coronary intervention (pPCI). Data on patient and system delay expressed in minutes were recorded and compared with recommended timelines. Cardiac scintigraphy was performed with 99m Tc-sestamibi single-photon emission computed tomography (SPECT). The median time of cardiac scintigraphy was 20 days. The correlation between the size of infarction and the time of initiation of reperfusion therapy was evaluated.

Results: The mean age of patients was 60.5±11.5 years, and 72.5% were male. The average system delay was 348 min, and the average patient delay was 173 min. The mean total ischemic time was 800 min. There was a correlation between time delays of reperfusion therapy and infarct size. Patients with a shorter time delay to patent artery after FMC showed smaller infarct size when compared to the patients with longer delay times. Multiple linear regression analysis showed that FMC, being male, and smokers had statistical significance when predicting infarct size.

Conclusions: There is a correlation between the size of myocardial infarction and the time of initiation of reperfusion therapy determined by perfusion myocardial scintigraphy. The study showed that there are time delays in starting the treatment of AMI with pPCI when compared to the recommended time, which requires an action plan in the near future to ensure earlier treatment for our patients.

Keywords: Angioplasty • Anterior Wall Myocardial Infarction • Technetium Tc 99m Sestamibi • Time Factors

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Background

Treatment of patients with ST elevation myocardial infarction (STEMI) consists of reperfusion therapy with the aim to restore blood circulation into the ischemic myocardium. The benefits of angioplasty are maximal when the procedure is performed within 2 h after the onset of symptoms, resulting in reduced mortality, heart failure, and rehospitalizations [1]. When primary percutaneous coronary intervention (pPCI) is performed between 3 and 6 h after the onset of symptoms the patient can still benefit, but to a lesser degree. A large number of observational studies have confirmed that any delay of at least 30 min in treatment resulted in a 7.5% per year increase of the risk of mortality in patients with myocardial infarction [2]. Thus, earlier time to reperfusion therapy is crucial. Additional risk factors leading to worse outcomes of AMI include comorbid diabetes, hypertension, peripheral artery disease, older age, reduced renal function, and history of stroke [3]. Infarct size and microvascular obstruction (MVO) are the main independent predictors of long-term mortality and heart failure in STEMI survivors [4,5]. MVO is defined as insufficient myocardial perfusion after successful mechanical opening of the infarct related artery (IRA), and is caused by various factors [6].

Use of single-photon emission computed tomography (SPECT) and cardiac magnetic resonance (CMR) for determination of myocardial infarct size is relatively new and may be useful for post-discharge risk stratification [7]. The purpose of this study was to assess delays and their impact on infarct size, as the data for our country are lacking, and thus assess a possible correlation between the size of AMI and the time of initiation of reperfusion therapy with cardiac perfusion scintigraphy. The Republic of Kosovo is part of the Western Balkan, South-East Europe region and has 1.78 million inhabitants [8]. Currently only 1 center, the University Clinical Center of Kosovo (UCCK), offers services for treatment of AMI with pPCI 24 h per day, 7 days per week. In early 2018, the start of 24-hour service at the Unit of Invasive Cardiology enabled treatment with pPCI for AMI. However, there is no functioning health insurance system or fully operational health information system, nor is there a database for tracking treatment delays, so this study is the first attempt at gathering national data.

Material and Methods

The data were collected retrospectively from the records of consecutive patients who were treated at the Clinic of Cardiac Surgery and Invasive Cardiology, University Clinical Center of Kosovo (UCCK) in Prishtina in the last 2 years. We excluded patients with missing records or missing data. Overall, 80 patients treated with pPCI with full records were identified in the last 2 years. The patients were most often treated with transfemoral

approach and less often with transradial approach. The retrospective study design and study execution were approved by departmental committee of UCCK.

All patients were admitted to our center as referrals from their family medicine center or were referred by regional hospitals. Sometimes, patients bypassed these primary institutes/first medical contacts (FMC) and were admitted directly to our department. FMC provided the time from the call for the ambulance to the time of arrival at the emergency department.

All cardiac scintigraphy procedures were performed at our department. The median time of cardiac scintigraphy was 20 days. Patients' records included location of the occlusion, extent of coronary artery disease and infarct size, type of pPCI, time of door-to-balloon inflation, time of patent IRA, and treatment outcome.

The infarct size was expressed as percentage of left ventricle muscular mass. Semiquantitative analysis of the infarction size with scintigraphy was determined as follows:

	% of left ventricle	Number of segments
Infarct size (defect)	Small 5-10%	1-2
	Average 15-20%	3-4
	Large >20%	5

Delays in treatment time were expressed in minutes, and the distance from the point of contact of FMC was expressed in kilometers. We also calculated the distance from the place of residence to the FMC (ie, family medicine center), the distance from the family medicine center to the regional hospital, and the distance from the regional hospital to the UCCK.

Data on time delays were obtained according to timepoints from the following sources:

- Patient contact of emergency service;
- Arrival of ambulance to FMC institution;
- Referrals from family medicine centers, when they were FMC;
- Referrals from regional hospitals and reports from their emergency centers as FMC;
- Arrival and admission time at the emergency center of the UCCK;
- Timing of electrocardiogram (ECG) at the main family center or regional hospital or emergency center of the regional hospital or emergency center of the UCCK before the intervention and after the pPCI procedure;
- Data from the Coronarography and Invasive Treatment consent form, under the section designated for signature, there is date and time of signature of the patient, attendant or family member;

Table 1. Basic characteristics of patients at admission.

Baseline data	N=80
Age (years), mean ($\pm$ SD)	60.1 $\pm$ 10.2
Sex	
Male <i>n</i> (%)	58 (72.5)
Female, <i>n</i> (%)	22 (27.5)
Risk factors	
Hypertension, <i>n</i> (%)	53 (66.3)
Diabetes mellitus, <i>n</i> (%)	15 (25.9)
Dyslipidemia, <i>n</i> (%)	26 (32.5)
Smoking, <i>n</i> (%)	39 (48.75)
Family history of cardiovascular diseases, <i>n</i> (%)	23 (28.8)
Scintigraphic infarct size, median (range)	23.0 (1.0-72.0)
Laboratory values	
Hemoglobin (g/L), mean ($\pm$ SD)	143.9 $\pm$ 14.4
Creatinine (μ mol/L), median (range)	110.0 (59.0-156.0)

Baseline data	N=80
Creatine kinase-MB (IU/L), median (range)	181.5 (9.0-1001.0)
Creatine kinase (IU/L), median (range)	456.5 (20.0-4966.0)
Troponin (ng/mL), mean ($\pm$ SD)	236.8 $\pm$ 65.76
Anterior infarction, <i>n</i> (%)	42 (52.5%)
Coronary angiographic findings	
Culprit lesion, <i>n</i> (%)	
RCA	23 (28.8%)
LAD	42 (52.5%)
LCX	15 (18.8%)
Total ischemic time (min), median (range)	800 (240-1040)
Time from FMC to pPCI (min), median (range)	65 (21-570)
Time to infarct size assessment (days), median (range)	5 (3-12)

- Anamnesis and detection of STEMI and decision to perform PCI;
- Time of contact with emergency cardiologist;
- From the urgent report of the coronary angiography procedure and PCI;
- From the printed report of coronarography and PCI.

Statistical Analyses

All statistical analyses were performed using SPSS Statistics 21 (IBM, New York, USA). For categorical data, correlation between groups was assessed with the Pearson's chi-square test or Fisher exact test; for continuous data, the differences were assessed by analysis of variance or the Kruskal-Wallis test for data with non-normal distribution. Continuous variables were presented as mean or median values. Time delay was defined as the time from the onset of symptoms to the FMC; it was considered as a continuous variable and was expressed in minutes. Patient delays were log-transformed for further analysis. The effect of each potential predictor for infarct size was assessed by multiple linear regression analysis. All analyses were performed at a level of 5% significance.

Results

The study included a total of 80 patients with AMI who underwent primary percutaneous coronary intervention (pPCI).

Data on basic patient characteristics are presented in **Table 1**. Coronary angiography findings showed involvement of the left anterior descending artery (LAD) in 42 (52.5%) patients, right coronary artery (RCA) in 23 (28.9%), and circumflex artery (LCX) in 15 (18.8%). Regarding the number of arteries, 40% of patients had single-vessel coronary heart disease, 31% had 2-vessel coronary artery disease, and 29% had 3-vessel coronary artery disease.

The average system delay was 348 min. The average patient delay was 173 min (range 45-180 min). The door-to-balloon inflation time was 114 min (0-65 min). The average distance to the regional hospital was 50 km, which resulted in an average delay of 950 min.

Patients were divided into 2 groups according to the timing of reperfusion therapy: the first group received reperfusion therapy within the first 180 min (3 h), and the second group after 180 min (more than 3 h). Patients with a different patent artery after FMC showed no significant differences between the 2 groups except for the FMC to patent artery (**Table 2**).

Our research did not differentiate the patients according to diabetes status, although this has been identified as a risk factor. We also did not compare mortality between the 2 PCI groups, as this was not the primary nor secondary endpoint of the study, but we rather focused on the size of infarction, which has been correlated in the past with higher mortality rates.

Table 2. Characteristics related to reperfusion time.

	FMC to patent artery <180 min (N=20)	FMC to patent artery ≥180 min (N=60)	P value
Age (years), mean (±SD)	61.2±10.7	62.7±11.2	0.480
Women n (%)	13 (65.0)	9 (15.0)	0.200
Risk factors			
Hypertension n (%)	15 (75.0)	38 (63.3)	0.220
Diabetes mellitus n (%)	6 (30.0)	9 (15.0)	0.990
Smoking n (%)	19 (95.0)	20 (33.3)	0.390
Hyperlipidemia n (%)	16 (80.0)	10 (16.7)	0.440
FMC to patent artery (min), mean (±SD)	101.0±47.74	271.84±143.75.5	<0.001
Previous revascularization/MI	0 (0)	0 (0)	

* FMC – first medical contact.

Figure 1. Pearson correlation analysis of total ischemic time and infarct size.

There was a good correlation between time delays of reperfusion therapy and infarct size, as shown in the **Figure 1**, with $r=0.36$. Patients with a shorter time of patent artery after FMC had smaller infarct size compared to patients with longer delay times. Moreover, multiple linear regression analysis showed that FMC, being male, and being a smoker were statistically significant ($P<0.05$) in predicting infarct size. Meanwhile, LAD as culprit artery did not show any significance (**Table 3**).

Discussion

The aim of this study was to assess the possible correlation between the size of AMI and the time of initiation of reperfusion therapy in patients from a single national center. There are 38 municipalities in our country; each has a Main Family Medicine Center (MFMC), but all AMI patients are referred to UCCK [8]. The road network consists of 630 km of main roads, and the country's road infrastructure is well developed [9], making transportation to the pPCI center relatively rapid. The

Table 3. Prediction of infarct size (dependent variable) based on multiple linear regression.

Variable	95.0% Confidence interval for B	P value
Age	0.48 (0.01-0.95)	0.045
LAD as culprit artery	-0.15 (-34.03-20.78)	0.630
FMC to patent artery	0.05 (0.003-0.10)	0.030
Smoker	13.1 (2.53-23.73)	0.010
Male	12.93 (1.57-24.29)	0.020
Diabetes	-9.1 (-21.74-3.48)	0.150
Hypertension	-0.51 (-11.90-10.86)	0.920

Cardiology Clinic within the UCCK offers pPCI for AMI 24 h a day, 7 days a week. However, there is currently no functioning health insurance system and health information system, what causes a lack of data on treatment delays with STEMI; thus, this study provided the first data on the national level.

Multiple studies have been conducted to determine factors affecting the final size of AMI with ST segment elevation. These studies dealt with the impact of infarct location [10], as well as the utility of troponin and creatine kinase in predicting myocardial infarct size and left ventricular dysfunction, with strong correlations [11]. Studies have proven correlations between time delays and mortality in AMI patients [12-14]. Our analysis of patients with STEMI also found a correlation of FMC with time delay and infarct size. Similar results were obtained by Tödt et al [15], who found a correlation between FMC and myocardial injury in STEMI patients treated with pPCI [15]. Furthermore, studies of infarct size, left ventricular function, and prognosis in women compared to men did not show significant differences [16], and the time of day of symptom onset was also not a significant variable [17]. On the contrary, we found that males were almost 13 times more likely to have a larger infarct site than females.

Overall, the effects of prehospital system delays on the efficacy of treatment of STEMI patients highlighted how important it is to reduce the time spent on STEMI patients at the scene by performing an ECG as soon as possible and immediately transporting the patient to a hospital with targeted pPCI treatment [18]. A meta-analysis of the relationship between infarct size and outcomes following pPCI [4] concluded that infarct size, measured by technetium-99m sestamibi SPECT or CMR after 1-month pPCI, is strongly associated with all-cause mortality and hospitalization within 1 year. Furthermore, symptoms onset-to-balloon time was also correlated with larger infarct size [19]. Patients who received pPCI within 3 h after symptom onset were reported to have smaller infarct size, being only 4% of the left ventricular myocardium [19,20].

Moreover, a study on BMI, infarct size, and clinical outcomes following pPCI showed that BMI was not associated with ischemic size, microvascular obstruction, left ventricular ejection fraction, or 1-year rates of death or heart failure hospitalization [21]. Due to use of several timepoints, the total ischemic time delay consisted of several leverage points. In a study by Tödt et al [15], the correlation between total delay time and infarct size was not significant when compared to the correlation between health care delay time and infarct size. They found no correlation between time from symptom onset, or FMC to a patent IRA and infarct size. Meanwhile, patients who demonstrated a patent artery within 90 min of FMC showed a trend of smaller infarct size than those who had longer delay times, in agreement with the present study. The time delay in

our population was unprecedented. The average system delay was 348 min, patient delay was 173 min, and door-to-balloon time was 114 min. Not including the travel time to UCCK, our time delays were far longer than the 193 min delay time observed by Tödt [15].

Furthermore, as was observed with our results, patients with shorter FMC to patent artery, older patients, smokers and male gender also showed predictive results for infarct size, but no difference in LAD or accompanied comorbidities such as diabetes or hypertension. Interestingly patients with LAD as the culprit artery actually showed negative correlation with larger infarct sizes. What is on the contrary with other studies [22,23]. On the other hand, a multiple linear analysis found that smoking is correlated with infarct size [15]. Even though it has been reported that earlier coronary reperfusion reduces mortality in patients with STEMI, reperfusion therapy was administered too late. If we make a simple calculation that the average system delay was 348 min, patient delay was 173 min, and door-to-balloon inflation time was 114 min, that means that prior to reperfusion we had an average delay of 635 min, which is unacceptable. This shows that infarct size may be useful as an endpoint and as an important prognostic measure when caring for patients with STEMI. A recent large-scale pooled analysis using individual patient data found that a relationship between pPCI time of day, infarct size, microvascular obstruction, and prognosis in ST-segment elevation myocardial infarction, but no association was found between the time of day of pPCI and infarct size, MVO, or prognosis after STEMI [24].

According to our analyses, the time delay should be reduced. Other reports have proposed that hospitals with short door-to-balloon time have implemented various strategies such as prehospital ECG, cardiologist always on site, continuous monitoring of time delays, and an interdisciplinary approach in the process itself [25]. Also, other authors identified unacceptable time delays, mainly due to delay in ECG, processes in the emergency room, and door-to-balloon time [26,27]. With a detailed action plan and strategy, Ward et al [26] managed to reduce door-to-balloon time from 136 to 82 min. Other investigators have been able to achieve similar improvements simply by monitoring performance on door-to-balloon time without changing the STEMI strategy [27].

In our study we found that patient and system delays are longer than the recommended timeline. Although Kosovo is a small country with a good highway system, the time from FMC to the center performing PCI was 65 min and total ischemic time was 800 min. The median time to infarct size assessment after pPCI was 5 days. There was a strong correlation between the infarct size and the time delay in commencing reperfusion therapy using pPCI. These results show the need for an action plan. There are several leverage points that need to be

addressed in our process, such as the need for a dedicated phone line to allow quicker transport to the PCI center in order to shorten delays. Increasing the number of centers performing PCI should also be considered. Moreover, a smoother process within health care centers could also be of great value.

Study Limitations

Our analysis has some limitations. The data were analyzed retrospectively, impacting the quality of the dataset. Measurements of time delays could be biased and thus result in errors. Only patients who had full records were included, resulting in a relatively small sample size. A larger-scale study might have found a stronger correlation between time delays and infarct size. Lastly, this was a single-center study with a small number of patients for the multiple timepoint measurements.

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Conclusions

We found a significant relationship between the size of myocardial infarction and the time of initiation of reperfusion therapy as determined by perfusion myocardial scintigraphy. The study showed that there are long delays in starting the treatment of AMI with pPCI compared to the recommended timelines. Evidence-based studies show that infarct size will improve with earlier management of STEMI patients, by better identification of those with large infarcts. Our results suggest the need for an action plan to reduce time delays, as well as the need for improved management systems to significantly reduce delays in treatment of STEMI patients.

Declaration of Figures Authenticity

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