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Pain to Hospital Times After Myocardial Infarction in Patients from Dalmatian Mainland and Islands, Southern Croatia

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Aim To analyze pre-hospital delay in patients with myocardial infarction from mainland and islands of Split-Dalmatian County, southern Croatia.

Methods The study included all patients with myocardial infarction transported by ambulance to the University Hospital Split in 1999, 2003, and 2005. Pre-hospital delay was analyzed in the following intervals: pain-to-call, call-to-ambulance, ambulance-to-door, and door-to-coronary care unit interval. Patients were categorized according to the location from which they were transported: Split, mainland >15 km from Split, and islands.

Results There were 1314 patients (62.9% men) transported and hospitalized for myocardial infarction. Total pre-hospital delay (pain-to-hospital) was significantly reduced from 1999 to 2005 (5.2 hours vs 4.3 hours, $P=0.011$). Seventy-five patients (5.7%) were admitted to the coronary care unit within the recommended time-frame of less than 90 minutes, none of which was from the islands, while 248 patients (18.9%) were admitted more than 12 hours from the onset of pain.

Conclusion Pre-hospital delay in patients with myocardial infarction in southern Croatia is still too long, especially in patients coming from outside of Split. Prognosis and survival of such patients may be improved by introducing changes to the health care system in remote areas, such as out-of-hospital thrombolysis, greater use of telemedicine, training of lay persons and paramedics in defibrillation, introduction of quality assessment mechanisms, and improved patient transport.

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Coronary or ischemic heart disease (CHD), manifesting as stable or unstable angina pectoris, acute myocardial infarction (AMI), functional heart impairment, cardiac arrest, or sudden heart failure, is the leading cause of death around the world. It affects approximately 17 million people worldwide, including 5 million a year in Europe (1).

In Croatia, it was the leading cause of death in 2008, causing one-fifth of all deaths in both women and men (2). From 1979 to 2001, AMI mortality in the capital city of Zagreb was very high: 50% of all patients with AMI died, with 31% being out-of-hospital deaths (3). In the Split-Dalmatia county, primary health care institutions reported 1022 patients with AMI in 2002, and only 391 (38%) of them (249 men and 142 women) were admitted to University Hospital Split (4). We may conclude that 62% of patients did not receive adequate care, a reason for which may be the existence of only one general hospital in Split-Dalmatia County, which is also the only one with a coronary care unit (CCU).

The mortality rate of AMI in the first 30 days after the onset of disease ranges from 30-50%, with about half of deaths occurring within the first 2 hours (5,6). In-hospital mortality of AMI in North America has decreased from 25-30% to 7-10% in the past 30 years. This decrease can be attributed to the introduction of CCUs, administration of beta blockers, and introduction of fibrinolytic therapy and percutaneous coronary intervention (PCI) (5,6).

The greatest barrier to optimal treatment is the delay between the onset of symptoms and initiation of therapy. This delay is of interest given the time-dependent benefits associated with early use of coronary reperfusion therapy (7). In order to treat AMI effectively, the time span from the onset of the first symptoms to administration of fibrinolytic therapy or PCI, known as pain-to-needle time, should be shorter than 90 minutes (8,9). According to the second Euro Heart Survey on acute coronary syndromes, conducted in 190 medical centers in 32 countries, the median time from symptom onset to arrival to the emergency department in 2004 was 2.8 hours (range, 1.3-7 hours), while median pain-to-call time was 1.75 hours (range, 0.7-5.1 hours) (10).

In Split, the average time interval from the onset of myocardial infarction symptoms to arrival to the coronary unit from 1981 to 1987 was 14.8±11.6 hours (range, 2-72 hours). The authors of the study concluded that this interval should be substantially reduced in order to decrease the mortality associated with CHD (11).

Pre-hospital delay assessment takes into consideration several intervals: pain-to-call, call-to-ambulance, ambulance-to-door, and door-to-CCU time. Pain-to-call time accounts for the greatest part of pre-hospital delay in urban areas, while the other intervals, which depend on the health care system, are more responsible for pre-hospital delay in rural and remote areas (12).

The aim of this study was to analyze pain-to-door time in patients with myocardial infarction from mainland and islands of Split-Dalmatian County, compare it with previous studies, and provide recommendations for more effective practice.

METHODS

This prospective clinical study included patients with chest pain indicative of myocardial infarction according to European Society of Cardiology (ESC) guidelines (13,14) who were transported by ambulance and admitted to the CCU of University Hospital Split in 1999, 2003, and 2005. Ethics committee of University Hospital Split did not require ethical approval and informed consent for this study.

We examined the admission of patients with myocardial infarction in 1999, 2003, and 2005. The year 1999 was used as baseline since in 2003 the emergency medical service underwent changes in terms of introduction of PCI during regular weekday hours, education of staff in life support by anesthesiologists, purchase of new vehicles; which coincided with improvements in the road system in the area. The year 2005 was chosen because another set of changes was introduced: 24-hour PCI, obligatory Advanced Life Support course (created by the European Resuscitation Council and provided by the Croatian Resuscitation Council) for all physicians and technicians, reorganization of dispatcher service to improve efficiency of ambulances, building of two new helicopter landing areas on the islands, purchase of new equipment, implementation of new protocols, and merging of all emergency medical services in the Split-Dalmatia county into a single institution.

The patients were divided into 3 groups according to their place of residence: the city of Split and its immediate surroundings (within 15 km), areas farther than 15 km from Split, and islands off the Dalmatian coast: Brač, 16 km nautical distance from Split; Šolta, 16 km; Drvenik Veli, 27 km; Drvenik Mali, 28 km; Hvar, 44 km; Vis, 56 km; Lastovo, 104 km; and Korčula, 112 km.

Inclusion criteria

The study included adult patients of both sexes with a diagnosis of AMI made according to clinical, electrocardiographic, and biochemical criteria set by the ESC. Clinical criteria were chest pain lasting more than 20 minutes and a failure to respond to nitroglycerine. Electrocardiographic criteria were ESC criteria for AMI from 1996 (13,14). For myocardial infarction with Q wave these criteria were Q waves in precordial leads V1 to V3, Q waves ≥30 ms in I, II, aVL, aVF, V4, V5, V6. The amplitude of Q waves had to be larger than 1 mm and they had to be present in any of two adjacent leads. For myocardial infarction without Q wave, the inclusion criterion was the absence of Q wave at least 12 hours from the onset of pain. Q-wave and non-Q myocardial infarction are equivalent to ST-segment elevation myocardial infarction and non-ST-segment elevation myocardial infarction, respectively.

Biochemical inclusion criterion was the increase of creatine phosphokinase with an MB (CK-MB) fraction of 10% or more. In order to include a patient in the study, all these criteria – clinical, electrocardiographic, and biochemical – had to be fulfilled.

Exclusion criteria

Patients with no pain, no electrocardiographic changes, or no increase in CK or CK-MB were not included in the study.

Tests and measurements

Each patient admitted to the CCU with a suspected myocardial infarction underwent a standard 12-channel electrocardiogram and the following laboratory tests: creatine phosphokinase with muscle and brain subunits (MB), alanine transferase, aspartate transferase, lactate dehydrogenase and, in 2003 and 2005, troponin I. Venous blood for laboratory tests was taken immediately on admission and again the next day.

Diagnostic tests included electrocardiography, creatinine phosphokinase, and the MB fraction of creatine phosphokinase. A standard 12-channel electrocardiogram was recorded on a 3-channel electrocardiograph (Cardiostat 31, Siemens-Elema AB, Solna, Sweden). The activity of creatine phosphokinase was determined using the IFCC-UV method at 30°C on a Hitachi 917 device (Roche Diagnostics, Basel, Switzerland). The reference range for creatine phosphokinase was 5-170 U/L. The activity of CK-MB was automatically measured from the activity of CK at 30°C on the Hitachi 917 device. The reference range was 6-25% of the total CK activity.

Measurement of pre-hospital and in-hospital delays.

For each patient, the following data were obtained from patients or accompanying persons and recorded on individual test lists: place of residence, time of onset of pain, time elapsed from the onset of pain to the emergency call (pain-to-call time), time from the call to arrival of the ambulance (call-to-ambulance), time from the arrival of ambulance to admission to emergency department (ambulance-to-door), and time from admission to emergency department to admission to coronary care unit (door-to-CCU).

Statistical analysis

Data analysis was performed with GraphPad Prism (GraphPad Inc, San Diego, CA, USA). The following tests were used: χ^2 test, Kruskal-Wallis analysis of variance, post-hoc Dunn test, Mann-Whitney test, Pearson test for association between categorical and continuous variables, and Spearman test for association between continuous variables. Statistical significance level was set at $P<0.05$. Continuous variables were expressed as median and interquartile range. Categorical variables were expressed as frequencies and percents.

RESULTS

A total of 1314 patients with myocardial infarction were transported by ambulance and admitted to the CCU of University Hospital Split during the 3 studied years (Table 1). There were no significant differences in the frequency of myocardial infarction between the years ($\chi^2=4.61$; $P=0.099$). Altogether 3194 patients were admitted to the CCU, 41% of whom were AMI patients transported by ambulance. Survival until discharge of patients with myocardial infarction significantly improved over the 3 years and in 2005 it doubled in comparison with 1999 ($P<0.001$). Most patients were transported from Split and its surroundings and fewest from the islands (Table 1). Overall, 1135 (86.4%) patients survived until discharge from hospital, which was 8 days on average (Table 1).

Of the 1314 patients included in this study, 223 (17%) were diagnosed with sub-acute myocardial infarc-

TABLE 1. Characteristics of patients with myocardial infarction who were transported by an ambulance and admitted to the University Hospital Split in 1999, 2003, and 2005

Variable	No (%) of patients in 1999	2003	2005	Total
Sex:				
female	154 (37.9)	170 (36.4)	163 (37.0)	487 (37.1)
male	252 (62.1)	297 (63.6)	278 (63.0)	827 (62.9)
Location:				
Split and surroundings ≤15 km	210 (51.7)	221 (47.3)	208 (47.2)	639 (48.6)
>15 km from Split	160 (39.4)	204 (43.7)	203 (46.0)	567 (43.2)
islands of Central Dalmatia	36 (8.9)	42 (9.0)	30 (6.8)	108 (8.2)
Intra-hospital survival:				
yes	330 (81.3)	403 (86.3)	402 (91.2)	1135 (86.4)
no	76 (18.7)	64 (13.7)	39 (8.8)	179 (13.6)
Total number of patients	406	467	441	1314

TABLE 2. Characteristics of patients with subacute and acute infarction

Parameter	Diagnosis: subacute myocardial infarction	acute myocardial infarction
Total number (%)	223 (17)	1091 (83)
Sex:		
female	102	365
male	121	706
Female/male ratio	1:1.18	1:1.83
Mean age (interquartile range), years*	70 (14)	67 (17)

*$P < 0.001$ (Mann-Whitney test).

tion and 1091 (83%) with AMI. The women-to-men ratio was lower in the group with sub-acute myocardial infarction (Table 2). Median age of patients with sub-acute myocardial infarction was significantly higher than that of patients with AMI (Table 2).

There were 5.7% (75/1314) of patients who were admitted to CCU within 90 minutes, which is the recommended time frame for optimal therapeutic benefit from coronary reperfusion therapies, and 19% of patients (248/1314) who were admitted to the CCU more than 12 hours after the onset of cardiac pain (Figure 1).

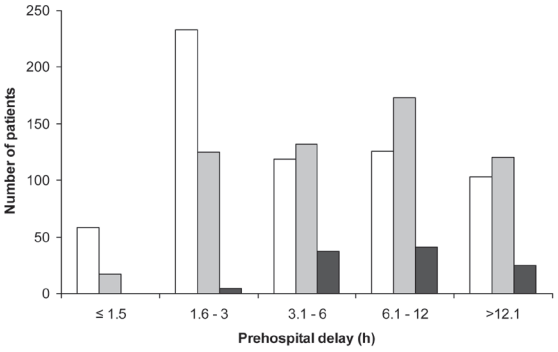
Patients from Split and its immediate surroundings called the emergency service earlier than those living inland or on the islands (Table 3). The time of ambulance arrival was significantly longer for inland and island patients, as was the time needed to transport a patient to hospital (Table 3). The longest ambulance-to-door time was 2.9 hours for patients from Split area, 10.5 hours for the

TABLE 3. Time elapsed from onset of pain to admission to coronary unit, by patients' residence

Pre-hospital delay (h)*	Residence: ≤15 km from Split	>15 km from Split	islands	$P^{\dagger}$
Pain-to-call	2.0 (5.7)	3.0 (7.5)	2.5 (5.8)	0.034
Call-to-ambulance	0.5 (0.5)	0.7 (0.5)	0.8 (0.5)	<0.001
Ambulance-to-door	0.5 (0.1)	1.0 (0.7)	2.5 (2.25)	<0.001
Total pain-to-coronary care unit time	3.5 (6)	6.5 (7.5)	7 (6.65)	<0.001

*Times are expressed as median (interquartile range).
†Kruskal-Wallis test. For variables the main effect of which was $P < 0.05$, Dunn post-hoc analysis revealed significant differences between all pairs of columns ($P < 0.001$).

Figure 1.



Time interval from onset of pain to admission to coronary care unit by patient residence. Open bars – ≤15 km Split; gray bars – >15 km from Split; closed bars – islands.

TABLE 4. Time elapsed from onset of pain to admission to coronary unit in 1999, 2003, and 2005

Pre-hospital delay (h)*	Year: 1999	2003	2005	$P^{\dagger}$
Pain-to-call	2.75 (5.85)	2.5 (6.1)	2.0 (10.7)	0.093
Call-to-ambulance	0.5 (0.3)	0.6 (0.4)	0.6 (0.4)	<0.001
Ambulance-to-door	0.6 (0.7)	0.8 (0.9)	0.7 (0.6)	<0.001
Door-to-coronary care unit	0.4 (0.2)	0.5 (0.1)	0.5 (0.1)	<0.001
Total pain-to-coronary care unit time	5.2 (6.1)	5.5 (6.4)	4.3 (11.0)	0.011

*Times are expressed as median (interquartile range).
†Kruskal-Wallis test. For variables the main effect of which was $P < 0.05$, Dunn post-hoc analysis revealed significant difference between all pairs of columns ($P < 0.001$).

area >15 km from Split, and 13 hours for islands. Analysis of patient arrival times to the CCU revealed a significant difference between the 3 areas (Table 3).

There was a downward trend for pain-to-call time in all myocardial infarction patients, but it did not reach significance. The other 3 pre-hospital delay intervals did not improve during the study period (Table 4). The total pre-hospital delay fluctuated significantly between the analyzed years, and was the lowest in 2005 ($P=0.011$). The greatest contributor to total pre-hospital delay was the pain-to-call time (Table 4).

Our hypothesis that women and elderly were more likely to wait longer than men and younger patients to seek medical care after the development of symptoms suggestive of myocardial infarction was not confirmed, as there was no correlation between pain-to-call time and either female sex (Pearson $r_{pb}=-0.105$, $P<0.001$) or age ($\rho=0.144$, $P<0.001$).

DISCUSSION

We found that pre-hospital delay in patients with myocardial infarction in the Split-Dalmatia county significantly improved from 1999 to 2005 and was much shorter than previously reported (11). However, there were 19% of patients who were admitted to the CCU more than 12 hours after the onset of pain. Also, when compared with major international studies, the admission to hospital of our AMI patients was late (15-17). Median time from the onset of pain to admission in the CCU in our study ranged from 4.3 to 5.5 hours and in the European Heart Surveys conducted in 2000 and 2004 just over 2 or 3 hours (10,18).

The main objective of treating patients with acute myocardial infarction is to re-establish myocardial perfusion within a few hours from the onset of pain, in order to save the ischemic myocardium and increase the chance of survival (19-21). The 2-fold increase in survival between 1999 and 2005 can be explained by the introduction of PCI procedure at University Hospital Split in 2003. For the first two years, PCI was available only during regular workday hours, while at the beginning of 2005 a 24-hour PCI service was introduced.

The current European Society of Cardiology guidelines state that "time is muscle" (22), ie, that target delay times should be <30-minute from ambulance arrival to the start of fibrinolytic therapy, and ≤120-minute from ambulance arrival to the first balloon inflation. Therefore, the increase in the survival rate of patients experiencing AMI requires early recognition of AMI, a prompt call, urgent arrival of the ambulance, early reperfusion treatment, recognition of the presence of life-threatening arrhythmias, early defibrillation, and cardiopulmonary reanimation (20,23-25).

The greatest contributor to pre-hospital delay in our study was pain-to-call time. This interval does not depend on the efficiency of emergency medical services or hospital staff, but entirely on patients or people around them. A previous Croatian study, conducted in Zagreb in 1996, showed that patients with AMI symptoms called for help very late, which indicates poor recognition of AMI symptoms among general public (3). The longest response time in our study was 112.8 hours, while median time ranged from 2 to 3 hours, depending on the year and location.

Many countries try to reduce pre-hospital delay in myocardial infarction (26). However, despite improved organization, the main contributor to pre-hospital delay still remains the time between the onset of chest pain and the call for medical help (26). Pain-to-call time is also referred to as the "decision time" and has been correlated with nocturnal onset, low pain severity, rural origin, and diabetes (27-29). Also, women and elderly have been found to call later (26,30,31), as well as people with poor knowledge about myocardial infarction (26). We, however, did not find an association between female sex or older age and a delayed response time.

The longest pre-hospital delay times were observed in patients who indicated that they did not know where to seek help and first visited their family physician. General practitioners still play a major role in the early care of myocardial infarction and are often the first to be called by patients (22). If they respond quickly, they can be very effective since they usually know the patients, are able to take and interpret an ECG, administer opioids, call the ambulance service, and defibrillate (32,33). However, multiple studies have shown that consultation with a general practitioner may be one of the reasons for an increased pre-hospital delay (34,35). To determine the interventions that might change this behavior, a systematic study of the behavior of all providers has been suggested (34).

Patients who were educated in myocardial infarction symptoms have been found to call before those who were not, and the main sources of information on AMI have been reported to be physicians, media, books,

other patients, friends, and, increasingly, the internet (26). Interestingly, lack of health insurance and living alone have not been found to affect the delay of call for help (26). Most interventions aimed at reducing pre-hospital delay have been restricted to broad-based public education campaigns, which have produced conflicting results and the efficacy of which has remained unclear (36).

If a patient cannot reach a hospital within 90 minutes, out-of-hospital thrombolysis should be considered (37). Use of pre-hospital thrombolytic therapy has been suggested not only in rural communities but also in urban areas where traffic congestion may contribute to the delay (12). This would be especially valuable in Dalmatia, as we showed that not a single patient from the islands and only 3% of mainland patients living more than 15 km from the city were delivered to the hospital within 90 minutes from the onset of myocardial infarction pain. Paramedics in Croatia do not perform thrombolysis, because Croatia is one of the few countries with physician-manned ambulances. However, even physicians in Croatia do not perform thrombolysis out-of-hospital, contrary to the ESC guidelines (22).

In many European countries and the US, assistance to myocardial infarction patients is prompt and efficient in urban areas and areas outside cities with plenty accessible roads, but less so in remote rural areas (38-40). In our study, patients were rarely admitted to hospital within 90-minute even if they were from the city: only 9.1% of city patients were admitted to the CCU within the recommended time. As opposed to this, in Worchester, Massachusetts, 45% of patients with AMI were admitted to hospital within 2 hours of acute symptom onset (30).

Of the island patients, 61.1% were admitted to hospital 6 hours after the onset of symptoms. All of them came from the closest islands of Brač and Šolta, and arranged the transport themselves by police boat or private speedboats in the early morning hours during the summer, when the sea was calm, rather than using organized medical service. These results cannot be compared with previous studies, since there are no similar studies in inhabitants of the Central Dalmatian islands. Medical service on the islands should be further investigated, with an emphasis on the association between the duration of patients' transport from the islands and seasons and climate conditions.

Kelly et al have listed the following factors behind longer pre-hospital delays in patients from rural than in urban settings: longer door-to-needle time in local hospitals, distance from facilities performing thrombolysis, ineffective use of resources (paramedics do not administer thrombolysis or perform defibrillation), and between-agency administrative processes, such as when emergency services must first identify a receiving hospital (37). Some of these factors are also present in Croatia and our results call for changes in the organization of emergency medical services in the country. This can be achieved by authorizing community practitioners to deliver thrombolysis. Also, a network of community hospitals equipped with videoconferencing and remote telemetry equipment has been described, allowing real-time consultation of a general practitioner with the local accident and emergency department and CCU (41). This intervention would be worthwhile, considering the increased prevalence of body weight and hypertension in the population of the Adriatic islands (42).

The ambulance (helicopter) service plays a critical role in the management of myocardial infarction and should be considered not only a mode of transport but a place for initial diagnosis, triage, and treatment (22). As such, patient transport service should be improved on the islands and in remote areas.

Furthermore, a key link in the chain of survival is defibrillation; it is one of the few interventions shown to improve the outcome of cardiac arrest if applied within 3-minute of collapse (43). Automated external defibrillators are sophisticated, reliable computerized devices that use voice and visual prompts to guide lay rescuers and health care professionals to safely attempt defibrillation in cardiac arrest victims (43). The European Resuscitation Council recommends training lay rescuers and advocates for public access to defibrillation (44). However, in Croatia only physicians are allowed to perform defibrillation, which is detrimental for public health, as lay rescuer defibrillation programs with rapid response times have achieved survival rates as high as 49-74% (44). It would be beneficial if all medical personnel and non-medical rescuers such as police officers, firefighters, and mountain rescuers, were trained and permitted to use automated external defibrillators.

ESC guidelines also state that quality of care, appropriateness of reperfusion therapy, delay times, and patient outcomes should be measured and compared at regular times, and appropriate measures for improvement should be taken (22). Such system of quality assurance should be introduced in Croatia.

There are several limitations to this study. Firstly, patients who had a myocardial infarction without pain and/or without electrocardiographic evidence were not included. Secondly, our study involved patients from selected years (1999, 2003, and 2005), whereas a larger time span and number of patients would increase the power of the study.

In conclusion, pre-hospital delay in patients with myocardial infarction in southern Croatia is too long, especially for patients coming from outside of the Split urban area. Prognosis and survival of patients with myocardial infarction may be improved by introducing changes to the health care system in remote areas, such as out-of-hospital thrombolysis, greater use of telemedicine, training of lay persons and paramedics in defibrillation, introduction of quality assessment mechanisms, and improved patient transport.

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