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EVALUATION OF IMPORTANCE OF DOOR-TO-BALLOON TIME AND TOTAL ISCHEMIC TIME IN ACUTE MYOCARDIAL INFARCTION WITH ST-ELEVATION TREATED WITH PRIMARY PERCUTANEOUS CORONARY INTERVENTION

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SUMMARY – The aim of the study was to evaluate the influence of door-to-balloon time and symptom onset-to-balloon time on the prognosis of patients with acute ST-elevation myocardial infarction (STEMI) treated with primary percutaneous coronary intervention (PCI) in the Croatian Primary PCI Network. A total of 1190 acute STEMI patients treated with primary PCI were prospectively investigated in eight centers across Croatia (677 non-transferred, 513 transferred). All patients were divided according to door-to-balloon time in three subgroups (<90, 90-180, and >180 minutes) and according to symptom onset-to-balloon time in three subgroups (<180, 180-360, and >360 minutes). The postprocedural Thrombolysis in Myocardial Infarction flow, in-hospital mortality, and major adverse cardiovascular events (mortality, pectoral angina, restenosis, reinfarction, coronary artery by-pass graft and cerebrovascular accident rate) in six-month follow-up were compared between the subgroups. The Croatian Primary PCI Network ensures results of treatment of acute STEMI comparable with randomized studies and registries abroad. None of the result differences among the door-to-balloon time subgroups was statistically significant. Considering the symptom onset-to-balloon time subgroups, a statistically significant difference at multivariate level was highest for in-hospital mortality in the subgroup of patients with longest onset-to-balloon time (4.5 *vs*.2.6 *vs*. 5.7%; p=0.04). Door-to-balloon time is one of the metrics of organization quality of primary PCI network and targets for quality improvement, but without an impact on early and six-month follow-up results of treatment for acute STEMI. Symptom onset-to-balloon time is more accurate for this purpose; unfortunately, reduction of the symptom onset-to-balloon time is more complex than reduction of the former.

Key words: *Primary percutaneous coronary intervention; Network; Reperfusion*

Introduction

According to the last European Society of Cardiology guidelines[1,2], in patients with presentation of ST-elevation myocardial infarction (STEMI) within 12 hours after symptom onset, early mechanical (primary percutaneous coronary intervention, primary PCI) or pharmacological reperfusion should be per-

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formed, with generally better results after primary PCI. Both randomized studies and registries have indicated that long delay times to primary PCI are associated with a worse clinical outcome[3,4]. The same guidelines[1,2] emphasize that balloon inflation in primary PCI should be performed within 90-120 minutes after first medical contact in all cases. For the same problem, the American College of Cardiology/American Heart Association in the last guidelines update[5] indicate that the system's goal should be first medical contact-to-balloon time within 90 minutes in at least 75% of patients[6,7]. One of the results of those goals is establishment of the American College of Cardiology's Door-to-Balloon Alliance[8,9].

The Croatian Primary PCI Network was introduced in the mid-2005 in the Republic of Croatia. The main goal was to achieve equal quality treatment of acute STEMI in all parts of Croatia. The principles of the network are:

1. step-by-step implementation principle (presentation of the problem to the authorities, media campaign, extension of primary PCI up to 150 km away from the largest cities of Zagreb and Rijeka in the first year, and after that extension of the network to the entire Croatia, implementation into the health care system of the Republic of Croatia);
2. proportional allocation of PCI centers in all parts of Croatia; and
3. continuous mutual communication of all participants (meetings, educational courses, evaluation).

During the study period, eight high-volume PCI centers all over Croatia have been included in this network covering around 75% of the population[10,11].

The main goal of this study was to evaluate the influence of door-to-balloon time and symptom onset-to-balloon time on the prognosis of patients with acute STEMI treated with primary PCI in the Croatian Primary PCI Network.

Methods

This study prospectively investigated 1190 acute STEMI patients treated with primary PCI in eight PCI centers in all parts of Croatia (four with and four without on-site cardiac surgery) included in the Croatian Primary PCI Network. In 677 study patients, acute STEMI was diagnosed in one of the centers with on-site PCI laboratory (cath-lab), where primary PCI was performed (non-transferred patients). In the remaining 513 patients, acute STEMI was diagnosed in hospitals without on-site cath-lab, so they were urgently transferred to the mentioned PCI centers for primary PCI (transferred patients). The patients were transferred mostly by ambulance on 24/7/365 basis. The diagnosis of STEMI was established and primary PCI performed using the actual criteria of the European Cardiac Society[12,13]. In brief, patients with an episode of chest discomfort within the last 12 hours and ST-elevation on ECG in at least two consecutive leads were included. The patients received loading dose of 300 mg salicylic acid, 600 mg clopidogrel, and intraprocedurally 70-100 IU/kg of unfractionated heparin and, according to the judgment of interventional cardiologist, a GPIIb/IIIa inhibitor. Patients who received lytic therapy were not included in this study.

After primary PCI, patients were hospitalized on average 2 to 3 days in coronary care units in PCI centers with continuous monitoring and treatment. After that, they finished their hospital treatment in cardiac departments of these hospitals (non-transferred patients), or were transferred back to their county hospitals (transferred patients). During their first hospital stay, general information (name, age, gender) and information on the time of first symptoms, time of arrival in the first hospital and/or PCI center, time of first balloon insufflation during primary PCI, affected myocardial wall and coronary artery, postprocedural flow, as well as the possible cardiogenic shock and lethal outcome were collected. Six months after discharge, data on the major adverse cardiovascular events (MACE) (pectoral angina, restenosis, reinfarction, mortality, coronary artery by-pass graft and cerebrovascular insult rate) were collected for study patients during their examination, by checking medical documentation or by telephone contact with the patients, their family members or home physicians. The study was performed between September 1, 2005 and August 31, 2007.

Cardiogenic shock was defined as a clinical state of hypoperfusion characterized by systolic blood pressure <90 mm Hg and/or capillary wedge pressure >20 mm Hg and/or cardiac index <1.8 l/min m^2. Postprocedural flow was classified according to the

Thrombolysis in Myocardial Infarction (TIMI) grading system with a 0-3 scale[12,13]. Total ischemic time or symptom onset-to-balloon time was calculated as the time between the onset of first continuous symptoms (confirmed with cardioselective marker values) and balloon insufflations during primary PCI, door-to-balloon time between arrival in the first hospital (with or without on-site cath-lab) and balloon insufflations during primary PCI, symptom onset-to-door time as the time between first symptoms and arrival in the first hospital (with or without on-site cath-lab). According to total ischemic time, all patients were divided in three subgroups (less than 180, 180 to 360, and more than 360 minutes) and according to door-to-balloon time also in three subgroups (less than 90, 90 to 180, and more than 180 minutes).

Nominal (categorical) variables were analyzed using Pearson χ^2-test and Fisher's exact test, and quantitative variables by Mann-Whitney test. Differences among the subgroups with elimination of influence of another variable were analyzed using multivariate log-linear analysis. The value of $p<0.05$ was considered significant for all tests used. Statistical analysis was performed by using Statistica 6.0 program.

An informed consent was obtained from each patient and the study protocol conformed to the ethical guidelines of the 1983 Declaration of Helsinki as reflected in *a priori* approval by the institution's human research committee.

Results

The average age of all study patients was 60 years; there were 73.3% of male patients; anterior myocardial wall was affected in 42.6% and inferior myocardial wall in 57.4% of patients; the percentage of cardiogenic shock was 6.7% (5.5% in transferred *vs*. 7.6% in non-transferred patients). None of differences in these results between transferred and non-transferred patients was statistically significant. The difference in symptom onset-to-door time between transferred and non-transferred patients was not statistically significant either (135 *vs*. 130 minutes); however, differences in door-to-balloon time (123 *vs*. 96 minutes) and in symptom onset-to-balloon time (298 *vs*. 255 minutes) were statistically significant ($p<0.01$). In the Croatian Primary PCI Network, during the study period, 37% of all study patients received primary PCI in the recommended 90 minutes after arrival in the first hospital. In non-transferred and transferred patients, this percentage was 47% and 25%, respectively. The average distance of transfer in the subgroup of transferred

Table 1. Descriptive statistics data and times to reperfusion in the Croatian Primary PCI Network

	All patients	Transferred patients	Non-transferred patients	p
Age median (range) (yrs)	60 (24-95)	59 (29-95)	60 (24-92)	0.08**
Gender (M/F) (%)	73.3/26,7	75.7/24.5	71.7/28.3	0.15*
Myocardial wall (anterior/inferior) (%)	42.6/57.4	39.8/60.2	44.8/55.2	0.12*
Coronary artery (LAD/Cx/RCA/LM/by-pass) (%)	41.7/13.8/43.4/0.7/0.5	40.6/15.6/42.7/0.4/0.7	42.5/12.3/44.0/1.0/0.2	0.27*
Cardiogenic shock (%)	6.7	5.5	7.6	0.19*
Symptom onset-to-door median (range)	130 (15-1365)	135 (15-1230)	130 (15-1365)	0.45**
Door-to-balloon median (range)	108 (10-540)	123 (35-540)	96 (10-465)	<0.01**
Symptom onset-to-balloon median (range)	265 (45-702)	298 (84-702)	255 (45-695)	<0.01**

LAD = left anterior descending coronary artery; ACx = circumflex coronary artery; RCA = right coronary artery; LM = left main position; symptom onset-to-door = time between first symptoms and arrival in the first hospital (with or without on-site cath-lab); door-to-balloon = time between arrival in the first hospital (with or without on-site cath-lab) and balloon insufflation during primary PCI; symptom onset-to-balloon = time between first symptoms and balloon insufflation during primary PCI; *χ^2-test (transferred *vs*. non-transferred patients); **Mann-Whitney U-test (transferred *vs*. non-transferred patients)

Table 2. Results of treatment in the Croatian Primary PCI Network

	All patients	Transferred patients	Non-transferred patients	p*	p**
Postprocedural TIMI 3 flow (%)	87.1	89.9	85.2	0.03	0.05
Mortality (in-hospital) (%)	4.4	2.9	5.4	0.04	0.20
Mortality (6-month follow-up) (%)	1.2	0.5	1.7	0.24	0.82
Pectoral angina (6-month follow-up) (%)	12.1	11.4	12.6	0.70	0.13
MACE (other) (6-month follow-up) (%)	6.4	5.8	7.1	0.59	0.08

MACE (other) = major adverse cardiovascular events (restenosis, reinfarction, coronary artery by-pass graft and cerebrovascular accident); *χ^2-test (transferred *vs.* non-transferred patients); **multivariate log-linear analysis (transferred *vs.* non-transferred patients)

patients was 72 kilometers. Postprocedural TIMI 3 flow was established in 87.1% of all study patients; in-hospital mortality was 4.4% with no statistically significant difference in these results and in the percentage of MACE in six-month follow-up between transferred and non-transferred patients. The reasons for the tendency of better results in the subgroup of transferred patients seem to be their younger age and lower incidence of cardiogenic shock[10].

Descriptive statistics data of the door-to-balloon time subgroups of study patients are shown in Table 1. The subgroup with the longest door-to-balloon time had a higher average age than the two other subgroups and the lowest percentage of patients in cardiogenic shock, but none of these differences was statistically significant, including differences in gender, affected myocardial wall and coronary artery.

The results of treatment in the door-to-balloon time subgroups of STEMI patients are shown in Table 2. The lowest percentage of optimal postprocedural TIMI 3 flow was found in the subgroup with the shortest door-to-balloon time and the highest in-hospital mortality rate in the next subgroup according to door-to-balloon time. Most MACE at the six-month follow-up were found in the first subgroup of patients, but none of these result differences was statistically significant.

Descriptive statistics data on the symptom onset-to-balloon time subgroups of study patients are shown in Table 3. The longer this time, the older were the patients. The percentage of cardiogenic shock was highest in the subgroup with shortest symptom onset-to-balloon time, and lowest in the next subgroup according to this time. While age difference was statistically significant, other differences (cardiogenic shock percentage, gender distribution, and distribution of myocardial wall and coronary artery affected) did not reach statistical significance.

Table 3. Descriptive statistics data of door-to-balloon time subgroups of all study patients

	<90 minutes	90-180 minutes	>180 minutes	p
Age (median, range)	59 (31-84)	59 (24-87)	61 (29-95)	0.11**
Gender (M/F) (%)	74.9/25.1	72.8/27.2	73.6/26.4	0.81*
Myocardial wall (% anterior/inferior)	44.2/55.8	42.9/57.1	44.1/55.9	0.94*
Coronary artery (%LAD/Cx/RCA/LM/ by-pass)	43.5/13.9/ 41.9/0.7/0	41.0/12.1/ 45.0/1.1/0.8	43.3/13.4/ 42.1/1.2/0	0.68*
Cardiogenic shock (%)	6.4	6.1	3.3	0.45*

LAD = left anterior descending coronary artery; ACx = circumflex coronary artery; RCA = right coronary artery; LM = left main position; symptom onset-to-door = time between first symptoms and arrival in the first hospital (with or without on-site cath-lab); door-to-balloon = time between arrival in the first hospital (with or without on-site cath-lab) and balloon insufflation during primary PCI; symptom onset-to-balloon = time between first symptoms and balloon insufflation during primary PCI; *χ^2-test; **Mann-Whitney U-test

Table 4. Results of treatment of door-to-balloon time subgroups of all study patients

	<90 minutes	90-180 minutes	>180 minutes	p*
Postprocedural TIMI 3 flow (%)	87.1	90.5	90.5	0.35
Mortality (in-hospital) (%)	3.2	4.2	4.1	0.77
Mortality (6-month follow-up) (%)	1.4	0.6	0	0.44
Pectoral angina (6-month follow-up) (%)	10.1	9.5	4.2	0.23
MACE (other) (6-month follow-up) (%)	9.5	6.2	2.1	0.08

MACE (other) = major adverse cardiovascular events (restenosis, reinfarction, coronary artery by-pass graft and cerebrovascular accident); *χ^2-test

The results of treatment of the symptom onset-to-balloon time subgroups of STEMI patients are shown in Table 4. The lowest percentage of postprocedural TIMI 3 flow and the highest percentage of MACE were found in the subgroup with the shortest total ischemic time, a subgroup that had the highest percentage of patients in cardiogenic shock and with culprit lesion in left main position. Nevertheless, the only statistically significant difference at multivariate level was the highest in-hospital mortality in the subgroup of patients with the longest symptom onset-to-balloon time.

Discussion

The average age and gender distribution, the affected myocardial wall and coronary artery, as well as the percentage of patients with cardiogenic shock in the Croatian Primary PCI Network are within the framework of such results reported from other randomized studies and registries[10,14-20]. In comparison with European randomized studies[14-16] and registries at the city or regional level[17-19], all times to reperfusion in this study were somewhat longer, but in comparison with the results outside Europe they were shorter[21-23]. The percentage of patients treated with the door-to-balloon time within 90 minutes in the Croatian Primary PCI Network is comparable to the percentage in the United States, which is 40%[24]. Moreover, in comparison with ACTION Registry[25] from the United States, the percentage of transferred patients treated with primary PCI within 90 minutes after arrival in the first hospital was higher in this study, the situation being opposite in non-transferred patients. The results of treatment of acute STEMI patients in the Croatian Primary PCI Network (postprocedural TIMI flow, in-hospital mortality, MACE) were also within the framework of such results reported from other randomized studies and registries[10,14-20,26-28]. A tendency of better postprocedural TIMI flow in transferred patients is also reported by other authors[18,29].

The importance of the door-to-balloon time length for the results of primary PCI is differently estimated in current literature. On the one hand, in 2005 Shavelle

Table 5. Descriptive statistics data of symptom onset-to-balloon time subgroups of all study patients

	<180 minutes	180-360 minutes	>360 minutes	p
Age (median, range)	58 (31-84)	59 (24-87)	63 (29-95)	0.02**
Gender (M/F) (%)	79.0/21.0	72.1/27.9	72.9/27.1	0.21*
Myocardial wall (% anterior/inferior)	42.1/57.9	44.7/55.3	42.1/57.9	0.78*
Coronary artery (%LAD/Cx/RCA/LM/by-pass)	40.3/16.1/42.1/1.3/0	44.0/13.2/41.7/0.9/0.2	39.9/10.6/47.5/1.0/1.0	0.53*
Cardiogenic shock (%)	7.7	4.5	6.0	0.30*

LAD = left anterior descending coronary artery; ACx = circumflex coronary artery; RCA = right coronary artery; LM = left main position; symptom onset-to-door = time between first symptoms and arrival in the first hospital (with or without on-site cath-lab); door-to-balloon = time between arrival in the first hospital (with or without on-site cath-lab) and balloon insufflation during primary PCI; symptom onset-to-balloon = time between first symptoms and balloon insufflation during primary PCI; *χ^2-test; **Mann-Whitney U-test

et al.[30] investigated short-term outcome in two groups of STEMI patients according to door-to-balloon time (within and more than two hours). In the group with longer door-to-balloon time, recurrent ischemia and pectoral angina occurred more frequently, they had a higher percentage of cardiogenic shock, higher short-term mortality and longer hospital stay. In 2008, Peterson *et al*.[31], also according to data from the National Registry of Myocardial Infarction, emphasize the importance of reducing door-to-balloon time for improvement of primary PCI results in patients with acute STEMI. Using the same registry data from 1990 through 2006, Gibson *et al*.[32] found that among patients undergoing primary PCI, door-to-balloon time in non-transferred patients declined linearly from 111 minutes in 1994 to 79 minutes in 2006, with a decline in mortality from 8.6% to 3.1%. They concluded that relative improvement in mortality attributable to improvement in door-to-balloon time was 7.5%. Pellicia *et al*.[33] found that critical pathway for STEMI at emergency department increased the use of evidence-based treatment strategies (among other things, shortening of door-to-balloon time) and improved outcome and quality of care of these patients. As already noted in the Introduction section, the current guidelines of the European Cardiac Society[1,2] and the American College of Cardiology/American Heart Association[5] also emphasize that the system's goal should be first medical contact-to-balloon time within 90 minutes.

On the contrary, Song *et al*.[28], according to the results of Korea acute myocardial infarction registry from 2008, found no influence of door-to-balloon time on one-month mortality rate. Results of the Emilia-Romagna STEMI Network[18] show that, in spite of longer door-to-balloon delay in transferred patients, in-hospital mortality, as well as one-year cardiac mortality did not significantly differ in comparison with non-transferred patients. Hahn *et al*.[34] measured infarction size and transmurality using contrast-enhanced magnetic resonance imaging in patients treated with primary PCI in the acute phase of STEMI. The authors found no association of door-to-balloon time with the two measures of extension of myocardial infarction. Results of the Croatian Primary PCI Network, as it can be seen in the Results section, revealed no statistically significant influence of the door-to-balloon time in acute STEMI on post-procedural TIMI flow, in-hospital mortality, mortality, pectoral angina and other MACE at six-month follow-up.

The importance of the symptom onset-to-balloon time length for the results of primary PCI is emphasized by almost all authors with rare exceptions. The importance of as short as possible time from symptom onset to first medical contact and reperfusion achievement during primary PCI for prognosis of acute STEMI patients is emphasized by several authors, especially in patients with cardiogenic shock[35-37]. However, it is often an hour or more after the onset of symptoms before medical aid is requested. Older patients, female diabetics, and congestive heart failure patients are more likely to delay seeking care[1]. Currently predominating opinion is that the overarching goal is to keep total ischemic time within 120 minutes (ideally

Table 6. Results of treatment of symptom onset-to-balloon time subgroups of all study patients

	<180 minutes	180-360 minutes	>360 minutes	p*	p**
Postprocedural TIMI 3 flow (%)	87.1	90.5	90.5	0.35	0.87
Mortality (in-hospital) (%)	4.5	2.6	5.7	0.13	0.04
Mortality (6-month follow-up) (%)	1.3	1.0	0	0.53	0.86
Pectoral angina (6-month follow-up) (%)	11.0	8.6	6.3	0.53	0.77
MACE (other) (6-month follow-up) (%)	7.3	4.6	5.9	0.70	0.50

MACE (other) = major adverse cardiovascular events (restenosis, reinfarction, coronary artery by-pass graft and cerebrovascular accident); *χ^2-test; **multivariate log-linear analysis

within 60 minutes) from symptom onset to initiation of reperfusion treatment[5]. In the study by Valente *et al.*[35], time from symptom onset to PCI was higher in patients with delayed cardiogenic shock, which is mainly due to mechanical complications and PCI complications. In their contrast-enhanced magnetic resonance imaging study of patients with acute STEMI treated with primary PCI, Hahn *et al.*[34] concluded that symptom onset-to-balloon time was significantly associated with infarction transmurality but not with infarction size. On the other hand, Song *et al.*[28] found that one-month mortality was not increased significantly with increasing delay in the symptom onset-to-balloon time. The Croatian Primary PCI Network investigation confirms the statistically significant importance of symptom onset-to-balloon time for early, in-hospital mortality in patients with acute STEMI treated with primary PCI. This importance of symptom onset-to-balloon time was not revealed for other investigated results of treatment (postprocedural TIMI flow, late mortality, pectoral angina and other MACE at six-month follow-up).

In conclusion, door-to-balloon time is one of the metrics of organization quality of acute STEMI patient care provided by some primary PCI networks and targets for quality improvement. Nevertheless, according to the results of the Croatian Primary PCI Network, it seems that door-to-balloon time has no impact on early and six-month follow-up results of primary PCI in acute STEMI, and that symptom onset-to-balloon time is more accurate for this purpose. Unfortunately, reduction of the symptom onset-to-balloon time is more complex than reduction of the door-to-balloon time requiring not only action of cardiology community, but also coordinated action of the whole health care system and society in general. Finally, the last conclusions are the results of the Croatian Primary PCI Network investigation and larger or different populations might yield different conclusions.

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Sažetak

ZNAČENJE VREMENA OD DOLASKA U PRVU ZDRAVSTVENU USTANOVU DO POSTIZANJA REPERFUZIJE I UKUPNOG TRAJANJA ISHEMIJE U BOLESNIKA S AKUTNIM INFARKTOM MIOKARDA S ST-ELEVACIJOM LIJEČENIH PRIMARNOM PERKUTANOM KORONARNOM INTERVENCIJOM

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Cilj studije bio je procijeniti utjecaj vremena od dolaska u prvu zdravstvenu ustanovu do postizanja reperfuzije (engl. *door-to-balloon time*) i vremena od početka simptoma do postizanja reperfuzije (engl. *symptom onset-to-balloon time*) na prognozu bolesnika s akutnim infarktom miokarda s ST-elevacijom (STEMI) liječenih primarnom perkutanom koronarnom intervencijom (PCI) u sklopu Hrvatske mreže primarne PCI. Autori su prospektivno istraživali 1190 bolesnika s akutnim STEMI liječenih primarnom PCI u osam centara u svim dijelovima Republike Hrvatske (677 netransferiranih, 513 transferiranih). Bolesnici su podijeljeni prema vremenu *door-to-balloon* u tri podskupine (<90, 90-180 i >180 minuta), kao i prema vremenu *symptom onset-to-balloon* (<180, 180-360 i >360 minuta). Između podskupina su uspoređivani postproceduralni TIMI protok, unutarbolnička smrtnost i veliki nepovoljni kardiovaskularni događaji (smrtnost, angina pektoris, restenoza, reinfarkt, aortokoronarno premoštenje i cerebrovaskularni incident) tijekom šestomjesečnog praćenja. Hrvatska mreža primarne PCI osigurava rezultate liječenja akutnog STEMI usporedive s inozemnim randomiziranim studijama i registrima. Između poskupina prema vremenu *door-to-balloon* niti jedna od rezultatskih razlika nije bila statistički značajna. Između podskupina prema vremenu *symptom onset-to-balloon* statistički značajna razlika na multivarijatnoj razini bila je ona najviše unutarbolničke smrtnosti u podskupini s najduljim navedenim vremenom (4,5 nasuprot 2,6 nasuprot 5,7%; p=0,04). Vrijeme *door-to-balloon* je jedna od mjera organizacijske kvalitete mreže primarne PCI i cilj za poboljšanje kvalitete iste, ali bez utjecaja na rane i šestomjesečne rezultate liječenja akutnog STEMI. Vrijeme *symptom onset-to-balloon* je preciznije za potonje potrebe. Skraćenje vremena *symptom onset-to-balloon* je, nažalost, složenije nego skraćenje prvoga vremena.

Ključne riječi: *Primarna perkutana koronarna intervencija; Mreža; Reperfuzija*