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The meaning of early percutaneous coronary intervention in acute coronary syndrome with preserved ST elevation

Research Article

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Abstract: To determine if delaying the primary precutaneous coronary intervention (PCI) for >6 hours for acute coronary syndrome with preserved ST elevation (STE-ACS) affects the PCI angiography effectiveness and clinical prognosis. The PCI was performed: for 71% of patients <6h (group 1), for 29% of patients >6h from the beginning of pain (group 2). For 1% of patients from group 1 and 3.4% of patients from group 2, no passage has been opened in the artery after STE-ACS. In spite of opening the passage mechanically, the phenomenon of lack of tissue reflow occurred in 2.7% of patients from group 1 and 12% of patients from group 2. Dangerous ventricular arrhythmias occurred more frequently in patients from group 2, including VF, asystole, haemodynamic complications classed 4° according to the Killip-Kimball scale and death. In an univariate logistic regression analysis, the following risk factors for death during the hospital phase were identified: delayed PCI >6 hours, 4° haemodynamic complications according to the Killip-Kimball scale, LVEF <40%, FV, p-k III block, TIMI <3, and no-reflow. In a multivariate logistic regression analysis, 4° according to the Killip-Kimball scale turned out to be the only risk factor for death during the hospital phase. Delaying PCI during STE-ACS for >6 hours significantly lowers the statistical chance to recover both full permeability and effective tissue reflow in the artery responsible for STE-ACS, which is connected with a significantly higher risk of serious complications, as well as with 8.5% risk of death during the hospital phase. The most significant, independent factor determining the survival of patients with STE-ACS after PCI is lack of cardiogenic shock.

Keywords: *Percutaneous coronary intervention • Time to treatment • Cardiogenic shock*

1. Introduction

Early administration of reperfusion therapy improves survival in patients with ST elevation myocardial infarction by reestablishing coronary blood flow within the occluded infarct-related artery. Reperfusion therapy for acute myocardial infarction (AMI) is thought to be beneficial when coronary reperfusion can be established early enough to salvage myocardium, with consequent improvement in left ventricular function and better survival rate [1]. Data from a number of randomized trials have shown that the mortality benefit from fibrinolytic therapy is strongly dependent on the time from onset until treatment, but the importance of time to treatment with primary percutaneus coronary intervention (PCI) is still controversial. Longer intervals between the onset of symptoms and balloon time have been correlated with poorer outcomes in several, but not all, studies of primary PCI. It is also possible that even though the extent of myocardial salvage may be similar for fibrinolytic therapy and primary PCI in the early period after the onset of symptoms, PCI is more effective in restoring flow and improving outcomes during later periods.

In the early phases of AMI necrosis occurs only in the subendokardium. Transmural progression of necrosis in the infarct zone may take several hours and depends on many factors such the size of the infarct-related artery, the extension of collateral flow, the existence of residual

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Table 1. Baseline characteristics of patients.

Parameters	p	Group 1 (≤6 hours)(n=148)	Group 2 (>6 hours)(n=59)
Age (years)	p=0,2432	61±11	60±10
Male (%)	p=0,2359	72	80
Previous MI (%)	p=0,4280	14%	22%
MI with Q (%)	p=0,6039	52	48
Anterior MI	p=0,9491	45	46
Diabetes mellitus (%)	p=0,3927	22	27,6
Smoking (%)	p=0,8496	56	57,5
Family history of CHD (%)	p=0,3746	51	44,5
Hypertension (%)	p=0,9371	58	58,6
Systolic blood pressure RR<100 mmHg (%)	p=0,4507	10,14	6,78
Hypercholesterolemia (%)	p=0,3946	59	52,5

or intermittent perfusion through the culprit lesion and the metabolic needs of the myocardium [2]. The magnitude of collateral circulation is one of the principal determinants of infarct size and has a significant influence on the time-interval in which the myocardium can still be saved.

1.1. Aim of the study

To determine if delaying the PCI of the artery responsible (RA) for STE-ACS >6h affects the PCI angiography's effectiveness, clinical prognosis, occurrence of dangerous complications and especially survival in the hospital phase.

2. Material and Methods

2.1. Study population

The study group consisted of 207 consecutive patients (54 females, 153 males, mean age 61±9 years) who were hospitalized from 2004 to 2006 in the Cardiology Clinic with acute coronary syndrome with preserved ST elevation, with anterior localization (44%) or inferior localization (56%). They were divided into two groups according to time to treatment:

Group 1 ≤6 hours, averaging 3 hours from the beginning of symptoms (148 patients); and Group 2 >6 hours, averaging 10 hours (59 patients).

The groups did not differ with regard to the demographic characteristics (Table 1).

Patients were separated into groups based on time from start of symptoms to first balloon inflation. All numbers are percentages except for the following, which are reported as median (25^{th}, 75^{th} percentiles): age, weight, height, systolic and diastolic blood pressure, and pulse.

2.2. Criteria for eligibility

The criteria for inclusion were: an age of 18 years or older, the presence of symptoms for at least 30 minutes but less than 24 hours, cumulative ST segment elevation of at least 2 mm in at least two contiguous leads, increase >99 percentile for health population and following decrease in markers of myocardium necrosis (mainly troponins).

2.3. Concomitant therapy

All patients received 300 mg of aspirin and 300-600 mg of clopidogrel orally. Before coronary intervention, an intravenous bolus of 5-15000 IU of unfractionated heparin (UFH) was administered. Beta-adrenergic blocking agents were used first intravenously then orally, unless contraindicated. Selective coronary angiography was performed using ionic and non-ionic contrast according to the decision of the physician.

2.4. Type of Intervention (PCI)

Percutanous coronary intervention in 63% of patients rest on the restoration of blood flow in the artery responsible for heart infarct, stent implantation and ReoPro (abciximab) infusion. 25% of patients had PCI used as primary reperfusion therapy with stent implantation and 12% of patients had only percutaneous transluminal coronary angioplasty performed.

2.5. Haemodynamic Complications

Haemodynamic complications were assessed using the Killip-Kimball scale of 1-4 with special separation of cardiogenic shock and electric complications that mean malicious ventricular arrhythmias like fixed ventricular tachycardia and ventricular fibrillation.

2.6. Definitions

Primary PCI:
PCI used as primary reperfusion therapy of STE-ACS within 12h from onset of symptoms;
Time to treatment was measured from the start of first symptoms of AMI to time of an artery puncture;
Coronary flow was evaluated according to the TIMI grading system:
0- no flow
1- minimal flow (very slow)
2- near normal flow
3- normal flow
Heart failure was considered evident when the patient was in the Killip-Kimball class I-IV haemodynamic state;
Cardiogenic shock before PCI was defined as hypotension refractory to volume expansion;
No-reflow phenomenon is a reduction in antegrade epicardial blood flow during PCI, despite an open infarct-related artery (IRA);
Chest pain-to-door time was defined as the delay between the onset of symptoms and admission to the catheterization laboratory.

2.7. Statistical analysis

The Shapiro-Wilk test was used for assessment of the normality arrangement of the analyzing features. Continuous variables were expressed as average values ± SD and the Student's t-test was applied for comparative analysis. Categorical variables were expressed as percentage values and the Fisher's test was applied for comparisons. Results were considered statistically significant at $p<0.05$. The Statistica software package was used for statistical analysis. For identifying the factors of mortality risk, univariate and multivariate logistic regression analysis had been carried out.

PCI was not performed in the following cases: in the presence of tight stenosis of an unprotected left main coronary artery, in the presence of advanced triple vessel disease with an already reperfused IRA or when IRA was very thin. During the procedure, intracoronary UFH was readministered to achieve an activated clotting time of at least 300 seconds. PCI was considered to be successful when the resulting TIMI grade was 2-3 and residual stenosis was lower than 50%. The insertion of an intraaortic balloon pump (IABP) or temporary cardiac pacemaker was used at the discretion of the treating physician. LVEF was measured by echocardiography between the 3rd and 5th day after AMI.

2.8. Data acquisition

Information about the course of hospitalization was acquired by review of medical reports of all patients.

3. Results

3.1. Baseline characteristics

The average delay between pain and admission was 6,2 hours. Infarct location was anterior in 45 patients from Group 1 and in 46 patients from Group 2. The groups did not differ with regard to the demographic characteristics (Table 1).

STE-ACS was the first coronary syndrome in the lives of 52% of pts from Group 1 and 36% of pts from Group 2. 14% of pts from Group 1 and 22% of pts from Group 2 had already suffered from an MI. **5%** patients from Group 1 and 12% from Group 2 were in cardiogenic shock at the time of admission to the hemodynamic center.

3.2. Angiographic Characteristics

In 45% of pts from Group 1 and 42% of pts from Group 2 the artery responsible for STE-ACS was the left anterior descending coronary artery (LAD), and in 39% of pts of early intervention and in 40% of pts of late intervention it was the right coronary artery (RCA). In 16% of pts from Group 1 and 18% of pts from Group 2 the artery responsible for STE-ACS was the circumflex coronary artery (LCx) or the marginal artery (Mg).

49% of pts from Group 1 and 32% of pts from Group 2 were diagnosed with critical changes (defined as a diameter stenosis ≥70% in a major coronary artery or a left main stenosis ≥50%) or occlusion of the responsible artery only, before ACS; however this occurred more often in group 2 ($p=0,035$). 30% of pts from Group 1 and 46% of pts from Group 2 were diagnosed with 3-vessel changes ($p=0,001$) and pts from Group 2 had been more frequently classified with deferment as CABG ($p=0,029$) after an average of 1.5 months. The angiographic characteristics of the patients are presented in Table 2.

72% of pts from Group 1 and 68% of pts from Group 2 were diagnosed with thrombus occlusion; the remaining pts were diagnosed with a critical 98% narrowing of the responsible artery after STE-ACS.

3.3. Comparison of therapy results according to time to treatment ≤6h and >6h

To assess the angiographic efficacy, the PCI TIMI scale 1-3 was applied and the occurrence of the no-reflow phenomenon in the artery responsible for heart infarct was noted.

Table 2. Angiographic characteristics of the patients.

Parameters	Group 1 (≤6h) n=148	Group 2 (>6h) n=59	p
The number of significantly narrowed coronary arteries (%)			
1 vessel	39	32	p=0,3475
2 vessels	31	22	p=0,1965
3 vessels	30	46	p=0,001
The artery responsible for STE-ACS (%)			
LAD	45	42	p=0,6952
RCA	39	40	p=0,8943
Mg/Cx	16	18	p=0,7272

Table 3. Comparison of PCI results between groups.

Parameters	Group 1 (≤6h) n=148	Group 2 (>6h) n=59	p
TIMI (%)*			
0	1	3,4	p= 0,2271
1	2	5	p=0,2434
2	1,3	3,6	p=0,2819
3	93	76	p=0,001
No-reflow (%)	2,7	12	p=0,014
LVEF (%, average±SD)	55 ≠ℜ10	52 ≠ℜ11	p=0,6959
Abciximab (Reo-Pro) (%)	61,5	47,5	p=0,0677
CABG** evaluation	6	17,24	p=0,029

**TIMI - Thrombolysis in myocardial infarction (TIMI) scale*
***CABG - Coronary Artery Bypass Graft*

93% of pts from Group 1 and 76% of pts from Group 2 (p=0,001) obtained a satisfactory angiography result (TIMI 3). Incomplete mechanical opening expressed by 1 and 2 degree on the TIMI scale was detected in 3,3% of the early intervention group, as compared to 8% of the late intervention group. For 1% of pts from Group 1 and 3,4% of pts from Group 2, no passage has been opened in the artery responsible for heart infarct after ACS. In spite of opening the passage mechanically, in the case of 2,7% of pts from Group 1 versus 12% of pts from Group 2 (p=0,014), the phenomenon of lack of tissue reflow occurred (no-reflow). There were no statistically significant differences with regard to left ventricular ejection fraction (LVEF) between pts from Group 1 (55±10%) and Group 2 (52±10%). Results of PCI in groups are presented in Table 3.

3.4. Early complications according to time to treatment ≤6h and >6h

Dangerous ventricle arrhythmias occurred more frequently in patients from group 2 than in those from group 1, including VF (17% vs. 6%, p=0,02), asystole (13,6% vs. 3,4%, p=0,018), serious haemodynamic complications classed 4° according to the Killip-Kimball scale (12% vs. 5%, p=0,03) and death (8,47% vs. 1,35%, p=0,021). These are presented in Table 4.

Over 98% of patients (n=146) in Group 1 who had received early intervention and 91,5% of patients who had received late angioplasty (p=0,021) survived the hospital phase.

In Group 1 one patient with Killip-Kimball class 4 haemodynamic complications died and the second one died suddenly.

In Group 2 all patients who died were in cardiogenic shock, after PCI had been performed average of 16 hour after the beginning of symptoms. Figure 1. Survival of patients with STE-ACS.

3.5. Univariate and Multivariate analysis

In a univariate logistic regression analysis, the following risk factors of death during the hospital phase were identified: delayed PCI >6h (p=0,016), 4° haemodynamic complications according to the Killip-Kimball scale (p=0,0001), LVEF <40% (p=0,006), FV (p=0,015), block a-v III^0 (p=0,016), TIMI <3 (p=0,028), and no-reflow (p=0,0001). In multivariate logistic regression analysis, 4° according to the Killip-Kimball scale (p=0,00083) turned out to be the only risk factor of death during the hospital phase –(Table 5 and 6).

4. Discussion

In Poland there had first been recommendations to perform PCI within 6 hours after the onset of AMI; later, it was recommended within 12 hours after the onset of

Table 4. Early complications of STE-ACS.

Parameters	Group 1 (≤6h) n=148	Group 2 (>6h) n=59	p
Killip-Kimball Classes			
I (% of pts)	92	83	p=0,0586
II (% of pts)	1,36	1,69	p=0,8581
III (% of pts)	2,72	3,39	p=0,7960
IV (% of pts)	4,76	11,86	p=0,021
PAT/FA (% of pts)	11	3,4	p=0,0835
VF (% of pts)	6	17	p= 0,02
Block a-v 2/3° (% of pts)	4	3,39	p=0,8361
Asystole (% of pts)	3,4	13,6	p= 0,018
Death (% of pts)	1,35	8,47	p=0,021

PAT - paroxysmal atrial tachycardia
FA - atrial fibrillation
VF - ventricular fibrillation

Figure 1. Survival of patients with STE-ACS.

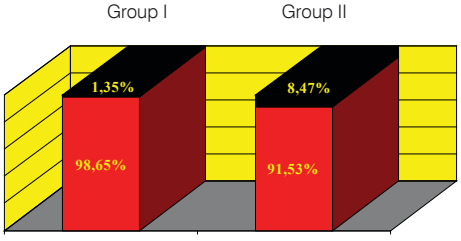

Table 5. Risk factors for death – univariate analysis.

Risk factors for death	OR	CI	p
Time to PCI >6h	6,75	1,2 – 36,23	p=0,016
IV0 K-K	59,68	9,9 – 359,8	p=0,0001
FV	8,62	1,75 – 42,33	p=0,015
Block a-v III0	2,44	1,30 – 4,57	p=0,0167
No TIMI 3	12	2,48 - 58	p=0,0028
No-reflow	36	6,8 - 198	p=0,0001

Table 6. Risk factors for death – multivariate analysis.

Risk factor for death	OR	CI	p
IV0 K-K	3,43	1,51 – 7,78	p=0,00083

40 K-K – Killip-Kimball class IV
FV – ventricular fibrillation
block a-v – atrioventricular block

AMI and within 90 minutes after the first contact with a doctor. In the latest recommendations in the world the time to do PCI in STE-ACS is prolonged to 20 hours from the beginning of symptoms. An analysis of 27080 patients in the National Registry of Myocardial Infarction-2 reveals a linear relationship between survival and time to treatment with angioplasty up to 12 hours, even after adjusting for other risk factors for mortality [3]. Some studies revealed unacceptably high mortality in hospitals where angioplasty was not performed rapidly. Brodie *et al*. [4] in a population of 1352 pts treated by primary PCI found the lowest mortality (4,3%) when the IRA was opened within 2h from AMI onset. When AMI lasted more than 2h,the resulting mortality was relatively independent of ischemic time (9% for ischemic time 2-4h; 9,3% for ischemic time 4-6h; 9,5% for ischemic time higher than 6h). Although the parameters of the left ventricular function were worse according to longer time to reperfusion, the results in the group of late reperfusion (>6h) were better than expected. Similar results were obtained in other research [5,6].

Simek *et al*. [7] assessed 339 consecutive AMI patients treated with PCI who were divided into 5 groups according to the time to treatment and ischemic time. The success rate of primary PCI to achieve normal flow in an IRA was high, but it decreased when treatment was started later than 3,5h from AMI onset. Knap *et al*. [8] showed that the probability to obtain TIMI 3 flow after PCI occurred more frequently in patients with shorter time to treatment and decreased significantly after 210 minutes from the AMI onset. LVEF between 3 and 5 days after AMI was significantly lower when the ischemic time was longer than 4h. Van't Hof *et al*. [9] found in a population of 496 pts treated by primary PCI that pts treated over 6h after the onset of AMI less frequently recovered TIMI 3 flow after PCI, but more frequently suffered reinfarction, more impaired LV function and higher 6-month mortality in comparison to pts treated earlier. In our research the probability of achieving TIMI grade 3 flow decreases with the duration of time to treatment. The no-reflow syndrome occurred more frequently in the group receiving late reperfusion, but there was no significant difference in left ventricular ejection fraction between groups. S. Simek *et al*. [7] and G. de Luca *et al*. [10] independently affirmed that for patients with AMI treated with PCI, time to treatment might be important only in a definite time interval. They noticed that in mice the

necrosis does not occur even after the occlusion of the coronary artery because of the extension of collateral flow. In people the collateral flow might range from very scanty to well developed, so the time to the necrosis of myocardium might be also variable. Dates from NMRI - 2 [11] allowed assessment of pts with sustained pain in the chest for longer than 12h after AMI. The results of PCI versus conservative medical treatment were compared. The results of therapy (ischemia recurrence, next MI, death) were better in pts treated with PCI (OR = 0,67; 95% CI; 0,49-0,92). This research showed dependence between invasive treatment and lower in-hospital mortality in pts with chest pain lasting more than 12h. In research carried out by Ma *et al*. [12] the effect of delayed (9.1 +/- 2.3 (2-14) days after onset) opening of the IRA by PCI on the late left ventricular remodeling after acute anterior myocardial infarction was assessed. The ventricular wall motion abnormality scores, left ventricular ejection fraction (LVEF), left ventricular end-diastolic and end-systolic volume indexes (LVEDVI and LVESVI) were similar in pts in both the PCI and control groups at the acute phase and 2 months after the onset of AMI. However, LVEDVI and LVESVI were significantly smaller in the successful PCI group than those in the control group ($p<0.01$, $p<0.05$). The rate of congestive heart failure events was 19% in the control group and 2.0% in the successful PCI group ($p>0.05$). Delayed PCI in AMI could prevent the late phase of left ventricular remodeling after AMI. In our research early (<6h) performance of PCI on the artery responsible for the myocardial infarction was a significant factor in determining survival in the hospital phase of STE-ACS, but the most significant independent factor in determining the survival of pts with STE-ACS after PCI is the absence of cardiogenic shock. For the pts with class IV haemodynamic complications according to the Killip-Kimball scale, the increase in odds with longer elapsed time was more marked. 5% of patients from Group 1 and 12% from Group 2 were in cardiogenic shock at the beginning of the angioplasty. Complication, like the no-reflow phenomena, ventricular fibrillation, and asystole that were observed in patients in cardiogenic shock, may be in part the reason for the unsatisfactory results of primary PCI especially in Group 2. Of the pts who died 86% had cardiogenic shock. Because the time from the beginning of symptoms to reperfusion has an impact on survival of pts with STE-ACS, it is important to reduce delay that is dependent on pts or connected with transport and in-hospital waiting for PCI. Pts should be encouraged to seek medical help when they suspect ACS.

4.1. Limitations of the study

The duration of a patient's symptoms is inherently subjective, and pts may not report their symptom duration accurately. Furthermore, infarct arteries often open and close in the course of an infarction, which might make the relationship between symptom duration and outcome less strong. It also may be that pts who are sicker in some ways come to the hospital more rapidly than less sick pts, which would introduce bias into the analysis.

On the other hand, we do not have information on the time to treatment in this study from pts in the catchment areas who had out-of-hospital MI and died prior to hospital arrival. Hence, there may be a superior-cohort effect, wherein those who present to the hospital after 6 to 12h have already survived the highest risk period for death, the first several hours. In Group 2 all pts who died were in cardiogenic shock. The prognosis of these pts is the worst.

5. Conclusions

1. Early (≤6 hours) performance of PCI on the artery responsible for the myocardial infarction is a significant, although not the most significant, factor determining survival beyond the hospital phase of STE-ACS.
2. Delaying PCI during STE-ACS for >6 hours significantly lowers the statistical chance to recover both full permeability (TIMI 3) and effective tissue reflow in the artery responsible for ACS, which is connected with a significantly higher risk of serious electric (ventricular fibrillation, asystole) and haemodynamic complications (cardiogenic shock), as well as with a 8,5% risk of death during the hospital phase.
3. The most significant independent factor determining the survival of patients with STE-ACS after PCI is lack of cardiogenic shock.

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