High cholesterol in patients with ECG signs of no-reflow after myocardial infarction

Dobrzycki S[1], Kożuch M[2], Kamiński K[2], Korecki J[2], Ostasz A[2], Podgrudna E[2], Bonda T[2], Musiał WJ[2]

[1]Department of Invasive Cardiology, Medical University of Bialystok, ul. Sklodowskiej 24a, 15-276 Bialystok, Poland
[2]Department of Cardiology, Medical University of Bialystok, ul. Sklodowskiej 24a, 15-276 Bialystok, Poland

Abstract

Purpose: Despite successful restoration of blood flow in epicardial artery after myocardial infarction (MI), some patients do not benefit sufficiently from modern revascularisation methods due to the impairment of microcirculation, also called no-reflow phenomenon. Hyperlipidaemia is well established risk factor of coronary heart disease and its detrimental actions on vessels are widely acknowledged. We attempted to investigate possible relations between hyperlipidaemia and electrocardiographic signs of no--reflow in myocardial infarction after successful primary angioplasty.

Materal and methods: A total of 150 consecutive patients with acute myocardial infarction (AMI) with ST elevation who underwent successful primary angioplasty were studied. ECG was obtained directly before and 30 minutes after successful reperfusion. ST segment deviation was measured. Lack of 50% reduction of ST-segment elevation in the lead with maximal initial elevation, 30 minutes after angioplasty was defined as ECG sign of no-reflow.

Results: ST-segment resolution occurred in 116 patients (77%), whereas 34 presented ECG signs of no-reflow (23%). Patients with persistent ST-segment elevation had higher blood LDL and total cholesterol (TC) levels than group with ST-segment restoration (146.5 vs. 128.7 $p<0.01$ and 219.5 vs. 200.9, $p<0.05$ respectively). Triglyceride, HDL, glucose on admission and fasting glucose levels did not differ significantly between groups. ECG signs of no-reflow were observed more often in patients with anterior AMI, history of prior myocardial infarction and longer pain-to--balloon time ($p<0.05$).

Conclusions: Positive relation between impaired tissue perfusion and high TC and LDL blood levels suggests that lipids may play a role in the pathogenesis of no-reflow phenomenon, possibly by impairment of endothelial function.

Key words: myocardial infarction, reperfusion injury, primary angioplasty, hypercholesterolemia, microvascular dysfunction.

ADDRESS FOR CORRESPONDENCE:
Karol Kamiński
Department of Cardiology, Medical University of Bialystok
ul. Sklodowskiej 24a, 15-276 Bialystok, Poland
tel. int: +48 85 7468656 fax int: +48 85 7468604
e-mail: fizklin@mp.pl

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Introduction

Early restoration of the patency of infarct-related artery (IRA) has become nowadays the main goal of acute myocardial infarction (AMI) treatment [1]. Despite of successful primary angioplasty, a substantial number of patients do not benefit sufficiently because of impaired tissue-level perfusion [2]. Because of this fact it is essential to focus on microvascular perfusion assessment as a marker of successful interventions [3]. Impaired tissue-level flow at the level of microvasculatory bed is called no-reflow phenomenon [4,5]. No-reflow is associated with poorer recovery of left ventricular function and more frequent development of congestive heart failure and death [6]. Different methods of detecting impaired myocardial perfusion were described: scintygraphy, PET, contrast echocardiography and angiographic assessment. The most frequently used, because of its simplicity and universal availability, is electrocardiographic ST-segment elevation resolution [7-9]. Persistent ST-segment elevation (STe) among patients with patent IRA correlates well with impaired microvascular perfusion [8,9].

The pathogenesis of no-reflow has been extensively studied for the last few years. It is known that reoxygenation of previously ischemic myocardium, causes generation of reactive oxygen species, followed by complement activation, activation of platelets, increased expression of adhesion molecules, endothelial damage, neutrophil activation and subsequent inflammatory process in surrounding tissues [10,11]. Microembolisation of capillaries with parts of thrombus as well as clusters of plate-

lets and leukocytes also plays an important role in impairment of the microvascular flow. However, precise pathomechanism of no-reflow phenomenon remains largely unexplored.

The hyperlipidemia is well established risk factor of coronary heart disease and lipid disturbances play an important role in atherogenesis [12]. High blood concentration of cholesterol may impair endothelial function and haemostatic balance [13,14]. The role of lipids in ischemia and reperfusion injury, however, has not been established yet. Because endothelial function deficiency seems to play a role in no-reflow phenomenon, we attempted to investigate possible influence of high blood lipids level on its occurrence.

Material and methods

Study population

Between October 1999 and December 2001, 150 patients with acute myocardial infarction with ST elevation, successfully treated with primary angioplasty, were enrolled to this study. An informed consent was obtained before any procedure was performed. Successful PTCA was defined as a restoration of TIMI grade 3 flow and less than 50% residual stenosis. All patients were admitted within 12 hours of symptom onset, presented typical chest pain (lasting more than 20 minutes), more than 0.1 mV ST elevation in at least 2 contiguous leads. The group was composed of 116 (77%) men and 34 (23%) women, with mean age 59 + 12.62 (41%) patients had anterior AMI.

Patients were examined on admission: blood pressure, heart rate, Killip/Kimball class were noted. History included time of onset of symptoms, history of coronary heart disease, prior AMI, hypercholesterolemia, hypertension, diabetes mellitus and smoking. Presence of Q-waves in electrocardiography (ECG) and NYHA functional class were assessed on the day of discharge.

Everyone received aspirin and heparin prior to angioplasty. Other medications were administered according to clinical indications.

The whole group was divided into two subgroups due to electrocardiographic evidences of impaired tissue-level flow: Group A with significant at least 50% ST-segment resolution and Group B without it.

Electrocardiographic analysis

The analysis of ST segment resolution was perfomed as described by Wong et al. [15] with minor modifications. In brief: a 12-lead ECG recordings were obtained on admission, about 30 minutes after successful reperfusion and on discharge from hospital. Electrographic tracings were analysed by two independent investigators blinded to angiographic and clinical data. The ST segment deviation was measured 0.08 s after J point in the lead with maximal initial elevation and compared to isoelectric line between T and P waves. Lack of 50% reduction of initial STe 30 minutes after PTCA was defined as ECG sign of no-reflow phenomenon.

The 32-point Selvester QRS score (SQS) was measured at discharge to assess myocardial damage [16]. The Selvester score system is calculated from the amplitude and size of Q, R and S waves [16]. This parameter correlates well with the mass of infarction, thus providing an important clinical insight which may affect prognosis [17].

Lipids measurement

Total cholesterol (TC), HDL and triglycerides (TG) blood concentrations were measured at the time of admission with enzymatic kits produced by Biomerieux (France). LDL levels were calculated from Friedewald's formula: LDL=TC – HDL - 0.2 x TG (mg/dl).

Statistical analysis

Distribution of every variable was tested with Kolmogorow-Smirnov test. Subsequently the Student's t test or the Mann-Whitney U test was used for statistical analysis where applicable. In order to assess the influence of variables on resolution of ST elevation, we used logistic regression analysis, which yielded consistent results with abovementioned methods. Additional analysis of correlations between non-categorical variables and extent of the ST resolution in per cent was performed using Pearson or Spearman tests, where applicable. Data are expressed as mean ± standard deviation (SD). Relative frequencies are used to present categorical variables with actual number of patients being given in brackets. These variables were assessed with Chi^2 test. A p value of less then 0.05 was considered as statistically significant.

Results

Baseline characteristic

ST segment resolution 30 minutes after successful angioplasty of IRA was observed in 116 patients (77%), who were classified as group A, whereas 34 (23%) presented ECG signs of no-reflow (group B). Baseline characteristic of studied subgroups are presented in *Tab. 1*. Group B had more often anterior AMI (59% vs. 36%; $p<0.05$), higher heart rate on admission (83.2 ± 14.6 vs. 75.3 ± 17.9; $p<0.05$) and longer pain-to-balloon time (300.9 vs. 255.4; $p<0.05$). Age, gender, Killip class and blood pressure (BP) on admission were comparable in both groups. We did not find significant differences in both glucose levels on admission and fasting glucose between the both groups (*Tab. 1*).

Everyone received acetylsalicylic acid and heparin prior to the angioplasty. In both groups almost 60% of patients received stents. During hospital stay, overall 92% of patients were given β-blockers, 71% ACE inhibitors, 75% ticlopidine and 47% gp2b3a inhibitors. The frequencies of administrated drugs were not statistically different between Group A and B (*Tab. 2*).

ST recovery, medical history and risk factors

We observed that in group with ECG signs of no-reflow there were more patients with prior myocardial infarction (21% vs. 8%; $p<0.01$) and history of hypercholesterolemia (68% vs. 47%; $p<0.05$). Smoking, history of hypertension and diabetes mellitus were comparable in both subgroups (*Tab. 3*).

ST segment recovery and lipids levels

Patients with persistent STe had higher blood LDL and TC levels than group with ST segment restoration (146.5 + 36 vs.

Table 1. Baseline characteristics of patients.

	GROUP A	GROUP B	p value
Age (yrs)	59.8 (±11.1)	57.3 (±11.9)	ns
Gender (male)	77% (89)	79% (27)	ns
Systolic BP on admmision (mmHg)	143.5 (±25.7)	149.3 (±33.6)	ns
Diastolic BP on admission (mmHg)	90 (±15.8)	92.8 (±22.1)	ns
Heart rate on admission (beats/minute)	75.3 (±17.9)	83.2(±14.6)	<0.05
Killip/Kimball class	1.43 (±0.5)	1.59 (±0.7)	ns
Anterior AMI	36% (42)	59% (20)	<0.05
Pain-to-Balloon time (minutes)	255.4 (±117.8)	300.9(±132.8)	<0.05
Fasting glucose (mg/dl)	108.3 (±42.3)	108.2 (±25.8)	ns
Glucose on admission (mg/dl)	160.0 (±60.7)	155.1 (±59.1)	ns

Group A – Patients with >50% reduction of initial ST elevation 30 minutes after angioplasty
Group B – Patients without ST segment resolution 30 minutes after successful angioplasty

Table 2. Adjunctive therapy in patients enrolled to study.

	GROUP A	GROUP B	p value
Acetylsalicylic acid	100% (116)	100% (34)	ns
Heparin	100% (116)	100% (34)	ns
Gp2b3a inhibitors	46% (53)	53% (18)	ns
Ticlopidine	72% (84)	82% (28)	ns
ACE inhibitors	69% (80)	76% (26)	ns
β-blockers	93% (108)	88% (30)	ns
Stent	56% (65)	59% (20)	ns

Group A – Patients with >50% reduction of initial ST elevation 30 minutes after angioplasty
Group B – Patients without ST segment resolution 30 minutes after successful angioplasty

128.7±29.6; p<0.01 and 219.5 + 34.9 vs. 200.9±35.9; p<0.05, respectively, *Fig. 1*). We also found statistically significant correlation between total cholesterol, LDL and extent of STe in per cent (R=0.189 P<0.05 and R=0.242 p<0.05 respectively, data not shown), what strongly supports our findings. However, TG, HDL did not differ significantly between groups (*Fig. 1*).

ST resolution and clinical parameters

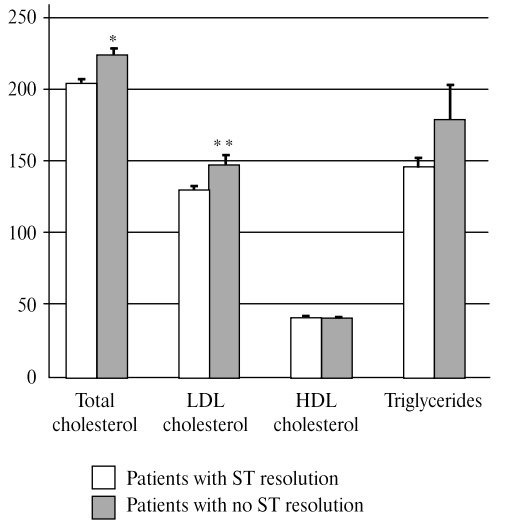
We did not find significant differences between both groups in respect to maximal CK and CK-MB activity, the length of stay in intensive cardiac care unit and presence of pathological

Table 3. Medical history and risk factors.

	GROUP A	GROUP B	p value
History of CHD	28% (32)	41% (14)	ns
Prior AMI	8% (9)	21% (7)	<0.01
History of hypercholesterolemia	47% (54)	68% (23)	<0.05
History of hypertension	42% (49)	47% (16)	ns
History of diabetes mellitus	14% (16)	18% (6)	ns
Smokers	62% (72)	50% (17)	ns

Group A – Patients with >50% reduction of initial ST elevation 30 minutes after angioplasty
Group B – Patients without ST segment resolution 30 minutes after successful angioplasty

Figure 1. Lipid levels in patients with (white boxes n=116) and without ST segment resolution (grey boxes n=34). Data are shown as mean ±SEM. * p<0.05 , ** p<0.01.



Q waves in ECG on discharge. The patients with ECG signs of no-reflow presented, however, significantly lower LV ejection fraction (44.5±9.3 vs. 40.9±9.6; p<0.05), higher NYHA functional class at the end of hospitalisation (2.2±0.5 vs. 2.1±0.3; p<0.03) and Selvester QRS scores (8±4.1 vs. 6.1±3.5; p<0.01) (*Tab. 4*). Both LV EF and Selvester QRS score significantly correlated with the extent of STe resolution in per cent (R=-0.199 p<0.05 and R=0.21 p<0.01 respectively, data not shown). This all may imply poorer prognosis of patients without ST resolution.

Discussion

Already several years ago, persistent ST elevation despite thrombolytic therapy has been used to stratify patients to the high-risk group, as these, in whom reperfusion was apparently

Table 4. Clinical parameters.

	GROUP A	GROUP B	p value
Peak of CK (IU/l)	2784.2 (±2626.1)	3097.9 (±2479.3)	ns
Peak of CKMB (IU/l)	283.5 (±217.5)	286.7 (±221.3)	ns
Ejection fraction (%)	44.5 (±9.3)	40.9 (±9.6)	<0.05
Selvester QRS score	6.1 (±3.5)	8 (±4.1)	<0.01
Q-wave AMI	89% (103)	94% (32)	ns
Days on Intensive Cardiac Care Unit	3.8 (±1.2)	3.7 (±1.3)	ns
NYHA class on discharge	2.1 (±0.3)	2.2 (±0.5)	<0.05

Group A – Patients with >50% reduction of initial ST elevation 30 minutes after angioplasty
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unsuccessful [18]. More recently, it has been shown that also patients with normal flow restoration in the epicardial artery may have persistent ST elevation [8], which is strictly associated with impairment of tissue flow [8,9], and may have prognostic significance [15,19].

In this study we were able to show that patients with ECG signs of impaired microvascular flow following primary angioplasty in AMI, presented higher blood concentrations of total cholesterol and LDL-cholesterol. This finding was also supported by fact that these patients more often had hypercholesterolemia prior to infarction. Interestingly, patients without ST resolution more often had a history of prior MI or currently the anterior wall of LV was involved. Impaired tissue perfusion might be also linked to delayed reperfusion, as time pain-to-balloon was significantly longer in no-reflow group, but also to increased sympathetic activation, reflected by higher heart rate on admission. Both groups of patients have received comparable treatment. It is noteworthy that the frequency of gp2b3a antagonists and ticlopidine were very similar in both groups, despite reports that these drug might limit the occurrence of no-reflow.

Notwithstanding recent report by Iwakura et al. [20] on the influence of hyperglycemia during AMI on hampered microvascular flow, we did not notice similar phenomenon. In our study, the patients had, however, relatively lower glucose concentrations.

On the other hand, microvascular injury may have influence on the degree of myocardial damage. We did not observe significant differences in respect to maximal CK and CK-MB activity. Activity of these enzymes which was used, in contrast to concentration, assessed using immunoenzymatic methods, does not correlate best with the extent of the injury. Nevertheless, we found that patients without STe resolution had significantly lower ejection fraction, worse NYHA functional class and larger infarcts, as assessed with QRS Selvester score. On the other hand, we are not able to distinguish if these poor outcome predictors depend more on microvascular dysfunction or on other factors like: anterior localisation of MI, time from pain to reperfusion, history of previous MI, all of which were more frequent in group without STe resolution.

Our study suggests association between high blood lipids and no-reflow. The potential causative relation may be based on evidences of detrimental influence of lipids on endothelial function, oxidative stress and on pro-inflammatory properties of oxidized lipoproteins. The LDL-cholesterol and triglycerides impair endothelium dependent vasodilatation by lowering eNOS expression and NO bioactivity [13,21]. Lacking NO means not only impaired relaxation of vessel wall, but above all, lacking antiaggregatory and antithrombotic effects, as well as increased expression of adhesion molecules [11,22]. Moreover, the low density lipoproteins themselves stimulate leukocytes rolling and adhesion to the endothelial surface [23,24]. Lipoproteins are not only the target of oxidation, but they also promote generation of superoxide radicals [25,26]. In addition, cholesterol rich molecules influence growth and apoptosis of endothelial cells, as well as thrombogenesis and fibrinolysis [27-29]. Our investigation was not designed to find precise molecular explanation of observed correlations, but it reports for the first time new facts that may be in accord with the experimental data and may also help to elucidate possible mechanism of no-reflow phenomenon.

Although previous studies have established correlations between glycaemia and no-reflow phenomenon [20], our analysis did not find it. There are also differences between our results attaching hypercholesterolemia and total cholesterol, which did not correlate with impaired tissue perfusion in other studies [20]. Divergence can be due to different methods used to detecting microcirculatory flow.

Our study has several limitations. First of all we did not analyse follow-up of the patients, hence we may not comment on prognostic value of lacking STe resolution in our group of patients. Second, we based our study on measurement of ST segment changes, as a common and easily accessible marker of patent or impaired microvasculatory bed. This method, however, is secondary to other methods, like SPECT, PET or contrast echocardiography, in establishing no-reflow on the tissue-level. Our findings are still to be confirmed with mentioned techniques which still remain preferred methods of microcirculatory flow evaluation. Also ST segment changes may be assessed in different ways [7-9,15]. Until now there are no prospective comparative studies giving hard evidence supporting one of these methods.

Despite its limitations, our study raises important clinical issue of deleterious effects of hypercholesterolemia on microvascular perfusion after primary angioplasty in acute myocardial infarction. Hence, the relation between preexisting endothelial injury, due to high cholesterol levels, and reperfusion injury together with and molecular basis for the observed phenomenon in clinical setting, should be elucidated.

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