High baseline fibrinogen concentration as a risk factor of no tissue reperfusion in ST-segment elevation acute myocardial infarction treated with successful primary percutaneous coronary intervention

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Abstract

Background: In a large group of patients with myocardial infarction, lack of tissue reperfusion following successful recanalisation of the infarct-related epicardial artery is seen. Blood flow in the microcirculation depends not only on structural changes in the microvasculature but also on rheological features of the blood itself.

Aim: To investigate the association between baseline fibrinogen concentration and myocardial reperfusion following successful coronary angioplasty.

Methodology: In 105 patients with acute ST-segment elevation myocardial infarction, baseline fibrinogen concentration was compared between patients with successful tissue reperfusion (n=79) and with no myocardial reperfusion (n=26) measured as the degree of ST-segment normalisation after successful recanalisation of the infarct-related artery.

Results: Baseline fibrinogen concentration was significantly higher in the *no-reperfusion* group than in the *reperfusion* group (523±198.02 mg/dl vs 395.56±144.98 mg/dl, p=0.0004). In the overall study population, fibrinogen level correlated positively with maximum creatine kinase MB fraction concentration (r=0.25, p=0.012) and duration of chest pain (r=0.31, p=0.002). Mean fibrinogen concentration was higher in patients with anterior myocardial infarction than in patients with the infarct-related artery other than the left anterior descending artery. The risk of no-reflow phenomenon assessed in multivariate analysis was higher if duration of chest pain was longer (OR=1.46, CI 95% 1.06-2.16, p=0.001) and baseline fibrinogen concentration higher (OR=1.51, CI 95% 1.011-4.58, p=0.021).

Conclusions: Baseline fibrinogen concentration following successful mechanical recanalisation of the infarct-related coronary artery is an independent risk factor of a lack of myocardial reperfusion and it positively correlates with maximum creatine kinase MB fraction concentration and duration of chest pain. High fibrinogen concentration may affect rheological parameters of the blood and play an important role in the pathomechanism of myocardial no-reperfusion phenomenon following successful mechanical recanalisation of the infarct-related coronary artery.

Key words: acute myocardial infarction, no-reflow phenomenon, fibrinogen, primary PCI

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Introduction

In a large group of patients with myocardial infarction (MI), no reperfusion of myocardial microcirculation is seen in spite of mechanical recanalisation of the infarct-related coronary artery (IRA). In the previously published report we showed that in patients after successful recanalisation of IRA but with no tissue reperfusion, blood rheological disturbances were more pronounced than in patients with successful myocardial reperfusion [1]. For example, patients with no myocardial reperfusion had enhanced erythrocyte aggregation and higher plasma viscosity [1]. Both parameters, especially under circumstances of low

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shear stress, significantly elevate blood flow resistance in the microvasculature, which may be one of the important contributors to the lack of microcirculatory reperfusion [2, 3]. Because both plasma viscosity and erythrocyte aggregation are increased in MI and correlate with fibrinogen concentration, we compared baseline fibrinogen level in patients with ST-segment elevation MI (STEMI) with or without microcirculatory reperfusion [4-9]. High fibrinogen concentration affects not only macrorheological (increases plasma viscosity) but also microrheological (enhances erythrocyte aggregation) properties of the blood that result in an elevation of blood flow resistance in the coronary microvasculature [10].

Methods

Patients

Analysis involved 105 patients (85 men and 20 women) treated by primary percutaneous coronary interventions (PCI) with stent implantation. Myocardial infarction was diagnosed based on typical chest pain accompanied by ST-segment elevation in electrocardiography and at least a twofold increase in creatine kinase MB fraction (CK-MB) concentration above the normal range. In all patients diagnosis was confirmed by coronary angiography that identified the IRA. Patients found in cardiogenic shock were not included in this study. Additionally, the following patients were excluded from the analysis: those with failed epicardial recanalisation of IRA (flow less than TIMI 3) or if a decrease in baseline blood flow following coronary intervention was observed (flow lower at least by one degree according to TIMI classification in comparison with baseline). Patients who received platelet GP IIb/IIIa receptor inhibitors during the procedure were also excluded from our study.

Myocardial reperfusion assessment

In order to evaluate myocardial tissue reperfusion, the sum of ST-segment elevations in three adjacent leads with the highest degree of ST elevation was compared. Measurements of ST level were performed 0.08 s from the J point. Successful and rapid myocardial reperfusion was considered as the sum of ST-segment elevations in ECG recorded 30 minutes after coronary intervention that decreased at least by 50% as compared to the baseline ECG.

According to the degree of ST-segment recovery, patients were divided into two subgroups: *reperfusion* group (79 patients) and *no-reperfusion* group (26 patients). Myocardial reperfusion was considered successful if the sum of ST elevations decreased by at least 50% compared with the baseline ECG.

Pathological Q waves in the baseline ECG were diagnosed if in the lead with the highest ST-segment elevation its depth was >25% of R wave amplitude and duration ≥40 msec, but only if it was accompanied by a pathological Q wave in the adjacent lead [11]. Presence of an isolated Q wave only in lead III was not considered significant.

Fibrinogen measurement

Plasma fibrinogen concentration was measured by means of von Claussa method based on linear correlation between time of thrombus formation and fibrinogen concentration (STA Fibrinogen Diagnostica Stago) [12].

Statistical analysis

Continuous parameters of normal distribution are presented as means ± standard deviations. Student's t-test was used to estimate statistical significance between variables of normal distribution. In case of variables not meeting normal distribution criteria, Mann-Whitney U test was used. Qualitative parameters were compared using χ^2 test. Univariate regression analysis was performed using the >50% ST-segment recovery following angioplasty as the dependent variable and biochemical or clinical parameters as independent ones. In order to identify independent predictors of ECG signs of the *no-reperfusion* phenomenon, multivariate regression analysis was performed with those variables identified as significant in the univariate model. Correlation power was evaluated by means of Spearman rank correlation index. A value of $p \leq 0.05$ was considered significant.

Results

Patients with no myocardial tissue reperfusion had significantly longer time from the onset of chest pain to coronary intervention (Table I).

In ECG recorded at the time of hospital admission, pathological ECG Q waves were present in all patients without myocardial reperfusion compared to 67% of patients in the *reperfusion* group (p=0.002). On admission, patients without myocardial reperfusion had higher mean fibrinogen concentration white blood cell count and lower left ventricular ejection fraction at discharge from hospital (Table II). In this patient group, the left anterior descending artery was more frequently identified as IRA. Higher mean value of plasma glucose concentration in patients with reperfusion was likely a result of slightly higher incidence of diabetes in this studied subgroup.

Fibrinogen level in the overall group positively correlated with peak value of CK-MB fraction (Figure 1) and time from the onset of chest pain to coronary intervention (Figure 2) (r=0.25, p=0.012, CI 95% 0.05±0.42 and r=0.31, p=0.002 CI 95% 0.11±0.47, respectively). Mean fibrinogen concentration was higher in patients

Table I. Characteristics of the study groups

	Reperfusion n=79	No-reperfusion n=26	p
Age (years)	60.16±11.61	65.10±12.88	NS
Men	67 (84.81%)	18 (69.23%)	NS
Arterial hypertension	40 (50.64%)	12 (46.15%)	NS
Diabetes mellitus	16 (20.26%)	2 (7.69%)	<0.07
Smoking	35 (44.30%)	12 (46.15%)	NS
Previous stroke	6 (7.59%)	2 (7.69%)	NS
Peripheral atherosclerosis	5 (6.3%)	1 (3.68%)	NS
Hypercholesterolaemia*	56 (70.89%)	19 (73.08%)	NS
Chest pain duration (hours)	4.92±3.99	9.57±6.16	<0.00001

**hypercholesterolaemia – total cholesterol concentration measured on the first day of MI >5.6 mmol/L*

Table II. Selected clinical and biochemical parameters in study groups

	Reperfusion n=79	No-reperfusion n=26	p
Pathological Q waves	63 (67.08%)	26 (100%)	0.002
Fibrinogen (mg/dL)	395.56±144.98	523±198.02	0.0004
Leukocytes (G/L)	11.74±3.49	12.9±3.2	0.04
Erythrocytes (T/L)	3.68±0.44	4.54±0.35	NS
EF (%)	45.21±8.57	41.5±6.19	0.005
Glucose (mmol/L)	10.54±8.27	7.94±2.9	0.013
Creatinine (µmol/L)	78.69±33.57	100.92±50.7	NS
CK-MB U/L	232.38±180.89	252±154.39	NS
Triglyceride (mmol/L)	1.69±1.44	1.3±0.85	NS
Cholesterol (mmol/L)	6.02±1.07	6.16±1.47	NS
LAD	22 (27.85%)	16 (61.54%)	0.02
RCA	38 (48.1%)	10 (20.83%)	0.04
CX	15 (18.99)	0 (0%)	0.037
OM	4 (5.06%)	0 (0%)	NS

EF – left ventricular ejection fraction, CK-MB – peak value of creatinine kinase MB fraction, LAD – left anterior descending artery, RCA – right coronary artery, CX – circumflex artery, OM – obtuse marginal branch

with anterior MI than in patients in whom IRA was other than the left interior descending artery (489±168.38 mg/dL *vs* 385±144.85 mg/dL, p <0.02, respectively). Moreover, patients with anterior MI had higher peak activity of CK-MB (304±310.53 U/L *vs* 202±142.19 U/L, p <0.012) and lower left ventricular ejection fraction at discharge from hospital (39.2±8.23% *vs* 47.19±6.67%, p <0.00001). Correlation between CK-MB and left ventricular ejection fraction was found to be significant (r=-0.47 p <0.00001, CI 95% -0.61 ÷ -0.29) (Figure 3).

In univariate analysis significant risk predictors of no myocardial tissue reperfusion were: occlusion of the left anterior descending artery (OR=4.15, CI 95% 1.62-10.63, p=0.028), baseline fibrinogen concentration (OR=1.56, CI 95%, 1.17-2.07, p=0023) and duration of chest pain (OR=1.49, CI 95% 1.23-1.81, p=0.0001), whereas in the multivariate analysis – fibrinogen concentration [100 mg/dL] (OR=1.51, CI 95% 1.011-4.58, p=0.021) and duration of chest pain [1 hour] (OR=1.46, CI 95% 1.06-2.16, p=0.001). These indices should be interpreted as a relative increase of *no-reperfusion* phenomenon risk on every 100 mg/dL fibrinogen concentration elevation or on every one-hour delay to coronary intervention.

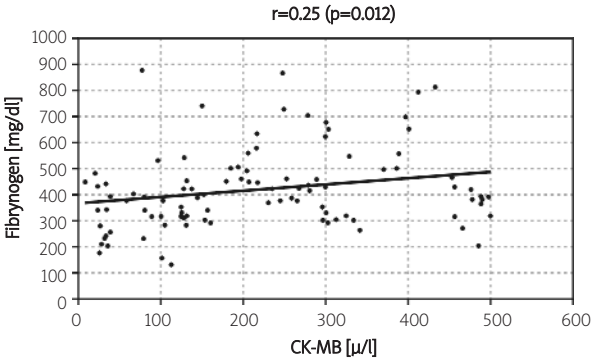

Figure 1. Correlation between peak value of CK-MB fraction and fibrinogen concentration

Discussion

In ECG recorded at the time of hospital admission, pathological Q waves were present more frequently in the *no-reperfusion* group than in patients with successful myocardial reperfusion. Leucocytosis evaluated on admission was significantly higher in the *no-reperfusion* group. This finding is consistent with other reports that revealed baseline white blood cell count and presence of developed pathological Q waves at the beginning of the therapeutic process as independent risk factors of the *no-reperfusion* phenomenon following successful mechanical recanalisation of IRA [13-15] that was partially explained by delay in treatment initiation. Presence or absence of Q waves was not found to be an independent predictor in either the univariate or multivariate regression analysis presented herein, because in all admission electrocardiograms in the *no-reperfusion* group Q waves were found.

In univariate analysis, anterior MI caused by left anterior descending artery occlusion was associated with an increased risk of insufficient myocardial tissue

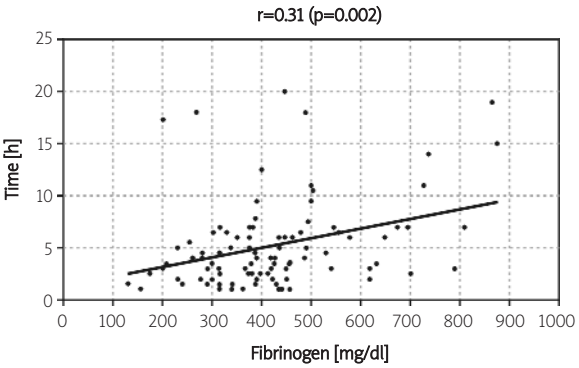

Figure 2. Correlation between chest pain duration prior to coronary intervention and fibrinogen concentration

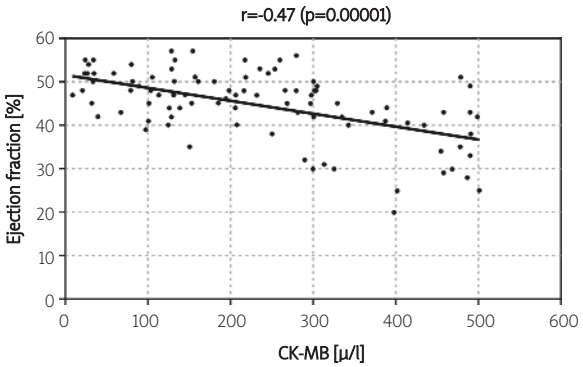

Figure 3. Correlation between creatinine kinase MB fraction and left ventricular ejection fraction

reperfusion. This phenomenon was also described by other investigators, although reason for that is not clear [16]. In our series, patients with anterior MI had higher baseline fibrinogen concentration than patients in whom MI was a result of occlusion of the coronary artery other than the left anterior descending artery.

So far, the correlation between flow restitution in the coronary microcirculation and baseline fibrinogen concentration has not been studied. In unstable angina, elevation of fibrinogen concentration is associated with increased risk of death and MI, while in patients with MI its high level is considered as an unfavourable prognostic factor both in short- and long-term follow-up [17-20]. In the population studied herein, fibrinogen level measured at the time of admission showed a positive correlation with CK-MB that indicated an association between extent of MI and fibrinogen concentration. De-Sutter et al. [21] also showed a positive relationship between fibrinogen concentration and size of MI based on peak value of CK-MB, extent of no-perfusion areas in thallium scintigraphy (r=0.58, p=0.001, r=0.64, p=0.001 respectively) and left ventricular ejection fraction (r=–0.44, p=0.01) in MI patients treated with primary coronary intervention. In our study, both in uni- and multivariate analysis fibrinogen concentration was found to be a significant risk factor of the myocardial *no-reperfusion* phenomenon (OR=1.56, CI 95%, 1.17-2.07, p=0.0023 and 1.51 CI 95% 1.011-4.58, p=0.021, respectively). A positive correlation between fibrinogen concentration and duration of chest pain [22-23] means not only structural changes in microvasculature but also rheological disturbances associated with increased fibrinogen concentration that worsen as the duration of acute myocardial ischaemia increases.

Red blood cells entering vessels of smaller or similar diameter to erythrocytes have to be deformed. Flow conditions are even more difficult if high fibrinogen concentration facilitates aggregation of erythrocytes. Two mechanisms neutralise erythrocyte aggregation: repulsion force related to their negative charge and disaggregation associated with blood flow [10, 24, 25]. As we showed in our report, in patients without myocardial tissue reperfusion plasma viscosity increased as well as propensity of red blood cells to form aggregates. Additionally, under those circumstances erythrocytes disaggregate more reluctantly, the phenomenon that we associate with high fibrinogen concentration in patients having insufficient flow in the microvasculature [1]. Flow in the coronary microcirculation depends on two main factors: degree of structural changes in the microvasculature and blood rheological characteristics [1, 26]. The importance of rheological disturbances in microcirculatory reperfusion was shown not only by our findings but also in the experimental study. The latter found an association between extent of MI and blood viscosity at the time of reperfusion [27]. However, our results may only indirectly indicate a contribution of blood rheological disturbances associated with elevated fibrinogen concentration to the mechanism of the *no-reperfusion* phenomenon.

Conclusions

Baseline fibrinogen concentration following successful mechanical recanalisation of IRA (TIMI 3) is an independent risk factor of the lack of myocardial reperfusion. Fibrinogen level positively correlates with peak CK-MB concentration and duration of chest pain. Its concentration is higher in the anterior MI than in patients with IRA other than left anterior descending. In our opinion, high fibrinogen concentration may affect rheological parameters of the blood and play an important role in the pathomechanism of the myocardial

no-reflow phenomenon following successful mechanical recanalisation of IRA.

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Wyjściowe wysokie stężenie fibrynogenu stanowi czynnik ryzyka braku reperfuzji mięśniowej w zawale serca z uniesieniem odcinka ST leczonym skuteczną pierwotną interwencją wieńcową

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Streszczenie

Wstęp: U znacznego odsetka chorych z zawałem serca, pomimo udrożnienia tętnicy dozawałowej, nie dochodzi do reperfuzji mięśniowej. Przepływ w mikrokrążeniu zależy nie tylko od zmian strukturalnych w drobnych naczyniach, lecz także od właściwości reologicznych krwi.

Cel: Ocena związku pomiędzy wyjściowym stężeniem fibrynogenu a reperfuzją mięśniową po skutecznej angioplastyce wieńcowej.

Metodyka: U 105 chorych z zawałem serca, których ze względu na stopień normalizacji odcinka ST po skutecznym udrożnieniu tętnicy dozawałowej podzielono na grupę z reperfuzją mięśniową (N=79) oraz grupę bez reperfuzji mięśniowej (N=26) oznaczono wyjściowe stężenie fibrynogenu.

Wyniki: Wyjściowe stężenie fibrynogenu było większe w grupie bez reperfuzji w porównaniu z grupą z reperfuzją (odpowiednio 523±198,02 *vs* 395,56±144,98, p=0,0004). W całej badanej populacji poziom fibrynogenu dodatnio korelował z maksymalną wartością frakcji MB kinazy kreatyninowej (r=0,25; p=0,012) oraz czasem trwania bólu zawałowego (r=0,31; p=0,002). Średnie stężenie fibrynogenu było większe u chorych z zawałem ściany przedniej w porównaniu z chorymi, u których tętnica dozawałowa była inna niż gałąź przednia zstępująca tętnicy wieńcowej. W analizie wieloczynnikowej ryzyko braku powrotu przepływu mięśniowego zwiększało się wraz z czasem trwania bólu zawałowego (OR=1,46; CI 95% 1,06–2,16; p=0,001) oraz ze wzrostem wyjściowego stężenia fibrynogenu (OR=1,51; CI 95% 1,011–4,58; p=0,021).

Wnioski: Wyjściowe stężenie fibrynogenu po skutecznym mechanicznym udrożnieniu tętnicy dozawałowej stanowi niezależny czynnik ryzyka braku reperfuzji mięśniowej i dodatnio koreluje z maksymalną wartością frakcji MB kinazy kreatyninowej oraz czasem trwania bólu zawałowego. Uważamy, że wysoki poziom fibrynogenu poprzez wpływ na parametry reologiczne krwi, w tym na wzrost lepkości osocza i nasilenie agregacji krwinek czerwonych, może odgrywać istotną rolę w patomechanizmie zjawiska braku powrotu przepływu mięśniowego po skutecznym udrożnieniu tętnicy dozawałowej.

Słowa kluczowe: ostry zawał serca, reperfuzja mięśniowa, fibrynogen, pierwotna angioplastyka wieńcowa

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