

Haemorheological factors and myocardial reperfusion in patients with ST-elevation myocardial infarction undergoing primary coronary intervention

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Abstract

Introduction: The no-reperfusion phenomenon occurs in a considerable number of patients despite restoration of the infarct-related artery (IRA) patency. Factors responsible for this phenomenon include myocardial structural changes, whereas haemorheological parameters that significantly contribute to microvascular resistance, have not been studied so far.

Aim: To determine the possible relationship between blood and plasma viscosity, red blood cell aggregation and their deformability, and myocardial reperfusion following effective mechanical intervention of IRA.

Methods: The analysis included 23 patients with myocardial infarction treated with primary coronary angioplasty with resultant TIMI (Thrombolysis in Myocardial Infarction) grade 3 flow. Myocardial reperfusion was found effective if myocardial perfusion grade (MPG) was 3. Blood and plasma viscosity were assessed using a Brookfield rotation viscometer. Red blood cell aggregation and deformability were measured with a Laser Optical Rotational Cell Analyzer (LORCA). Patients were divided into two groups with respect to obtained MPG: reperfusion group (14 subjects) and no-reperfusion group (9 patients).

Results: Corrected whole blood viscosity and plasma viscosity were significantly higher in the no-reperfusion group and exceeded the values obtained in the reperfused patients by 14% ($p < 0.05$) and 10.5% ($p < 0.01$), respectively. Red blood cell deformability index at shear stress ranging from 1.75 Pa to 60.03 Pa was significantly lower in the no-reperfusion group. Red blood cell aggregation index was significantly higher (by 14.3%, $p < 0.05$), whereas aggregation halftime was significantly shorter (by 58%, $p < 0.05$) in the no-reperfusion group.

Conclusions: Our results indicate that haemorheological disturbances may be an important factor contributing to no-reperfusion after effective mechanical opening of IRA.

Key words: haemorheological factors, STEMI, PCI, no-reflow

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Introduction

The no-reperfusion phenomenon occurs in a significant number of patients with myocardial infarction (MI) despite restoration of the infarct-related artery (IRA) patency. Mechanical opening of IRA and deployment of stent both failed to improve the outcome if slow blood flow was observed in the patent culprit artery (TIMI 2) [1, 2]. These facts indicate that not only a mechanical occlusion, but also structural changes of small vessels, and possibly compromised haemorheological parameters associated with MI, are

responsible for increased microvascular resistance [3-5]. The most important haemorheological factors adding to microvascular resistance are plasma viscosity, red blood cell (RBC) aggregation and deformability.

Blood and plasma viscosity show a positive correlation with fibrinogen, LDL cholesterol, VLDL, triglycerides, interleukin-6, von Willebrand factor, uric acid and C-reactive protein, and negative correlation with HDL cholesterol [6-9]. Even slight deviation of one of these variables may considerably influence plasma viscosity and the other haemorheological parameters.

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Elevated plasma viscosity and erythrocyte aggregation have been associated with coronary artery disease, MI [5, 10-13], atherosclerosis of peripheral arteries [11], neurological complications of atherosclerosis [13, 14], and the following atherogenic pathologies: diabetes mellitus, obesity, arterial hypertension, metabolic syndrome and renal failure [15-18]. Blood and plasma viscosity are higher in males than premenopausal females [7, 19], and increase after menopause [7] as well as while using contraceptives [20]. Plasma viscosity is higher in smokers than non-smokers [21].

Rheological blood disturbances show a positive correlation with the severity of atherosclerosis in coronary arteries [22, 23]. They are predictors of first cardiovascular event [24, 25]. In patients with unstable coronary artery disease they increase risk of MI [26], and after MI increase risk of death [27]. They also negatively correlate with left ventricular ejection fraction [28].

Lipid-lowering therapy decreases plasma viscosity and RBC aggregation while improving RBC deformability [29-31]. Apheresis reduces plasma viscosity by almost 8% [32]. Streptokinase, through degradation of fibrinogen, reduces plasma viscosity and RBC aggregation, and, according to some investigators, improves RBC deformability, which may create a protective mechanism for myocardial blood flow after pharmacological reperfusion [33-35].

The role of haemorheological properties in pathogenesis of no-reperfusion is indirectly indicated by results of a few experimental studies and some observational studies. In the ischaemia-reperfusion experimental model myocardial damage was increased by hypercholesterolaemia and decreased by lipid-lowering therapy [36, 37]. Patients without ST segment resolution after mechanical opening of IRA are characterised by higher total cholesterol and LDL cholesterol levels compared to subjects with electrocardiographic signs of reperfusion [38]. In patients with chest pain lasting more than 4 hours, and thus higher risk of disturbance of microvascular blood flow, streptokinase administered prior to mechanical intervention improved long-term prognosis, which may be related to its effect of improving blood viscosity [33-35, 39].

We are not aware of any reports on the relationship between haemorheological parameters and myocardial perfusion in patients with MI treated with primary coronary intervention (PCI). The aim of this study was to determine whether there is any association between blood and plasma viscosity, RBC aggregation and their deformability, as well as myocardial reperfusion following effective mechanical opening of IRA.

Methods

Study group

The analysis involved 23 subjects treated with primary PCI (19 males and 4 females). Myocardial infarction was diagnosed based on typical chest pain with concomitant ST-segment elevation and increase of creatine kinase activity above at least twice the upper normal limit. The diagnosis was confirmed with coronary angiography identifying IRA. Patients with cardiogenic shock and treated with intravenous GP IIb/IIIa inhibitors were not enrolled. The analysis excluded also patients in whom blood flow through IRA was not restored, blood flow became incrementally worse or ST elevation increased after intervention (increase of ST elevation of at least 1 mm in two adjacent leads measured 0.08 s from J point).

Coronary angiography

Coronary angiography was performed using femoral artery access. Coronary blood flow was assessed using TIMI score. Myocardial reperfusion was found to be effective if myocardial perfusion grade (MPG) was 3 [40]. Patients were divided into two groups with respect to achieved MPG: reperfusion group (14 subjects) and no-reperfusion group (9 patients).

Rheological assessments

Rheological tests were performed using routine blood samples collected on admission. Blood collection to coronary intervention time did not exceed 30 minutes in all patients. Tripotassium ethylenediaminetetraacetic acid (K_3EDTA) at a dose of 1 mg/ml was used as an anticoagulant. Whole blood viscosity was determined with a Brookfield rotation viscometer at a shear rate of 150/s. Relative mean squared error of single measurement did not exceed 1%. Plasma viscosity was measured at a shear rate of 300/s, with up to $\pm 2.5\%$ precision. Temperature of samples was 37°C. Adjusted blood viscosity (η_{sk}) to a standard haematocrit of 45% was calculated using the following formula

$$\eta_{sk} = \eta_0 \left(\frac{\eta_k}{\eta_0} \right)^{\frac{45}{H}}$$

where: η_0 – plasma viscosity, H – sample haematocrit, η_k – viscosity of the whole blood at H.

Red blood cell deformability was measured with a Laser Optical Rotational Cell Analyzer (LORCA). Samples of 25 μ l were diluted 1:200 with 0.14 mmol/l buffered polyvinylpyrrolidone solution. Physicochemical properties of the solution were as follows: pH 7.4, osmotic pressure 300 mOsm/kg, viscosity 30 mPa. Shear

stresses that caused RBC deformation were between 0.3 Pa and 60.03 Pa and were controlled with dedicated software. Laser light passing through the solution was diffracted on erythrocytes and the diffraction pattern expressed by an ellipsoid was analysed by dedicated software. Deformation was measured with the deformation index (DI) calculated as $DI = (A - B)/(A + B)$, where: A – ellipse long axis, B – ellipse short axis.

Red blood cell aggregation and its kinetics were also measured with a LORCA [41].

Red blood cell aggregation index (AI) and parameters characterising aggregation kinetics were determined with a sylectogram, which is a light reflection(I) – time

(t) curve, before and after sudden stop of shear stress motor. The curve is described by the formula below:

$$I = I_0 + I_1e^{-t/T_1} + I_2e^{-t/T_2}$$

where: I_0 – intensity of dispersed and reflected light in time $t \rightarrow \infty$; I_1 and I_2 – intensity of dispersed light of slowly and fast decreasing parts, respectively; T_1 and T_2 – time constant of the first and second parts, e – base of natural logarithm.

The following aggregation parameters were chosen: aggregation index (AI) and sylectogram amplitude, which characterise aggregation intensity; halftime ($T_{1/2}$), reflecting aggregation kinetics; borderline shear rate (γ_0), which shows deformability and stability of aggregation; as well as time constants T_1 and T_2 , which are used for differentiation of pathologic conditions.

Table I. Characteristics of the study groups. All differences were NS

	No-reperfusion group n=9	Reperfusion group n=14
Age [years]	58.4±9.02	55.28±8.93
Males	77.7	92.8
Arterial hypertension	44.4	71.4
Diabetes mellitus	33.3	21.4
Past myocardial infarction	44.4	42.8
Smoking	55.5	64.2
Positive family history	55.5	42.8
Pain to PCI time [hours]	4.4±2.7	4.1±1.6
Nitrate*	88.9	85.7
Heparin*	100	100
Acetylsalicylic acid*	100	100
Narcotic analgetics*	88.9	92.9
Mean systolic blood pressure [mm Hg]**	129±17	136±13
Mean diastolic blood pressure [mm Hg]**	82±8	89±9
Hear rate [bpm]**	86±17	87±5
Haemoglobin level [mmol/l]**	8.31±1.05	8.57±0.64
Mean corpuscular volume (MCV) [fl]	92.4±3.99	91.93±3.84
Mean corpuscular haemoglobin (MCH) [f mol]**	1.92±0.09	1.95±0.065
Mean corpuscular haemoglobin concentration (MCHC) [mmol/e]**	20.63±0.49	21.2±0.54
RBC [T/l]**	4.27±0.46	4.38±0.35
WBC [G/l]**	12.37±3.58	14.3±5.75
PLT (G/l)**	193.63±66	213.14±54

*Preadmission treatment

** Tests performed on admission

Statistical analysis

Kolmogorow-Smirnow test was employed to verify normal distribution of experimental data. Arithmetic mean and standard deviation were estimators of normal distribution.

Significance of differences between variables was determined using analysis of variance (ANOVA), Student's t-test and structure indices test. Differences were found significant when p value was <0.05.

Results

There were no differences between no-reperfusion and reperfusion groups with respect to clinical characteristics and haematological parameters (Table I). Biochemical parameters (creatinine kinase, creatinine, uric acid, total cholesterol, glucose, total protein) and previous treatment (data not presented) also showed no significant differences between the groups. Pain-to-intervention time was 4.2±2.1 hours and was similar in both groups.

Viscosity of the whole blood with actual haematocrit, plasma viscosity, haematocrit and blood viscosity corrected to a haematocrit of 45% are summarised in Table II.

Compared to the reperfusion group, no-reperfusion subjects had viscosity of the whole blood with actual haematocrit higher by 9%, but no statistical significance was reached, whereas corrected viscosity in the no-reperfusion group was significantly higher by 14% (p <0.05 with right-sided statistical significance).

Plasma viscosity was significantly higher (by 10.5%, p <0.01) in patients without myocardial reperfusion.

Table III presents RBC deformability matched to shear stress. For lower shear stress ranging from 0.3 to

Table II. Blood and plasma viscosity and haematocrit in patients with no-reperfusion and reperfusion

	No-reperfusion group	Reperfusion group	t	p
Viscosity of whole blood with actual haematocrit [mPa · s] D = 150/s	4.633±1.224 (3.19-7.29) 26%	4.379±0.445 (3.65-4.98) 10.2%	0.668	NS
Plasma viscosity (mPa · s) D = 300/s	1.466±0.130 (1.260-1.650) 8.9%	1.325±0.087 (1.15-1.460) 6.6%	2.970	<0.01
Haematocrit [%]	38.70±4.3 (31.0-45) 11.1%	42.15±4.0 (35-48) 9.4%	1.878	NS
Corrected whole blood viscosity (mPa · s) D = 150/s	5.504±1.031 (6.062-7.90) 18.7%	4.82±0.7 (3.94-6.27) 14.5%	1.806	<0.05*

* Right-sided significance range
Results are shown as mean±SD, ranges given in brackets, coefficient of variance in %, t and p – statistical significance indices

0.97 Pa, deformation index showed no statistical difference in both groups, whereas for shear stress of 1.75 to 60.03 Pa it was significantly decreased in the no-reperfusion group. The largest relative difference was about 10% at stress of 10.26 Pa.

Red blood cell aggregation indices are listed in Table IV. Compared to the reperfusion group, the following parameters were significantly higher in no-reperfusion subjects: RBC aggregation index (by 14.3%), time constant T_2 (by 12%) and borderline shear rate (by 54%). Aggregation half-time was significantly shorter (by 58%). Sylectogram amplitude and time constant T_1 were insignificantly lower.

Discussion

Blood viscosity depends both on macro- and microrheological factors. Macrorheological factors include haematocrit and plasma viscosity, whereas microrheological factors are RBC aggregation and deformability.

Plasma viscosity plays an important role in RBC flow. Its increase, observed in the no-reperfusion group, may be one of the factors making migration of erythrocytes through the small vessels and capillaries difficult.

Red blood cell flow through capillaries of diameters equal to or lower than RBC diameter can be achieved by RBC elongation, which is more difficult in stiffer cells. Previous investigations showed that decreased deformability of RBC in MI was associated with

Table III. Red blood cell deformation index in no-reperfusion and reperfusion groups matched to shear stress

Shear stress (Pa)	Deformation index [%]		t	p
	No-reperfusion group	Reperfusion group		
0.30	3.87±0.51 (2.7-4.5) 13.18%	3.79±1.22 (2.5-6.3) 32%	0.170	NS
0.54	9.66±1.48 (7.3-11.3) 15.3%	9.30±1.38 (7.7-11.3) 14.8%	0.620	NS
0.97	17.5±1.73 (13.8-19.7) 10.15%	17.58±2.05 (14.9-21.5) 11.7%	0.498	NS
1.75	25.3±1.93 (22.7-28.3) 7.6%	26.58±1.31 (24.3-29.5) 4.9%	2.193	<0.05
3.16	31.82±2.94 (27.2-35.9) 9.24%	33.74±1.21 (31.2-36.0) 3.6%	1.889	<0.05*
5.69	40.17±4.0 (31.9-45.5) 9.96%	43.32±2.12 (40.1-46.6) 4.9%	2.272	<0.05
10.26	44.6±5.07 (37.0-51.9) 11.36%	49.13±2.43 (45.0-52.0) 4.9%	2.563	<0.05
18.49	50.0±4.37 (41.0-54.9) 8.74%	53.47±2.76 (47.9-56.6) 5.6%	2.172	<0.05
33.20	53.7±4.3 (44.4-58.7) 8%	57.1±2.7 (51.4-59.7) 4.7%	2.110	<0.05
60.03	56.7±4.3 (47.9-61.6) 7.6%	60.0±2.5 (54.5-62.5) 4.16%	2.158	<0.05

* Left-sided significance range

increased production of free oxygen radicals and oxygenation of RBC membrane lipids [42, 43]. Our study documented that RBC deformability was significantly reduced in patients without myocardial reperfusion, which might have caused increased flow resistance in capillaries.

Increased RBC aggregation is a risk factor for coronary artery disease, and is associated with acute coronary syndromes and neurovascular complications of atherosclerosis [11, 13]. Increase of aggregation is associated with increased activity of free oxygen radicals, and fibrinogen and CRP levels [7, 42-45].

In our study group, RBC aggregation index was higher by 14.3% in patients with no-reperfusion compared to subjects with restoration of myocardial perfusion. Increased $T_{1/2}$ by 58% indicates that patients

Table IV. Red blood cell aggregation and indices of aggregation kinetics in no-reperfusion and reperfusion groups

	No-reperfusion group	Reperfusion group	t	p
Aggregation index (IA) [%]	67.42±8 (49-80) 11.86%	59±9.5 (36-74) 16.1%	2.10	<0.05
Sylectogram amplitude [ua]*	15.5±4.4 (6.26-21.43) 28.3%	17.7±1.6 (15.52-19.84) 9%	1.12	NS
Aggregation halftime (T _{1/2}) [s]	1.86±0.9 (0.84-4.12) 48%	2.94±1.6 (1.28-7.16) 54%	1.800	<0.05**
Borderline shear rate (γ ₀) [1/s]	185±123 (100-400) 66%	120.4±75 (50-300) 62%	2.228	<0.05
Time constant (T ₁) [s]	2.52±0.72 (2.32-4.75) 28.6%	3.84±1.66 (2.01-6.92) 43.22%	1.446	NS
Time constant (T ₂) [s]	29.1±5 (22.65-40.86) 17.2%	26±2.7 (21.75-29.64) 10.4%	1.806	<0.05***

* Arbitrary unit

** Left-sided significance range

*** Right-sided significance range

with no-reperfusion had significantly higher rate of creation and growth of RBC aggregates. Increase of borderline shear rate by 54% shows that aggregates were bound with stronger bonds which caused difficulties on disaggregation. This may be associated with pathological aggregation of RBC, involving adhesion with their lateral surfaces with formation of a three-dimensional net. Such aggregation increases capillary resistance.

The importance of the whole blood viscosity for blood flow in vessels of <500 μ diameter is insignificant. Haematocrit, which is the key rheological factor determining blood flow in large vessels, decreases inversely with vessel diameter, allowing blood viscosity to remain almost constant at all levels of coronary vessels despite lower flow rate. Compared to the reperfusion group, haematocrit-corrected viscosity in the no-reperfusion group was significantly higher.

Our results suggest that actions to improve haemorheological parameters may be a therapeutic perspective in patients with myocardial no-reperfusion. Ischaemic structural changes in capillaries seem to be out of therapeutic range. However, improvement of blood fluidity, mainly through decrease of plasma viscosity and RBC aggregation, may be obtained using isovolemic haemodilution or apheresis [46, 47], which are currently being studied in patients with ischaemic stroke [48].

Study limitations

Pathogenesis of insufficient myocardial perfusion following coronary angioplasty also involves the no-reflow phenomenon (worsening of baseline flow), which pathomechanism is different from no-reperfusion (no restoration of myocardial perfusion). No-reflow should be diagnosed after coronary intervention, when it is followed by worsening of blood flow, due to reflex vascular spasm and/or distal embolisation with thrombotic material or components from atherosclerotic plaque, e.g., no-reflow is observed during angioplasty of cholesterol-rich lesions in the venous graft. To reduce the contribution of this mechanism to myocardial reperfusion assessment in MI we excluded from analysis patients with progressing ST elevation as well as subjects with worsening of baseline flow immediately after coronary intervention.

Conclusions

1. Haemorheological disturbances may be an important factor contributing to myocardial no-reperfusion after effective mechanical intervention in the culprit artery.
2. Increased baseline plasma viscosity, compromised RBC deformability and increased RBC aggregation significantly add to elevation of capillary resistance.
3. Haemorheological disturbances may result in marked limitation or no perfusion within the infarcted area.
4. Pathogenesis of no-reperfusion comprises in large part plasma viscosity and microrheological properties of blood that depend on the large and most numerous blood cells – erythrocytes.

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Właściwości reologiczne krwi a reperfuzja mięśniowa w zawale serca z uniesieniem odcinka ST leczonym za pomocą pierwotnej interwencji wieńcowej

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Streszczenie

Wstęp: U znacznego odsetka chorych, pomimo udrożnienia tętnicy dozawowej, nie dochodzi do reperfuzji mięśniowej (no-reperfusion). Uważa się, że za to zjawisko są odpowiedzialne m.in. zmiany strukturalne w miokardium, natomiast mające duże znaczenie w kształtowaniu oporu przepływu w mikrokrażeniu parametry reologiczne krwi nie były dotąd przedmiotem badań.

Cel: Określenie, czy istnieje związek pomiędzy lepkością krwi, osocza, agregacją krwinek czerwonych i ich odkształcalnością a reperfuzją mięśniową po skutecznym mechanicznym udrożnieniu tętnicy dozawowej.

Metodyka: Analizie poddano 23 chorych z zawałem serca leczonych za pomocą pierwotnej angioplastyki wieńcowej, u których uzyskano przepływ TIMI 3 (ang. *Thrombolysis in Myocardial Infarction*). Za skuteczną reperfuzję mięśniową uznano przepływ MPG 3 (ang. *myocardial perfusion grade*). Lepkość krwi i osocza oceniono wiskozymetrem rotacyjnym Brookfielda. Agregację i odkształcalność krwinek czerwonych zmierzono laserowym analizatorem optycznym (ang. *laser optical rotational cell analyzer*, LORCA). W zależności od uzyskanego przepływu MPG chorych podzielono na dwie grupy: reperfusion (14 chorych) i no-reperfusion (9 chorych).

Wyniki: Lepkość skorygowana krwi pełnej oraz lepkość osocza były znacząco większe w grupie no-reperfusion, odpowiednio o 14 ($p < 0,05$) i 10,5% ($p < 0,01$). Wskaźnik odkształcalności krwinek czerwonych przy naprężeniach 1,75–60,03 Pa był istotnie mniejszy w grupie no-reperfusion. Indeks agregacji erytrocytów był istotnie większy (o 14,3%, $p < 0,05$), natomiast czas polowiczny agregacji był istotnie krótszy (o 58%, $p < 0,05$) w grupie no-reperfusion.

Wnioski: Uzyskane wyniki wskazują, że zaburzenia reologiczne mogą być jednym z istotnych czynników odpowiedzialnych za brak reperfuzji mięśniowej po skutecznym mechanicznym udrożnieniu tętnicy dozawowej.

Słowa kluczowe: zaburzenia reologiczne krwi, reperfuzja mięśniowa, zawał serca, pierwotna interwencja wieńcowa

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