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Clinical Outcomes Following Percutaneous Coronary Intervention, as Determined by Rheological Properties in Patients with Stable Ischemic Heart Disease

Spartak Lekveishvili, Vera Kapetivadze, Maka Mantskava

Tbilisi State Medical University, Tbilisi, Georgia

Abstract

Background: Hemorheological abnormalities contribute to impaired microcirculation and myocardial ischemia in coronary artery disease (CAD). Their prognostic significance after percutaneous coronary intervention (PCI) remains insufficiently defined.

Objective: To evaluate changes in blood cell aggregation after PCI and their association with long-term clinical outcomes in patients with stable CAD.

Materials and Methods: This prospective observational study included patients with stable angina undergoing PCI between March and September 2025. Blood samples were collected before PCI and at 3, 8, and 90 days after intervention. Erythrocyte, leukocyte, and platelet aggregation were assessed using standardized laboratory techniques. Patients were followed for 12 months and divided into two groups according to clinical outcome: Group I (favorable outcome without recurrent ischemia) and Group II (repeat intervention due to recurrent angina and/or restenosis). Statistical analysis included repeated-measures ANOVA and Student's t-test.

Results: Patients with stable CAD demonstrated significantly increased erythrocyte and leukocyte aggregation compared with controls ($p < 0.05$).

Patients with favorable outcomes showed progressive normalization of hemorheological parameters during follow-up, whereas patients requiring repeat PCI demonstrated persistent erythrocyte hyperaggregation and elevated leukocyte aggregation. Platelet aggregation showed less pronounced intergroup differences.

Conclusion: Persistent hemorheological abnormalities, particularly erythrocyte hyperaggregation, are associated with recurrent ischemia and repeat coronary intervention after PCI. Assessment of blood rheology may improve risk stratification in stable CAD.

KEYWORDS: coronary artery disease; hemorheology; erythrocyte aggregation; microcirculation; PCI; restenosis.

Introduction

Coronary artery disease (CAD) remains one of the leading causes of mortality and disability worldwide [1]. Stable angina is among the most common clinical manifestations of CAD and is characterized by transient myocardial ischemia resulting from an imbalance between myocardial oxygen demand and coronary blood supply [1]. Despite major advances in diagnostic and therapeutic strategies, recurrent ischemic events and repeated coronary interventions remain significant clinical challenges [2]. Current European guidelines for chronic coronary syndromes emphasize that revascularization is only one component of management and that long-term outcome depends equally on secondary prevention and on the control of residual risk factors [17].

Percutaneous coronary intervention (PCI) is currently one of the standard methods for myocardial revascularization in patients with symptomatic CAD [2]. Restoration of epicardial coronary blood flow substantially improves symptoms and quality of life. Nevertheless, the long-term clinical effect of PCI varies among patients. Some individuals experience sustained clinical improvement, whereas others develop recurrent ischemia requiring repeat revascularization [2,3].

In-stent restenosis remains the principal cause of repeat target-lesion revascularization after PCI. Although drug-eluting stents have markedly reduced its incidence compared with bare-metal stents, restenosis has not been eliminated, and its treatment remains technically demanding and associated with further recurrence [13]. The established predictors of restenosis are largely procedural and anatomical, including small vessel diameter, long lesions, stent underexpansion and diabetes mellitus [2]. Systemic

factors that modify the local hemodynamic and inflammatory environment of the treated segment have received considerably less attention.

In addition to structural coronary artery lesions, increasing attention has been directed toward abnormalities in blood rheology and microcirculation [4,5]. Blood rheological properties play a critical role in tissue perfusion and oxygen delivery [4]. Elevated blood viscosity, increased aggregation of blood cells, impaired erythrocyte deformability, and endothelial dysfunction may contribute to myocardial ischemia independently of the degree of coronary stenosis [5]. Hemorheological abnormalities have been documented across the whole spectrum of CAD: erythrocyte aggregation, plasma viscosity and whole-blood viscosity are elevated in stable angina and increase further in unstable angina and acute myocardial infarction, suggesting that rheological disturbance tracks disease severity [9]. In patients with unstable angina, increased plasma viscosity and erythrocyte aggregation have been associated with an unfavorable clinical course [10], and in population studies higher blood viscosity and plasma fibrinogen predict future cardiovascular events [11,12].

Erythrocyte aggregation is considered one of the principal determinants of blood viscosity, particularly in low-flow conditions characteristic of the microcirculatory bed [5,6]. Excessive erythrocyte aggregation impairs capillary perfusion, increases peripheral vascular resistance, and reduces oxygen transport efficiency [6]. Leukocyte activation and aggregation additionally contribute to endothelial injury and inflammatory responses, while platelet activation promotes thrombosis and vascular obstruction [7].

The coronary microcirculation is the segment of the coronary tree in which these properties matter most. Coronary microvascular dysfunction can cause angina and myocardial ischemia in the absence of obstructive epicardial disease and frequently coexists with it [15]. After PCI, impaired microvascular perfusion may persist despite a widely patent epicardial artery; in its most severe form this is recognized as the no-reflow phenomenon, in which embolization, endothelial injury and plugging of capillaries by blood cells limit tissue perfusion [14]. Blood with increased cellular aggregation is therefore expected to be particularly disadvantageous in the post-PCI microcirculation.

Previous studies have demonstrated the importance of hemorheological abnormalities in cardiovascular disease [8]. However, limited data are available regarding the relationship between blood cell aggregation and long-term clinical outcomes after PCI [3,8]. Identification of rheological markers associated with recurrent ischemia may improve risk stratification and facilitate individualized therapeutic strategies [2]. The aim of this study was to evaluate changes in blood cell aggregation after PCI and to investigate their association with long-term clinical outcomes in patients with stable CAD. Specifically, the study examined whether the trajectory of erythrocyte, leukocyte and platelet aggregation during the first three months after PCI differs between patients with a favorable 12-month outcome and those who require repeat intervention.

Materials and Methods

Study design and population

This prospective observational study included patients with stable angina who underwent PCI at the Cardiology Department of the University Hospital between March 2025 and September 2025. The study population consisted of patients aged 55 ± 5.4 years with documented stable CAD requiring coronary intervention according to current clinical guidelines [2].

Inclusion criteria:

- Stable angina pectoris;
- Indication for PCI confirmed by a cardiologist;
- Age > 45 years.

Exclusion criteria:

- Anemia;
- Active inflammatory disease;
- Malignancy;
- History of chemotherapy or radiation therapy within the previous year;
- Type 2 diabetes mellitus;
- Severe renal or hepatic dysfunction.

Patients were followed for 12 months after PCI.

Study groups

Patients were divided into two subgroups according to clinical outcomes during follow-up:

- **Group I (Favorable outcome group):** patients without recurrent ischemic symptoms or repeat coronary intervention during follow-up.
- **Group II (Repeat intervention group):** patients who required repeat PCI because of recurrent angina and/or angiographically confirmed restenosis [2].

The control group consisted of apparently healthy age- and sex-matched volunteers.

Laboratory assessment

Venous blood samples were collected before PCI and at 3 days, 8 days, and 3 months after intervention. Parameters assessed included fibrinogen, total cholesterol,

low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglycerides.

Blood rheology assessment

Erythrocyte aggregation was evaluated using the Georgian quantitative aggregation technique described by Mchedlishvili [5]. Blood samples were diluted in autologous plasma and analyzed using the Texture Analysis System (TAS-plus, Leitz, Germany). The erythrocyte aggregation index (EAI) was defined as the ratio of aggregated erythrocyte area to total erythrocyte area [5,6].

Platelet aggregation was assessed using a dual-channel laser platelet aggregation analyzer according to standard principles [7].

Leukocyte aggregation was determined using a hematological counter.

Statistical analysis

Continuous variables are presented as mean ± standard deviation (SD). Normality was assessed via the Shapiro–Wilk test. Between-group comparisons were performed using Student's t-test or Welch's t-test. Repeated measurements were analyzed using repeated-measures ANOVA with post hoc Bonferroni correction. Categorical variables were analyzed using the χ^2 test. A p-value < 0.05 was considered statistically significant (SPSS v27.0).

Results

Baseline characteristics

A total of 62 patients with stable CAD undergoing PCI were enrolled. During 12-month follow-up, 32 patients (51.6%) demonstrated favorable clinical outcomes (Group I), whereas 30 patients (48.4%) required repeat PCI (Group II). The control group consisted of 25 healthy volunteers. Age and sex distribution were comparable between the control group and the patient cohort (Table 1).

Compared with controls, patients with stable CAD had higher total cholesterol (by approximately 29%), LDL-C (by approximately 42%) and fibrinogen (by approximately 41%). The erythrocyte aggregation index was approximately 48% higher in patients than in controls (0.43 ± 0.06 vs. 0.29 ± 0.04; $p < 0.05$). These differences are shown in Fig. 2.

TABLE 1. BASELINE CHARACTERISTICS OF THE CONTROL GROUP AND PATIENTS WITH STABLE CAD

Parameter	Control group	CAD patients
Age (years)	54 ± 4.8	55 ± 5.4
Male sex (%)	62	65
Total cholesterol (mmol/L)	4.5 ± 0.7	5.8 ± 0.9*
LDL-C (mmol/L)	2.6 ± 0.5	3.7 ± 0.8*
Fibrinogen (g/L)	2.9 ± 0.4	4.1 ± 0.6*
Erythrocyte aggregation index	0.29 ± 0.04	0.43 ± 0.06*

*p < 0.05 vs. control group.

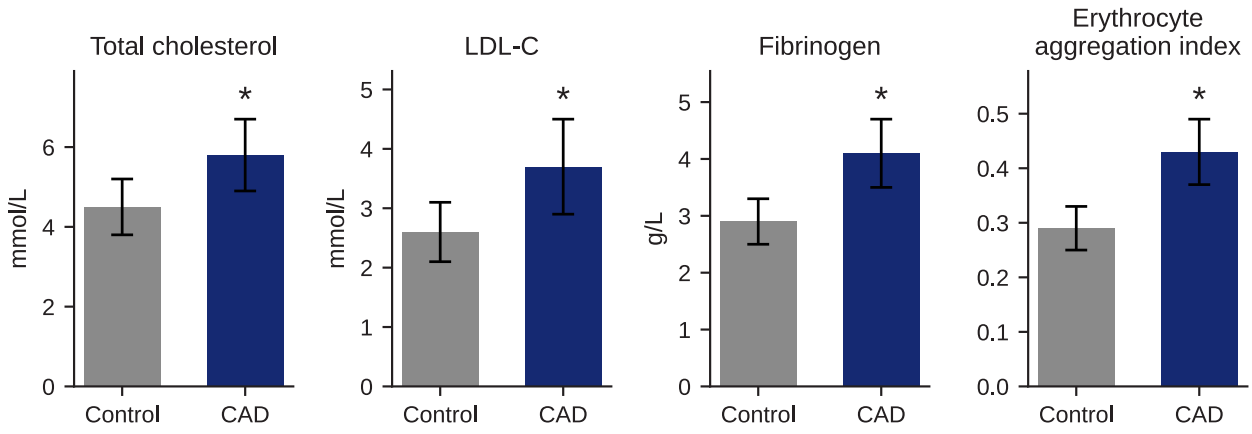


Fig. 2. Lipid parameters, fibrinogen and erythrocyte aggregation index in the control group and in patients with stable CAD before PCI. Data are presented as mean ± SD. *p < 0.05 vs. control group.

Changes in erythrocyte aggregation after PCI

Before PCI, erythrocyte aggregation was elevated in both patient groups compared with controls. Patients with favorable outcomes demonstrated progressive reduction during follow-up, whereas patients requiring repeat intervention showed persistent elevation.

In Group I, the erythrocyte aggregation index decreased from 0.42 ± 0.05 before PCI to 0.31 ± 0.03 at 3 months, a relative reduction of approximately 26%; the 3-month value approached that of the control group (0.29 ± 0.04). In Group II, the index changed from 0.46 ± 0.07 to 0.44 ± 0.06 over the same period, a relative reduction of approximately 4%, and remained at the level observed in the overall CAD cohort before intervention. Group II also had a numerically higher erythrocyte aggregation index before PCI (0.46 vs. 0.42). The time course in both groups is presented in Table 2 and Fig. 1.

TABLE 2. ERYTHROCYTE AGGREGATION INDEX AFTER PCI BY OUTCOME GROUP

Time point	Group I (Favorable)	Group II (Repeat Intervention)
Before PCI	0.42 ± 0.05	0.46 ± 0.07
Day 3	0.39 ± 0.05	0.45 ± 0.06
Day 8	0.35 ± 0.04*	0.43 ± 0.05
3 months	0.31 ± 0.03*	0.44 ± 0.06**

*p < 0.05 vs. baseline; **p < 0.05 vs. Group I.

Leukocyte and platelet aggregation

Leukocyte aggregation decreased significantly after PCI in Group I but remained elevated in Group II. Platelet aggregation showed less pronounced differences between groups, likely reflecting routine dual antiplatelet therapy.

Statistical analysis of hemorheological changes

Repeated-measures ANOVA demonstrated a significant reduction in erythrocyte aggregation over time in Group I ($F = 16.8$, $p < 0.001$; Bonferroni $p < 0.01$ at Day 8 and Month 3). Group II demonstrated a non-significant reduction ($F = 2.4$, $p = 0.084$). At 3 months, erythrocyte aggregation was significantly higher in Group II vs. Group I (0.44 ± 0.06 vs. 0.31 ± 0.03, $p < 0.001$; partial $\eta^2 = 0.31$). Leukocyte aggregation decreased significantly in Group I ($F = 11.2$, $p < 0.001$) but remained elevated in Group II ($F = 3.1$, $p = 0.051$). Platelet aggregation showed no between-group difference ($p = 0.18$).

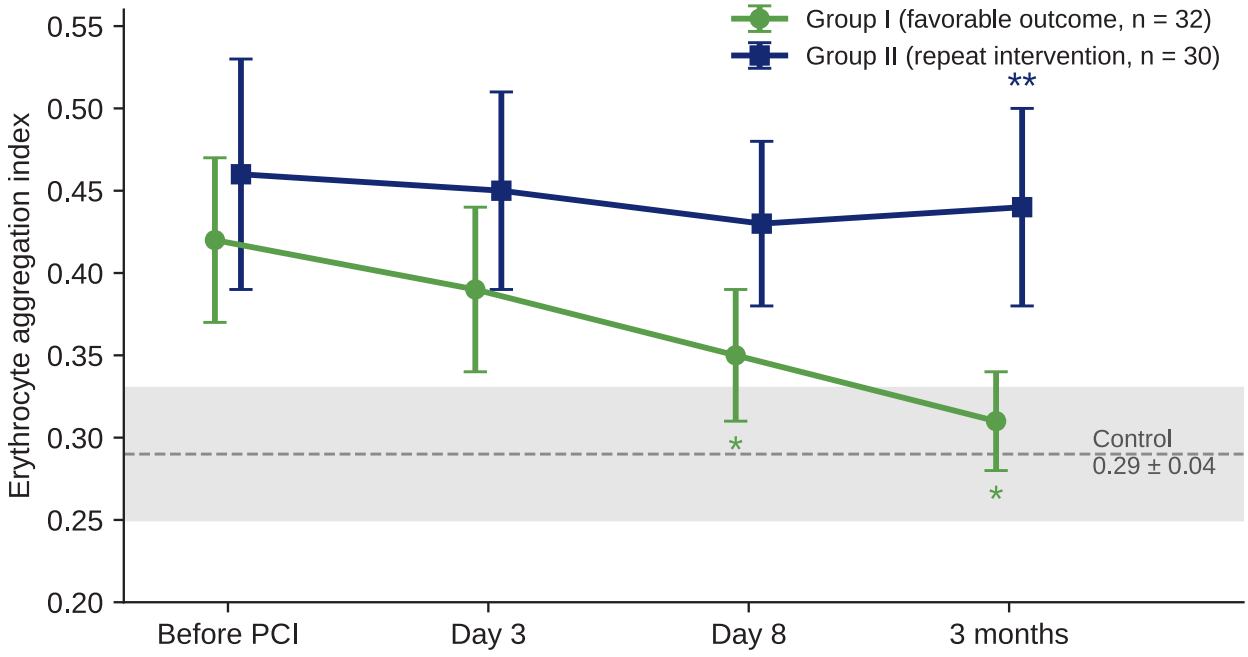


Fig. 1. Erythrocyte aggregation index before and after PCI in patients with a favorable outcome (Group I) and patients who required repeat intervention (Group II). Data are presented as mean ± SD. The dashed line and shaded band show the control group (mean ± SD). *p < 0.05 vs. baseline; **p < 0.05 vs. Group I.

TABLE 3. REPEATED-MEASURES ANOVA OF ERYTHROCYTE AND LEUKOCYTE AGGREGATION OVER THE FOLLOW-UP PERIOD

Parameter	Group	F	p
Erythrocyte aggregation	Group I	16.8	< 0.001
	Group II	2.4	0.084
Leukocyte aggregation	Group I	11.2	< 0.001
	Group II	3.1	0.051

Erythrocyte aggregation at 3 months, Group II vs. Group I: $p < 0.001$, partial $\eta^2 = 0.31$. Platelet aggregation, between-group comparison: $p = 0.18$.

Discussion

The present study demonstrated significant disturbances in blood rheology in patients with stable CAD undergoing PCI [4,8]. Sustained clinical improvement after PCI was associated with persistent normalization of blood rheology, whereas patients requiring repeat intervention demonstrated persistent hyperaggregation [2,3].

The baseline findings are consistent with earlier reports. Increased erythrocyte aggregation and blood viscosity have been described in stable angina, with greater abnormalities in acute coronary syndromes [9], and an adverse rheological profile has been linked to a worse course in unstable angina [10]. The present data extend these observations to the period after elective PCI and suggest that the direction of rheological change after revascularization, rather than the baseline value alone, separates patients with different long-term outcomes. In patients with a favorable outcome, the erythrocyte aggregation index returned close to the control level within three months, whereas in patients who later required repeat intervention it remained essentially unchanged.

Role of fibrinogen

Fibrinogen is the main plasma protein promoting erythrocyte aggregation, and patients in this study had markedly higher fibrinogen than controls. Large prospective data show that plasma fibrinogen is associated with the risk of coronary heart disease and stroke [12], and blood viscosity has likewise been linked to cardiovascular events in the general population [11]. Elevated fibrinogen may therefore be one of the links between systemic inflammation, erythrocyte hyperaggregation and adverse outcome after PCI. Analysis of fibrinogen dynamics during follow-up in relation to aggregation would help to clarify whether the persistent hyperaggregation in Group II reflects a persistent plasma-protein abnormality or an intrinsic change in erythrocyte properties.

Leukocyte aggregation and vascular inflammation

The behavior of leukocyte aggregation paralleled that of erythrocyte aggregation: it decreased significantly in patients with a favorable outcome and remained elevated in patients who required repeat intervention. Atherosclerosis is fundamentally an inflammatory disease in which activated leukocytes interact with the endothelium, migrate into the vessel wall and sustain the local response to injury [18]. Balloon dilatation and stent implantation add an acute mechanical injury to this chronic process. Persistent leukocyte activation after PCI may therefore indicate an ongoing inflammatory response, and the parallel course of erythrocyte and leukocyte aggregation in the present study suggests that both may reflect a common systemic state rather than independent abnormalities. Because leukocyte aggregation was determined by a hematological counter and

its values are reported here only descriptively, this interpretation should be confirmed by quantitative analysis and by concurrent measurement of established inflammatory markers.

Baseline aggregation and the course after PCI

Patients who later required repeat intervention already had a numerically higher erythrocyte aggregation index before PCI than patients with a favorable outcome (0.46 vs. 0.42). The present analysis focused on the change over time and on the comparison at 3 months, and it cannot establish whether the pre-procedural value alone carries prognostic information. Two interpretations are possible: patients with a more pronounced rheological disturbance at baseline may be less likely to normalize after revascularization, or the failure to normalize may itself be the relevant factor. Distinguishing between these possibilities requires a larger cohort in which baseline values, their change after PCI and clinical covariates can be analysed together in a multivariable model.

Relationship with coronary microvascular dysfunction

Coronary microvascular dysfunction represents an important mechanism linking hemorheological abnormalities with adverse outcomes after PCI. Restoration of epicardial patency does not automatically ensure microvascular normalization. Erythrocyte hyperaggregation increases blood viscosity at low shear rates, impairing capillary perfusion and oxygen transport [6]. Microvascular dysfunction is increasingly recognized as a cause of persistent angina after technically successful revascularization [15], and capillary obstruction by aggregated blood cells is one of the mechanisms implicated in impaired post-procedural reperfusion [14]. Persistent hyperaggregation may therefore produce recurrent ischemic symptoms even in the absence of significant restenosis, which may partly explain why recurrent angina and angiographic restenosis were combined in the definition of the adverse outcome group.

Potential mechanisms of restenosis

Persistent erythrocyte hyperaggregation promotes local flow disturbances and increases shear stress heterogeneity. Elevated fibrinogen further accelerates thrombo-inflammatory responses. Activated leukocytes release cytokines and reactive oxygen species, driving smooth muscle proliferation and neointimal hyperplasia. Low and oscillatory wall shear stress is a recognized promoter of endothelial dysfunction and atherogenesis [16], and the neointimal response within a stent is sensitive to the local flow environment. In this context, the relatively small change in platelet aggregation is not unexpected: all patients received routine antiplatelet therapy after PCI [17], which likely at-

tenuated differences between groups, whereas erythrocyte and leukocyte aggregation are not directly targeted by standard post-PCI pharmacotherapy.

Clinical implications

Assessment of erythrocyte aggregation provides prognostic insight beyond angiography. Hemorheological monitoring during follow-up can identify high-risk individuals who may benefit from intensified secondary prevention. The erythrocyte aggregation index is obtained from a small venous blood sample, and its absolute values in the two outcome groups differed substantially at 3 months. If confirmed in larger cohorts, a persistent elevation of the index at follow-up could serve as a signal for closer clinical surveillance and stricter control of modifiable risk factors in line with current recommendations [17]. At present, however, the data do not support any specific rheology-targeted treatment.

Future directions

Larger multicenter cohorts and extended longitudinal follow-up beyond 12 months are necessary to evaluate MACE outcomes and potential targeted hemorheological therapies.

Study Limitations

Single-center observational design, limited sample size, indirect microvascular assessment, and lack of direct whole-blood viscosity measurements represent the main limitations.

Several further points should be considered when interpreting the results. First, with 62 patients the study is not powered to assess hard clinical endpoints, and the findings should be regarded as hypothesis-generating. Second, the analysis compares outcome groups without adjustment for potential confounders such as lesion characteristics, stent type, lipid-lowering therapy and treatment adherence. Third, erythrocyte deformability, plasma viscosity and whole-blood viscosity were not measured, so the contribution of aggregation to overall blood fluidity cannot be quantified. Fourth, leukocyte and platelet aggregation are reported mainly descriptively. Finally, because the outcome groups were defined by events during the 12-month follow-up, the timing of repeat intervention relative to the 3-month blood sampling should be taken into account; the association observed is not evidence of a causal relationship.

Conclusion

Patients with stable CAD demonstrate significant abnormalities in blood rheology before PCI. Improvement in hemorheological parameters post-PCI correlates with favorable long-term outcomes, whereas persistent erythrocyte hyperaggregation is associated with recurrent ischemia and restenosis.

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Data availability. Available upon reasonable request from the corresponding author.

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