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High residual platelet aggregation in patients with coronary artery disease: a new methodological approach to detection

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ABSTRACT

Aim. To develop a new methodological approach to assessment of collagen-induced platelet aggregation in patients with coronary artery disease (CAD) and to determine the quality of various methods for detecting high residual platelet reactivity (HRPR) to predict the risk of myocardial perfusion disturbance.

Materials and methods. 36 patients (10 men and 26 women) aged 41–83 years and having stable CAD were examined. All patients had been undergoing continuous antiaggregation therapy for 6 months. We evaluated platelet aggregation using a laser analyzer with collagen as an aggregation inducer by the standard method 1 and our own patented method 2. The degree of platelet aggregation (%) and the size of aggregates in relative units (r.u.) in platelet-rich plasma were estimated. Myocardial perfusion scintigraphy with 99mTc-methoxy-isobutylisonitrile was performed according to a two-day stress-rest protocol. The summed stress score (SSS) values were used for analysis. SSS < 4 was regarded as normal myocardial perfusion.

Results. The degree of platelet aggregation according to method 1 was 12 (5; 64)%, the aggregate size was 3 (2; 7) r.u. The degree of platelet aggregation according to method 2 was 44 (13; 78)%, and the aggregate size was 5 (4; 8) r.u. Method 2 allowed to diagnose the presence of myocardial ischemia with an aggregation degree ≥ 44.9% with sensitivity of 84% and specificity of 92% (area under the curve (AUC) = 0.89; $p < 0.0001$; odds ratio (OR) 2.18; 95% confidence interval (CI) 0.57–0.98) and an increase in aggregate size ≥ 4.80 r.u. with sensitivity of 84% and specificity of 84% (AUC = 0.95; $p < 0.00001$; OR 5.83; 95% CI 0.72–0.99).

Conclusion. In patients with CAD, the detection of high rates of collagen-induced platelet aggregation using the patented technique is associated with the risk of impaired myocardial perfusion. The developed new methodological approach to detection of HRPR allowed to determine high risk of atherothrombotic complications in additional 22% of the examined patients.

Key words: aggregation, platelet, collagen, coronary artery disease, residual reactivity.

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Высокая остаточная агрегационная активность тромбоцитов у пациентов с ишемической болезнью сердца: новый методический подход к выявлению

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РЕЗЮМЕ

Цель – разработать новый методический подход к оценке коллаген-индуцированной агрегации тромбоцитов у пациентов с ишемической болезнью сердца (ИБС) и определить информативность методик выявления высокой остаточной реактивности тромбоцитов для прогнозирования риска нарушения миокардиальной перфузии.

Материалы и методы. Обследованы 36 пациентов (10 мужчин и 26 женщин) в возрасте 41–83 лет со стабильной формой ИБС, находящихся на непрерывной антиагрегационной терапии в течение 6 мес. Оценку агрегации тромбоцитов проводили на лазерном анализаторе с индуктором агрегации коллагеном по стандартной методике 1 и по собственной запатентованной методике – методике 2. Оценивали степень агрегации тромбоцитов (%) и размер агрегатов (отн. ед.) в суспензии тромбоцитов. Перфузионную сцинтиграфию миокарда с 99mTc-метокси-изобутилизонитрилом выполняли по двухдневному протоколу «нагрузка – покой». Для анализа использовали значения SSS, при SSS < 4 делали вывод о нормальной миокардиальной перфузии.

Результаты. Степень агрегации тромбоцитов по методике 1 составила 12 (5; 64)%, размер агрегата – 3 (2; 7) отн. ед. Степень агрегации тромбоцитов по методике 2 составила 44 (13; 78)%, а размер агрегата – 5 (4; 8) отн. ед. Методика 2 позволила диагностировать наличие нарушений миокардиальной перфузии при степени агрегации ≥44,9% с чувствительностью 84% и специфичностью 92% (AUC = 0,89; $p < 0,0001$; отношение шансов (ОШ) 2,18; 95%-й доверительный интервал (ДИ) 0,57–0,98) и увеличение размеров агрегатов ≥4,80 отн. ед. с чувствительностью 84% и специфичностью 84% (AUC = 0,95; $p < 0,00001$; ОШ 5,83; 95%-й ДИ 0,72–0,99).

Заключение. У пациентов с ишемической болезнью сердца выявление высоких показателей коллаген-индуцированной агрегации тромбоцитов с помощью запатентованной методики ассоциируется с риском нарушения миокардиальной перфузии. Разработанный новый методический подход по выявлению высокой остаточной реактивности тромбоцитов позволил определить наличие высокого риска развития атеротромботических осложнений дополнительно у 22% обследованных пациентов.

Ключевые слова: агрегация, тромбоцит, коллаген, ишемическая болезнь сердца, остаточная реактивность.

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

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INTRODUCTION

Coronary artery disease (CAD) remains the most common disease of the cardiovascular system, with a high risk of vascular events and death. High residual platelet reactivity (HRPR) in CAD patients is associated with development of ischemic complications, which was proven by numerous studies and meta-analysis data [1, 2]. However, in the daily practice of a cardiologist, platelet function is not evaluated due to a weak evidence base. Monitoring of platelet aggregation is advisable only in certain clinical situations (class IIb recommendations) [1, 2]. Nevertheless, despite the recommendations, the discussion about the routine use of platelet function testing continues. It is known that the gold standard for assessing platelet aggregation is light transmission aggregometry [1]. However, the sensitivity of the currently used methods for assessing residual platelet aggregation is often insufficient.

In this work, along with the standard examination of patients with CAD, the assessment of HRPR values by light transmission aggregometry using two methodological approaches was performed. The threshold values of platelet aggregation parameters were determined. Their relationship with myocardial perfusion disorders was evaluated according to myocardial perfusion scintigraphy. Knowledge in this research area is relevant both for clinical and fundamental medicine as well as for development of new diagnostic methods.

The aim of the study was to develop a new methodological approach to assessment of collagen-induced platelet aggregation in CAD patients and to determine the quality of various methods for HRPR detection to predict the risk of myocardial perfusion disturbance.

MATERIALS AND METHODS

A cross-sectional (single-stage) study was performed. The patients were recruited on the premises of Cardiology Research Institute in accordance with the principles of the Declaration of Helsinki. 36 patients with stable CAD who had been receiving continuous antiaggregation therapy for 6 months were examined. The study included patients aged 41–83 years (10 men and 26 women). All the examined patients received regular combination therapy in accordance with current guidelines for CAD treatment. Laboratory and instrumental methods of investigation, including platelet aggregation and ECG-synchronized myocardial perfusion scintigraphy, were used in all the patients in accordance with the recommendations for CAD diagnosis and treatment. The criteria for inclusion in the study were stable CAD and continuous antiaggregation therapy for 6 months (cardiomagnil, 75mg). The criteria for exclusion from the study encompassed non-adherence to the therapy; acute vascular complications less than 6 months ago; severe comorbidities; clinical and laboratory signs of acute inflammation; serum creatinine levels higher than 120 μmol / l; atrial fibrillation; ventricular arrhythmia of high grades in the Lown grading system, and refusal to participate in the study.

A special study to assess platelet aggregation was performed using the Born method, modified by Z.A. Gabbasov on a two-channel laser analyzer 220 LA (BIOLA SCIENTIFIC, Russia) using two methods. Method 1 (standard approach): collagen was used as an aggregation inducer; it was introduced once at a final concentration of 2 μmol / l for 10 seconds. Method 2: five-fold introduction of collagen at 2 μmol / l for 10 seconds with platelet aggregation being measured at 1st, 2nd, 3rd, and 4th minutes of the research. The new methodological approach is described in detail in the patent for the invention RUS 2686700 of 01.08.2018 [4].

Peripheral venous blood with 3.8% sodium citrate as an anticoagulant was used to isolate the platelet suspension. Experimental values of light transmission were determined for each patient's blood sample, where platelet-poor plasma was taken as 100% and platelet-rich plasma was taken as 0% of aggregation in this patient. The maximum value of light transmission was used to determine the degree of platelet aggregation (%). The average aggregate size (r.u.) was used to determine the size of an aggregate. Aggregation values determined by the light transmission curve in the range of 45–100% indicated HRRP in the patients.

Myocardial perfusion scintigraphy (MPS) with 99mTc-methoxy-isobutylisonitrile (99mTc-MIBI) was performed according to the two-day stress-rest protocol. The research was carried out on a hybrid 64-slice Discovery NM/CT 570c scanner (GE Healthcare, USA), equipped with a gamma camera with cadmium zinc telluride (CZT) detectors. An intravenous infusion of adenosine at a dose of 140 mg / kg /min for 4 minutes was used as a stress test. Myocardial perfusion was assessed using specialized software Corridor 4DM SPECT (INVIA, Ann Arbor, MI, USA). According to the generally

accepted approach, myocardial perfusion disorders were determined by the summed stress score (SSS), summed rest score (SRS), and summed difference score (SDS) for the entire left ventricular myocardium [5]. SSS values < 4 were regarded as normal myocardial perfusion.

Statistical data processing was performed using SPSS statistical packages (version 19) and Statistica 10.0. The Shapiro – Wilk test was used to evaluate the distribution of quantitative features. The distribution of quantitative aggregation indicators did not follow the normal distribution law; the aggregation data was represented as the median and the interquartile range *Me* (Q_1; Q_3). MPS data were presented as an absolute value and a relative value (*n*, %). The significance of differences for paired or dependent samples was evaluated using the Wilcoxon T-test. The nonparametric Spearman test was used to evaluate the correlation between variables. ROC analysis was used to determine the sensitivity and specificity of aggregation levels in risk stratification of adverse cardiovascular events. The AUC value > 0.70 was considered significant. To identify factors that have a significant impact on the course of the disease, the odds ratio (OR) was calculated with a 95% confidence interval (CI). The differences between the samples were considered statistically significant at $p < 0.05$.

RESULTS

In the group of the examined patients, the following cardiovascular risk factors were widely distributed: smoking – 27 (75 %) patients, overweight and obesity – 14 (39 %) patients, hypertension – 31 (86 %) patients, dyslipidemia – 33 (92 %) patients, type 2 diabetes – 12 (33 %) patients. Patients with FC III and II angina pectoris (15 (42%) and 11 (30%) patients, respectively) predominated. In the anamnesis, 8 (22%) patients had a Q-myocardial infarction (MI) that occurred 6 months or more before the study. In the majority of cases, the included patients were diagnosed with a multivascular lesion of the coronary arteries (30 (83 %) patients).

The study of platelet aggregation in CAD patients revealed significant differences between the parameters of platelet aggregation and the size of aggregates obtained during the implementation of the standard method, as opposed to the patented method.

Using the new methodological approach developed by us (method 2), it was found that CAD patients showed a significant increase in the size of aggregates and a rise in the degree of platelet aggregation in comparison with the corresponding values obtained during method 1 implementation (Table). Method 1 helped to identify HRPR in 9 (25%) patients. When using method 2, HRPR was detected in additional 8 (22%) patients, which amounted to 47% of all patients.

The indications for MPS in 16 (39%) patients were the diagnosis of CAD with pretest probability of 16–85%, in 12 (33%) patients – assessment of myocardial perfusion and the state of coronary stents, in 8 patients (22%) – assessment of coronary artery bypass grafts. According to MPS data, in 7 (19%) patients, myocardial perfusion at stress was within the normal values (SSS < 4). Minimal myocardial perfusion disturbance (SSS 4–8) was observed in 14 (39%) patients, moderate (SSS 9–13) – in 9 (25%) patients, and severe (SSS > 13) – in 6 (22%) patients.

Table

Parameters of platelet aggregation and logistic regression of patients with CAD according to two methods

Parameter	Method 1			Method 2		
	Aggregation values *Me* (Q_1; Q_3)	OR	95% CI	Aggregation values *Me* (Q_1; Q_3)	OR	95% CI
Degree of aggregation, %	12 (5; 64)	1.46	0.58–0.93	44 (13; 78)*	2.18	0.57–0.98
Size of aggregate, r.u.	3 (2; 7)	1.79	0.61–0.95	5 (4; 8)*	5.83	0.72–0.99

* difference between the methods with the level of statistical significance $p < 0.05$.

A correlation analysis showed the presence of associations between the aggregation degree and the size of the aggregate according to method 1 and the value of SSS of an average-strength relationship ($r = 0.54$ and $r = 0.61$, respectively; $p < 0.002$). Method 2 revealed a high-strength relationship ($r = 0.78$ and $r = 0.61$, respectively; $p < 0.002$).

The results of a logistic regression analysis showed that platelet aggregation parameters obtained in method 2 were associated with an increased risk of myocardial ischemia (Table).

To study and compare the diagnostic and prognostic characteristics (sensitivity and specificity) of various methods for evaluating aggregation activity,

a ROC analysis was performed. The indicator of the presence (absence) of myocardial ischemia was used as a predictor. According to the results of the ROC analysis, the study of platelet aggregation in CAD patients using method 1 revealed the presence of myocardial perfusion disturbances with an increase in the degree of aggregation ≥ 16.6% ($p < 0.0001$) and the size of the aggregates ≥ 2.97 r.u. ($p < 0.0004$). Method 2 was characterized by greater specificity. Thus, it was shown that method 2 allowed for diagnosis of myocardial perfusion disturbances at the degree of aggregation ≥ 44.9% ($p < 0.0001$) and an increase in the size of the aggregates ≥ 4.80 r.u. ($p < 0.0001$) (Figure).

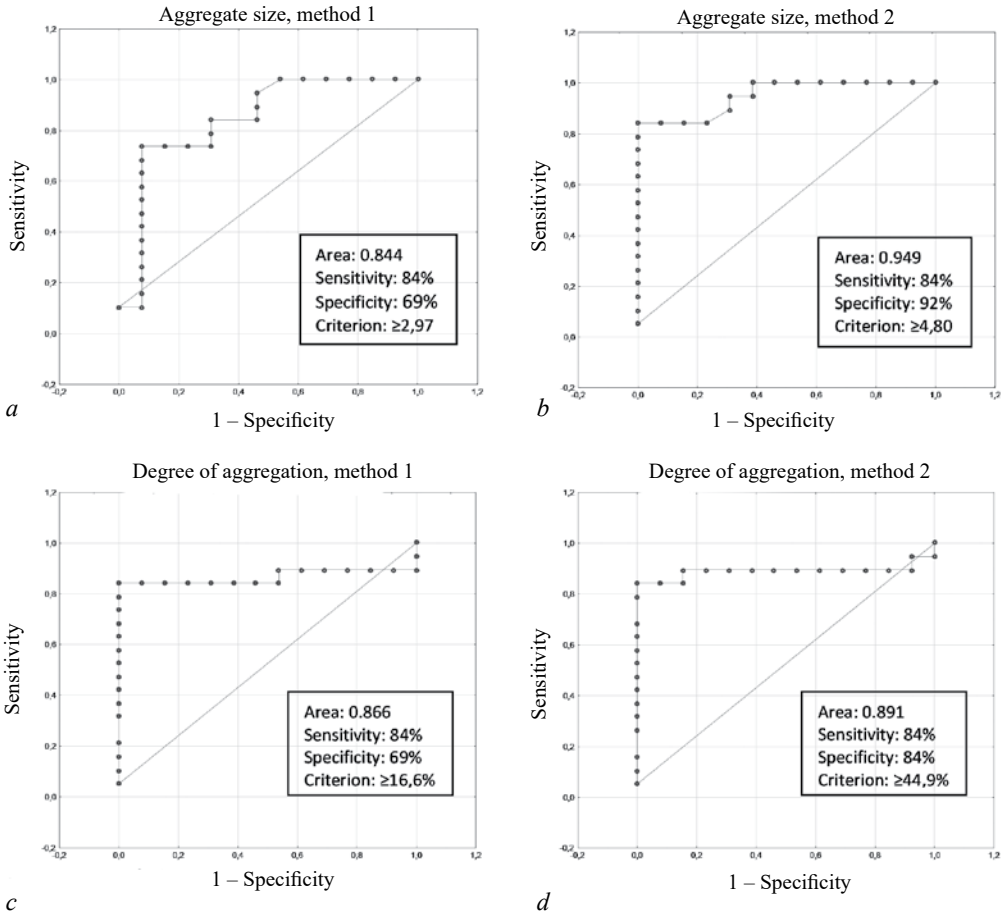

Figure. ROC analysis of platelet aggregation in patients with CAD using two methods as a predictor of myocardial ischemia: *a* – aggregate size (method 1), *b* – aggregate size (method 2), *c* – degree of aggregation (method 1), *d* – degree of aggregation (method 2)

DISCUSSION

Modern therapy in a hospital setting is very expensive, so the search for simple and inexpensive diagnostic tests is becoming more and more relevant. The discussion about the feasibility of studying platelet aggregation in CAD patients is still ongoing, which determines the need for research in this area.

The present study is an open, single-center, and cross-sectional observation. In the conducted study, light transmission aggregometry determined the threshold values of aggregation parameters for this subpopulation of CAD patients. Reaching these parameters meant that patients had HRPR. According to the standard method 1, the conclusion about the presence of myocardial ischemia can be made at the degree of aggregation ≥ 16.6% and the average size of aggregates ≥ 2.97 r.u. In the study of aggregation by method 2, the threshold values were 44.9 % for the degree of aggregation and 4.80 r.u. for the size of the aggregates. In addition, it was shown that standard aggregation research methods are not always sufficient to detect HRPR. The use of increased concentrations of a collagen inducer, added five times during the platelet aggregation study, increases the accuracy of evaluating collagen-induced aggregation in patients with CAD.

Data on the relationship between the risk of developing cardiovascular complications and insufficient suppression of platelet activity in CAD patients remain contradictory. The results of several independent meta-analyses involving more than 10,000 patients showed that HRPR was associated with a significant increase in the incidence of MI, stent thrombosis, and death from cardiovascular causes [2, 5, 6]. At the same time, there is evidence that there is no relationship between cardiovascular risk and HRPR in patients.

Therefore, the VerifyNow French Registry (VERIFRENCHY) was published, where the prognostic value of assessing the platelet function was studied. The results of a one-year follow-up did not reveal significant differences in the frequency of certain (probable) stent thrombosis, cardiovascular death, or MI (1,001 patients, VerifyNow device, Instrumentation Laboratory, USA) [1]. From our point of view, the negative results obtained in these studies may be associated with the fact that all currently used methods of aggregometry have limited sensitivity, specificity, usability, and predictive value.

In accordance with the data obtained to date, the process of formation of platelet aggregates proceeds in the following way. Damage to a vessel exposes collagen on its wall, which is both a substrate and a strong activator of platelet aggregation. Platelets adhere to the damaged endothelium of the vascular wall with the help of specific collagen receptors, which is one of the triggers in the development of a parietal thrombus of the coronary arteries. Subsequently, the platelets activate one other, forming a platelet thrombus [7, 8]. Therefore, we believe that only repeated addition of the collagen inducer to platelet-rich plasma in the study of platelet aggregation activity can provide objective information about the presence of HRPR in patients. The use of a new methodological approach developed by us with additional introduction of a collagen aggregation inducer in assessment of collagen-induced platelet aggregation allows to obtain additional information about the risk of myocardial ischemia, which determines the novelty of our study.

The ROC analysis results showed that our own patented method (method 2) is more specific for stratifying the risk of developing myocardial ischemia in patients with CAD. The data obtained are consistent with the results of studies by various authors that confirmed the association of HRPR with the development of adverse cardiac complications [1, 2, 5].

Comparison of methods demonstrated that repeated addition of a collagen inducer can detect platelets with high residual activity and a tendency to form large aggregates. The lack of response to a single addition of collagen may be due to partial activation of platelets with a tendency to subsequent disaggregation. Performing an aggregation study using adenosine diphosphate (ADP) or arachidonic acid as inducers may lead to a false conclusion about the effectiveness of antiaggregation therapy, while in reality the propensity of platelets to activate in response to interaction with the damaged endothelium remains elevated. Currently, clinical data indicate that neither acetylsalicylic acid nor clopidogrel in standard doses in the absence of platelet activity control can fully guarantee the effectiveness of antiaggregation therapy aimed at reducing the risk of recurrent acute vascular events [5, 7]. Medications that effectively act on collagen receptors are not currently patented and are not used.

From our viewpoint, the detection of HRPR using a new methodological approach will not only determine an increased cardiovascular risk in patients, but also suggest possible reasons for the ineffectiveness of antiaggregation therapy.

Limitations of the study include its cross-sectional design and a relatively small number of patients examined. However, the results emphasize the need for further research to study the clinical consequences of HRPR in patients with CAD and to improve methods for primary and secondary prevention of cardiovascular events.

CONCLUSION

This paper analyzes the clinical and prognostic significance of HRPR in patients with CAD. We showed that the detection of high rates of collagen-induced platelet aggregation in the patients using our own patented method is associated with the risk of impaired perfusion according to myocardial perfusion scintigraphy. The study of platelet aggregation showed that the newly developed methodological approach to detection of HRPR allowed to determine a high risk of atherothrombotic complications in additional 22% of patients, compared to the standard method.

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Authors contribution

Trubacheva O.A., Gusakova A.M., Kologrivova I.V. – conception and design, carrying out of the experimental part of the study, analysis and interpretation of data, drafting of the manuscript. Suslova T.E., Zavadovsky K.V., Petrova I.V. – critical revision of the manuscript for important intellectual content and final approval of the manuscript for publication. Schneider O.L. – selection of patients, interviewing of patients, carrying out of the required list of examinations.

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