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Platelet aggregation under the conditions of vortex flow *in vitro* in patients with chronic heart failure

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ABSTRACT

Aim. To compare the effect of increased concentrations of aggregation inducers (five-fold addition) under standard conditions and under the conditions of vortex flow *in vitro* on platelet aggregation in patients with chronic heart failure (CHF).

Materials and methods. The study included 28 patients. The activity of platelet aggregation in platelet-rich plasma (PRP) was evaluated according to light transmission curves (%) and the average size of aggregates (relative units (rel. units)). The aggregation inducer was added once at 10 seconds of the study (standard procedure) and five times at 10 seconds, 1, 2, 3, and 4 minutes of the study with a constant stirring rate of 800 rpm. The same parameters were evaluated under the conditions of vortex flow, which was created by changing the stirring rate of the PRP from 800 rpm to 0 rpm and again to 800 rpm by pressing the centrifugation button on the analyzer.

Results. In the course of the study, the size of the aggregates increased in patients with CHF only under the conditions of vortex flow. When a collagen aggregation inducer was added both at the concentration of 2 mmol / l and 10 mmol / l, platelet aggregation parameters increased under the conditions of vortex flow. During the study of epinephrine-induced platelet aggregation in patients with CHF, an increase in the aggregation parameters was revealed, both at five-fold addition of the inducer and under the conditions of vortex flow compared with the standard method.

Conclusion. The proposed methodological approaches to creating the conditions for vortex flow *in vitro* and to five-fold addition of epinephrine showed an increase in the size of the aggregates and the degree of platelet aggregation. Collagen-induced aggregation under the conditions of vortex flow revealed 7 (25%) patients with high residual platelet reactivity (HRPR), and epinephrine-induced aggregation detected 15 (54%) patients with HRPR.

Keywords: aggregation, platelets, collagen, epinephrine, chronic heart failure, residual reactivity

Conflict of interest. The authors declare the absence of obvious or potential conflict of interest related to the publication of this article.

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Агрегация тромбоцитов в условиях «вихревого» потока *in vitro* у пациентов с хронической сердечной недостаточностью

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РЕЗЮМЕ

Цель – сравнительное изучение влияния повышенной концентрации индукторов агрегации при пятикратном добавлении в стандартных условиях и в условиях «вихревого» потока *in vitro* на агрегацию тромбоцитов у пациентов с хронической сердечной недостаточностью.

Материалы и методы. В исследование включены 28 пациентов. Активность агрегации тромбоцитов в богатой тромбоцитами плазме (БТП) оценивали по кривым светопропускания (%) и среднего размера агрегатам (в относительных единицах, отн. ед.). Определение проводили с индуктором агрегации при однократном добавлении на 10-й с исследования (стандартная методика) и при пятикратном добавлении индуктора на 10-й с, 1, 2, 3 и 4-й мин исследования, при постоянном перемешивании со скоростью 800 об/мин. Эти же параметры оценивали в условиях «вихревого» потока плазмы, что достигалось изменением скорости перемешивания БТП с 800 до 0 об/мин и вновь до 800 об/мин с помощью кнопки выключения и включения центрифугирования на анализаторе.

Результаты. В ходе проведенного исследования у пациентов увеличился размер агрегатов только в условиях «вихревого» потока. При добавлении индуктора агрегации коллагена как в концентрации 2 ммоль/л, так и 10 ммоль/л показатели агрегации тромбоцитов увеличились в условиях «вихревого» потока. В ходе исследования эпинефрин-индуцированной агрегации тромбоцитов у пациентов выявили возрастание параметров агрегации, как при пятикратном добавлении индуктора, так и в условиях «вихревого» потока по сравнению со стандартной методикой.

Заключение. Предложенные нами методические подходы по созданию условий «вихревого» потока *in vitro* и по пятикратному добавления индуктора эпинефрина показали увеличение размеров агрегатов и степени агрегации тромбоцитов. Коллаген-индуцированная агрегация в условиях «вихревого» потока позволила выявить 7 (25%) пациентов с высокой остаточной реактивностью тромбоцитов, а эпинефрин-индуцированная – 15 (54%) пациентов.

Ключевые слова: агрегация, тромбоцит, коллаген, эпинефрин, хроническая сердечная недостаточность, остаточная реактивность

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

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Соответствие принципам этики. Все пациенты подписали информированное согласие на участие в исследовании. Исследование одобрено локальным этическим комитетом НИИ кардиологии Томского НИМЦ (протокол № 139 от 18.11.2015).

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INTRODUCTION

Cardiovascular diseases (CVDs) are the main cause of morbidity worldwide, while chronic heart failure (CHF) is a progressive disabling condition with a high mortality rate. Despite advances in treatment, patients with CHF have an increased risk of thrombosis. The causes of thrombosis in patients with CHF include impaired hemodynamics, changes in rheological properties of the blood, coagulation disorders, and increased platelet activity. Platelets are crucial for the development of blood clots in blood vessels [1, 2]. In case of vascular le-

sions, pathological activation of platelets may occur, leading to uncontrolled growth of a blood clot, which causes subsequent ischemic events. High residual platelet reactivity (HRPR) in patients is associated with the development of ischemic events, which has been proven in numerous studies and meta-analyses [2–6].

The mechanisms of platelet aggregation are investigated by standard methods without taking into account turbulence or vortex flow. However, in cardiovascular pathology, the rheology of the blood changes, and vortex flow has strong prothrombotic effects. The adhesion of several platelets creates a snowball effect, inducing pronounced platelet aggregation with high residual reactivity, which results in rapid vessel occlusion. It is known that the gold standard and the most accessible method for assessing platelet aggregation is light transmission aggregometry (LTA), which analyzes aggregation by light transmission curves and aggregate sizes [6]. However, the sensitivity of the methods currently used in routine practice for assessing residual platelet aggregation is insufficient [7]. Therefore, there is a need to search for new promising methods for the diagnosis of increased proaggregant potential of platelets for preventing thrombosis. Thus, the study of platelet aggregation in patients with CVDs under the conditions of vortex flow in platelet-rich plasma (PRP) is relevant. 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 compare the effect of increased concentrations of aggregation inducers (five-fold addition) under standard conditions and under the conditions of vortex flow *in vitro* on platelet aggregation in patients with CHF.

MATERIALS AND METHODS

A single-stage cross-sectional study was conducted. Recruitment of patients was carried out at the Cardiology Research Institute upon planned hospitalization in the Department of Myocardial Pathology (under the guidance of Professor A.A. Garganeeva) in accordance with the principles of the Declaration of Helsinki. The study included 28 patients aged 41–83 years (18 men and 10 women). Inclusion criteria: stable coronary artery disease in combination with functional class (FC) I–III CHF according to the New York Heart Association classification and continuous use of antiplatelet therapy for 6 months. All the examined patients received regular combination therapy in accordance with modern recommendations for the treatment of coronary artery disease with comorbid CHF. Laboratory and instrumental research methods were used in all patients in accordance with the recommendations for the diagnosis and treatment of coronary artery disease with comorbid CHF. Exclusion criteria: non-adherence to therapy; acute vascular complications which occurred no later than 6 months ago; severe concomitant pathology; clinical and laboratory signs of acute inflammation; atrial fibrillation; high-grade ventricular arrhythmia according to the Lown grading system; and refusal to participate in the study.

A special study on assessing platelet aggregation was carried out using the Born method as modified by Z.A. Gabbasov on a laser two-channel analyzer (220 LA, Biola Scientific, Russian Federation). To isolate a suspension of human platelets, peripheral venous blood was used, collected in the morning on an empty stomach in a 7 ml vacuum tube with 3.8% sodium citrate as an anticoagulant, with a 6:1 blood / anticoagulant ratio.

Experimental values of light transmission were determined for each patient's blood sample, where platelet-poor plasma is taken as 0%, and platelet-rich plasma is taken as 100% aggregation in this patient. Platelet aggregation activity in platelet-rich plasma was evaluated by light transmission curves (%) and average size of aggregates (in relative units (rel. units)). The aggregation inducer was added once at 10 seconds of the study (standard procedure) and five times at 10 seconds, 1, 2, 3, and 4 minutes of the study with a constant stirring rate of 800 rpm. The same parameters were evaluated using the method for studying platelet aggregation under the conditions of vortex flow, which was created by a five-time change in the stirring rate of platelet-rich plasma from 800 rpm to 0 rpm and again to 800 rpm, with five-fold centrifugation on the analyzer for 10 seconds, 1, 2, 3, and 4 minutes with a delay of 10 seconds. The five-fold addition of the inducer and creation of vortex flow conditions with changes in the stirring rate were selected experimentally. Collagen and epinephrine (Helena, Great Britain) were used as natural inducers at concentrations of 2 mmol / l (standard procedure) and 10 mmol / l (with five-fold addition of 2 mmol / l of the inducer at 10 seconds, 1, 2, 3, and 4 minutes of the study).

Statistical data processing was carried out using SPSS (version 19) and Statistica 10.0 software packages. The Shapiro – Wilk test was used to assess the distribution of quantitative variables. The distribution

of quantitative aggregation parameters did not follow normal distribution; the aggregation data were presented as the median and the interquartile range *Me* (Q_1; Q_3). The significance of the differences for paired or dependent samples was evaluated using the Wilcoxon T-test. The differences between the samples were considered statistically significant at $p < 0.05$.

RESULTS

Among the recruited individuals, patients with functional class III angina pectoris prevailed (15 (53%) patients); functional class II was established in 11 (30%) cases, functional class I – in 2 (7%) cases. In the anamnesis, 8 (29%) patients had a Q-wave myocardial infarction (MI) ≥ 6 months before. In most cases, patients included in the study were diagnosed with multivessel coronary artery disease (22 (79%) patients). Cardiovascular risk factors were also widespread among the patients: smoking – in 17 (61%) patients, overweight and obesity – in 22 (78%) patients, arterial hypertension – in 20 (71%) patients, dyslipidemia – in 13 (46%) patients, type 2 diabetes – in 13 (46%) patients.

In the course of the study in patients with CHF, spontaneous platelet aggregation indices determined by the standard method were 3.1 (1.5; 4.0) % and 1.7 (1.1; 2.0) relative units. Under the conditions of vortex flow, only the size of the aggregate significantly increased to 5.4 (3.2; 6.1) relative units ($p = 0.04$). The size of the aggregates in patients with cardiovascular pathology should not exceed 4 relative units; an increase in the parameter indicates HRPR. When assessing spontaneous platelet aggregation in vortex flow in terms of the aggregate size, 5 (18%) patients with HRPR were identified among the CHF patients.

The degree of platelet aggregation and the size of the aggregates in patients with CHF with the addition of collagen at a concentration of 2 mmol / l (standard procedure) were 9.3 (2.1; 65.4) % and 3.1 (1.9; 10.1) relative units, respectively. When the stirring rate changed from 800 rpm to 0 and then to again 800 rpm, the aggregation rate significantly increased to 47.9 (40.6; 95.0)% ($p = 0.00$), and the size of the aggregates was 3.8 (1.3; 10.7) relative units. However, these parameters did not exceed the reference values (up to 50% for the degree of aggregation and up to 4.5 relative units for the size of aggregates).

Under the conditions of five-fold addition of collagen at 10 seconds, and 1, 2, 3, and 4 minutes of the study, no significant changes were observed, and the parameters were 22.3 (17.3; 89.6)% for the degree of aggregation and 6.42 (2.1; 39.8) relative units for the size of the aggregates. Under the conditions of vortex flow, the parameters of collagen-induced platelet aggregation increased, the degree of aggregation amounted to 80.1 (13.5; 165.0) % ($p = 0.04$), and the size of the aggregates increased to 32.9 (1.1; 43.7) ($p = 0.00$) relative units. According to the results of the study on collagen-induced aggregation in patients with CHF under the conditions of vortex flow, 7 (25%) patients with HRPR were identified, whereas with five-fold addition of the inducer, no significant differences were identified compared with the standard method.

The parameters of standard epinephrine-induced platelet aggregation in patients with CHF at the inducer concentration of 2 mmol / l were 46.7 (35.8; 66.2)% for the degree of aggregation and 15.0 (11.4; 18.9) relative units for the size of the aggregates. With a change in the stirring speed (800 rpm – 0 rpm – 800 rpm), the parameters significantly increased to 52.7 (41.3; 76.5)% ($p = 0.00$) and 19.4 (17.3; 20.6) ($p = 0.04$) relative units, respectively.

Under the conditions of five-fold addition of epinephrine, only the degree of aggregation significantly increased and amounted to 52.5 (41.9; 74.5)% ($p = 0.03$), while the size of the aggregates remained unchanged and amounted to 15.8 (12.2; 18.4) relative units ($p = 0.02$). Under the conditions of vortex flow, the parameters of epinephrine-induced aggregation significantly increased. The degree of aggregation was 75.4 (62.0; 80.5)% ($p = 0.04$), while the increase in the size of the aggregates was multiple and reached 356.0 (230.5; 462.5) relative units ($p = 0.03$). Thus, during the study of epinephrine-induced platelet aggregation in patients with CHF, we revealed an increase in aggregation parameters, both with five-time addition of the inducer, and under the conditions of vortex flow compared with the standard method. As a result of the study, HRPR was detected in 15 (54%) patients, which was the largest number of detected HRPR cases among all the methodological approaches used.

DISCUSSION

Significant changes in platelet aggregation parameters obtained during the study, with five-fold addition of the inducer and under the conditions of vortex flow, compared with the standard technique, indicate the need to study new methodological approaches to assessing platelet aggregation and identifying patients with residual platelet reactivity to prevent possible ischemic events in CHF patients. Modern therapy in

a hospital setting is very expensive, so the search for simple and inexpensive diagnostic tests is becoming more relevant. Discussion about the relevance of studying platelet aggregation in patients with CHF is still going on, which determines the need for further research in this area [5, 8, 9].

The present work was an open, single-center, cross-sectional study. We have shown that standard methods for studying platelet aggregation are not always sufficient to identify HRPR. The use of increased concentrations of epinephrine with five-fold addition during the research at 10 seconds, 1, 2, 3, and 4 minutes of the study and the use of spontaneous, collagen- and epinephrine-induced platelet aggregation under the conditions of vortex flow with a change in the stirring rate (800rpm – 0rpm – 800rpm) increase the accuracy of aggregation assessment in detecting HRPR in patients with CHF. 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 CVDs [1, 2, 4].

Blood circulating in the vessels under the conditions of a pressure drop impacts blood cells and blood vessel walls [10]. The blood flow is laminar, with a maximum velocity in the center of the vessel lumen and zero velocity at the vessel wall [11]. Biomechanical forces created by the blood pressure are crucial for aggregation or separation of the main components involved in blood clotting. Within normal hematocrit levels (~ 40%), erythrocytes mainly circulate along the central axis of the blood vessel due to axial migration. Consequently, platelets move in close proximity to the vessel walls, which facilitates their binding to adhesive ligands in the reactive endothelial layer in damaged regions of the vessel [11–13]. Under physiological conditions, the flow of blood in large arteries is laminar, but arterial stenosis due to atherosclerotic lesions or pre-existing blood clots can alter the blood flow [8, 10, 14, 15].

Over decades of study, it has been established that platelets are crucial for blood clot formation in healthy and pathologically altered blood vessels. When the integrity of the vessels is impaired, circulating platelets linger at the site of injury, where they aggregate, forming hemostatic thrombi, thereby preventing further bleeding. However, under the conditions of turbulence or vortex flow, transient aggregates are formed without prior activation or shape change, which stabilizes discoid platelet aggregates and leads to uncontrolled growth of unstable and weakly adhered thrombi, which, in turn, can clog a blood vessel or embolize it, causing subsequent ischemic events [16].

The molecular processes that cause pathological blood clotting are in many ways similar to the processes that control physiological blood clotting. The biggest problem of antiplatelet therapy is differentiation between pathological and physiological platelet responses. Currently, antiplatelet drugs that are available on the market are not effective against targeted pathological blood clots without impairment of normal hemostasis. Transition from laminar to vortex blood flow, occurring in the bloodstream, leads to platelet aggregation in atherosclerosis. The turbulent blood flow in clogged blood vessels can be two times faster than in healthy vessels. The use of vortex flow in the microenvironment of a blood clot allows to differentiate between thrombosis and physiological hemostasis and develop selective antiplatelet therapy.

It should be noted that modern antiplatelet therapy fails to selectively prevent pathological thrombosis without interfering with the physiological hemostasis. One of the significant differences between these two processes is the difference in the types of blood flow in the vessels, and the pathological turbulent blood is identified in pathological blood clots at the sites of vascular occlusion or atherosclerotic plaque rupture [17]. It is known that no existing, clinically used antiplatelet drug is able to specifically respond to this biomechanical force at the site of pathological thrombosis. Aspirin, which is the gold standard for antiplatelet therapy, cannot completely inhibit platelet aggregation, as shown in numerous studies [18, 19]. In pathological blood flow, selective inhibition of cyclooxygenase-2 can even enhance platelet aggregation by reducing basal production of prostacyclin (prostaglandin I2; PGI 2), a powerful inhibitor of platelet aggregation [20, 21]. To date, there are no methods that would take into account these changes in the blood flow. Analysis of platelet aggregation by the aggregate size curve and the degree of aggregation under conditions of vortex flow proves the possibility of detecting HRPR in patients with CHF, taking into account changes in the blood flow.

The comparison of the methods showed that five-fold addition of the inducer and creation of vortex flow by changing the stirring rate make it possible to identify platelets with high residual activity and a tendency to form large aggregates. From our point of view, identification of HRPR by new methodological approaches will allow to determine increased cardiovascular risk in patients with CHF.

Limitations of the study include its single-stage design and a relatively small number of examined patients. However, the results obtained prove the need for further studies on investigating platelet aggregation and identifying HRPR in patients in order to improve techniques and prevent cardiovascular events.

CONCLUSION

Standard methods for studying platelet aggregation are not always sufficient to detect an increased proaggregant potential of platelets, which is important for the diagnosis and prevention of cardiovascular complications. The proposed methodological approaches to creating the conditions for vortex flow *in vitro* and to five-fold addition of epinephrine in collagen-induced and epinephrine-induced aggregation showed an increase in the size of the aggregates and the degree of platelet aggregation, which proves the prospects of these methodological approaches for detecting HRPR in patients with CHF.

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Authors contribution

Trubacheva O.A., Kologrivova I.V. – conception and design, carrying out of the experimental part of the study, analysis and interpretation of the data, drafting of the article. Suslova T.E., Garganeeva A.A. – justification of the manuscript, final approval of the manuscript for publication. Swarovskaya A.V. – interview and selection of patients, carrying out of the necessary examinations.

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