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Use of increased concentrations of adenosinediphosphate for high residual platelet reactivity in patients with coronary heart disease

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Аннотация

Выявление у пациентов с ишемической болезнью сердца (ИБС) склонности к повышенному тромбообразованию имеет важное прогностическое значение при подборе лекарственных средств, направленных на достижение стойкого антитромботического эффекта. **Цель исследования** – оценить использование повышенных концентраций индуктора АДФ для повышения точности АДФ-индуцированной агрегации тромбоцитов пациентов с ишемической болезнью сердца. **Материал и метод.** Исследовано 48 пациентов с ИБС, находящихся на непрерывной двойной антиагрегационной терапии в течение 6 месяцев (аспирин 75мг и клопидогрель 75мг в сутки). Агрегационную активность суспензии тромбоцитов исследовали с помощью метода Борна Г. в модификации Габбасова З.А.. Активность тромбоцитов оценивали по степени агрегации богатой тромбоцитами плазмы по кривой светопропускания под влиянием индуктора аденозиндифосфат (АДФ) в концентрации 2 мкмоль/л и по собственной запатентованной методике на фоне дополнительного внесения АДФ. **Результаты.** У пациентов агрегация тромбоцитов снижалась до 5-35% ($p < 0,005$) по сравнению с нормативными значениями, которые составляют 50-60%. При этом значения агрегации тромбоцитов при дополнительном внесении индуктора агрегации АДФ в соотношении 2:1 по 2 мкмоль/л на 1, 2, 3 и 4 минутах регистрации агрегации тромбоцитов, приводила к повышению показателя агрегации от 55% до 75% ($p < 0,001$), что свидетельствует о высокой остаточной реактивности тромбоцитов на фоне двойной антитромбоцитарной терапии. Также были выявлены корреляционные связи степени агрегации на повышенные концентрации АДФ с многососудистым артериальным поражением и дислипидимией $r=0,86$ и $r=0,92$, соответственно. **Заключение.** Использование повышенных концентраций аденозиндифосфата при агрегации тромбоцитов у пациентов с ишемической болезнью сердца повышает

точность оценки АДФ-индуцированной агрегации тромбоцитов на фоне приема двойной антиагрегантной терапии и способствует выявления высокой остаточной реактивности тромбоцитов.

Ключевые слова: тромбоцит, агрегация, аденозиндифосфата, ишемической болезнью сердца, остаточная реактивность тромбоцитов.

Abstract

Detection of a tendency to increased thrombosis in patients with coronary heart disease (CHD) is of important prognostic value in the selection of drugs aimed at achieving a persistent antithrombotic effect. The aim of the study was to evaluate the use of elevated ADP inducer concentrations to improve the accuracy of ADP-induced platelet aggregation in patients with coronary heart disease. **Material and method.** Material and method. We studied 48 patients with CHD who were on continuous double antiplatelet therapy for 6 months (aspirin 75mg and clopidogrel 75mg per day). The aggregation activity of the platelet suspension was studied using the Born method G. in the modification of Gabbasov Z. A. Platelet activity was evaluated by the degree of aggregation of platelet-rich plasma along the light transmission curve under the influence of the inducer adenosine diphosphate (ADP) at a concentration of 2 mmol/l and by its own patented method against the background of additional ADP application. **Results.** In patients, platelet aggregation decreased to 5-35% ($p < 0.005$) compared to the standard values, which are 50-60%. The values of platelet aggregation with the additional introduction of the inducer of aggregation ADP in a ratio of 2:1 to 2 $\mu\text{mol/l}$ for 1, 2, 3, and 4-minute registration of platelet aggregation, resulted in increased aggregation from 55% to 75% ($p < 0.001$), indicating high residual platelet reactivity on the background of double antiplatelet therapy. Correlations of the degree of aggregation for elevated ADP concentrations with multivessel arterial lesion and dyslipidemia were also found, $r = 0.86$ and $r = 0.92$, respectively. **Conclusion.** The use of elevated concentrations of adenosine diphosphate in platelet aggregation in patients with ischemic heart disease increases the accuracy of assessing ADP-induced platelet aggregation against the background of dual antiplatelet therapy and contributes to the detection of high residual platelet reactivity.

Key words: platelet aggregation, adenosine diphosphate, ischemic heart disease, residual platelet reactivity.

Cardiovascular diseases remain the leading cause of death and disability in most European countries, especially when combined with risk factors such as oxidative stress, obesity, hypertension, and type 2 diabetes [1,2]. In addition, the detection of a tendency to increased thrombosis in patients with coronary heart disease (CHD) is of important prognostic value in the selection of drugs aimed at achieving a persistent antithrombotic effect [3,4,5]. To date, drugs of the antiplatelet group occupy one of the leading places in the prevention of CHD [6,7,8,9]. However, repeated cardiovascular events, deterioration of patients' condition, and indications for surgical treatment force doctors to prescribe double antithrombotic therapy [6].

According to the recommendations of the Committee on practice guidelines and the European society of cardiology, an annual increase in the number of patients who have indications for dual antiplatelet therapy (DAT), involving a combination of aspirin and an oral P2Y₁₂ receptor inhibitor of platelets to adenosine 5'-diphosphate [10,11]. However, there is still no consensus on the choice of the optimal scheme and duration of DATT in patients with CHD who receive drugs of the antiplatelet group [4,8,11,12]. High platelet reactivity when taking P2Y₁₂ receptor inhibitors is associated with the risk of ischemic events [5,13]. These data contribute to the justification of individual antiplatelet therapy based on monitoring of platelet function, in order to identify patients with insufficient response, but even dual therapy in some cases leads to the development

of individual platelet resistance to antiplatelet therapy [9,14,15]. The role of platelets in the development of arterial thrombosis was established in an experiment and proved by clinical studies that showed the effectiveness of antiplatelet drugs in relation to the risk of heart attacks and strokes in patients with various forms of CHD [5,13,15]. It is known that the classical method for assessing platelet aggregation is light transmission aggregometry [16]. Adenosine diphosphate (ADP) is used as an aggregation inducer. ADP, released from damaged cells into the vascular bed, is one of the most important physiological stimuli of platelets. ADP receptors on platelets differ from purine receptors of other cells, primarily in that for them ATP is an antagonist, and not an agonist, as in the case of other cells. Platelet activity against the background of an ADP inducer is indicated by the increasing degree of light rays passing through the platelet suspension [16]. At the same time, in patients with CHD who take aspirin and clopidogrel for 6 months, the presence of increased platelet activity is a sign of individual platelet resistance to dual antiplatelet therapy.

The aim of the study was to evaluate the use of elevated ADP inducer concentrations to improve the accuracy of ADP-induced platelet aggregation in patients with coronary heart disease taking aspirin (75 mg) and clopidogrel (75 mg) for at least 6 months.

Material and method. A single-stage cross-sectional study was performed. We studied 48 patients with coronary heart disease who were on continuous double antiplatelet therapy for 6 months (cardiomagnil 75 mg and clopidogrel 75 mg). The aggregation activity of the platelet suspension was studied using the Born G. method modified by Gabbasov Z. A. on a two-channel laser analyzer (220 LA "NPF Biola", Russia). The degree of aggregation was estimated by the light transmission curve in %. For each patient's blood sample, experimental light transmission values were determined, which leads to individual calibration of the device, where platelet-rich plasma is taken as 0%, and platelet-poor plasma is taken as 100% aggregation in each patient. Platelet activity was evaluated by the degree of aggregation of platelet-rich plasma along the light transmission curve under the influence of the adenosine diphosphate (ADP) inducer at a concentration of 2 mmol / l and against the background of additional ADP application of 2 mmol / l at 1,2,3 and 4 minutes of the study according to our own patented method [10]. The data were analyzed using the Statistica 10.0 program. The differences were considered significant at a significance level of $p < 0.05$. Correlation analysis was performed using Spearman's method.

Results and discussion. In patients with ischemic heart disease, taking aspirin and clopidogrel for at least 6 months, platelet aggregation decreased to 5-35% ($p < 0.005$) compared to the standard values, which are 50-60%. The values of platelet aggregation with the additional introduction of the inducer of aggregation ADP in a ratio of 2:1 to 2 $\mu\text{mol/l}$ for 1,2,3 and 4 minute registration of platelet aggregation, resulted in increased aggregation from 55% to 75% ($p < 0.001$), indicating high residual platelet reactivity on the background of double antiplatelet therapy (aspirin 75mg and clopidogrel 75mg per day). Correlations of the degree of aggregation for elevated ADP concentrations with multivessel arterial lesion and dyslipidemia were also found, $r = 0.86$ and $r = 0.92$, respectively. The presence of high residual platelet reactivity against the background of double antiplatelet therapy in patients with CHD was not detected using the generally accepted method of platelet aggregation, but is detected only in conditions of additional and repeated introduction of an ADP inducer. (aspirin 75mg and clopidogrel 75mg per day). This may be due to an increased content and incomplete response of platelets with a tendency to disaggregate on a single ADP addition, and, consequently, a "false positive" result on the therapy. Increased values of platelet aggregation in patients with CHD are important in the selection of therapy aimed at reducing thrombosis and preventing cardiovascular events, which allows optimizing the individual selection of therapy.

Conclusion. The study proves that standard diagnostic methods are not always sufficient to detect high residual reactivity of platelets to double antiplatelet therapy. The use of elevated concentrations of adenosine diphosphate in platelet aggregation in patients with coronary heart disease increases the accuracy of assessing ADP-induced platelet aggregation against the background of antiplatelet agents.

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