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The current state of the problem of aspirin resistance in ischemic heart disease

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Abstract
From the standpoint of evidence-based medicine, the prescription of antiplatelet drugs for the primary and secondary prevention of acute cardiovascular events is an essential component of the pharmacotherapy of ischemic heart disease (IHD). Currently, one of the most prescribed drugs for oral antiplatelet therapy for cardiovascular diseases, the "gold standard" is acetylsalicylic acid (ASA), which has the greatest evidence base among all antiplatelet drugs. However, recently there has been an increasing number of concerns where it has been shown that a third of patients develop resistance to aspirin, especially in patients who take it for a long time in low doses. A serious problem remains the relatively high frequency of recurring ischemic events in these patients, and they seem to have a worse prognosis than patients with clear ASA-dependent do inhibition of platelet function. This phenomenon, called aspirin resistance, dictates the need for a differentiated approach to the prevention and treatment of IHD.
The article is about current problems of aspirin resistance to antithrombotic therapy in IHD. The question of the etiological factors and epidemiology of aspirin resistance is being considered. Various laboratory methods for evaluating this phenomenon are given.

Keywords: ischemic heart disease, aspirin resistance, platelet aggregation

Introduction

Coronary heart disease (CHD) in prevalence and risk of complications for more than half a century has been a leader in the list of the most significant social problems, as well as leading to temporary and permanent disability of the population in the world [1, 2]. The prevalence of coronary heart disease by 2030 will increase by 9.3%, and direct medical costs will increase by 198% compared with those in 2010 [3].

Among the main etiopathogenetic factors of IHD, coronary atherosclerotic thrombosis is considered as the main factor in the progressive course of the disease, the development of acute coronary syndrome, as well as sudden fatal events [4]. Platelets play a central role in the pathophysiology of CVD: platelet activation and aggregation is one of the key mechanisms of blood clot formation. Thrombosis is the immediate primary cause of almost all occlusive vascular events. Hypercoagulation, a slowdown in blood flow, and a decrease in the process of fibrinolysis can also lead to the formation of a thrombus [5]. Increased platelet aggregation activity in coronary heart disease is associated with hypertrombocytosis, increased platelet aggregation function (spontaneous and induced), level and multidimensionality of von Willebrand factor [6].

Therefore, antiplatelet drugs play a significant role in the treatment of these diseases. The appointment of antiplatelet agents reduces the functional activity of platelets, thereby preventing their response to aggregation-inducing effects of pathophysiological processes of post-infarction remodeling of the cardiovascular system.

For several decades, aspirin (acetylsalicylic acid ASA) has been known as a drug with antiplatelet properties and is the most widely used in CVD patients for the prevention of thrombotic and vascular complications [7]. Aspirin, the effectiveness and safety of which is confirmed by numerous controlled studies and meta-analyzes, is today considered as the "gold standard" of antithrombotic therapy. In other words, the treatment of ASA is recognized as an indisputable standard in preventing the complications of atherosclerosis with the help of drugs that affect the platelet link of hemostasis. ASA has firmly entered into clinical practice in the treatment of coronary heart disease with the goal of secondary prevention of cardiovascular complications in high-risk patients [8].

The mechanism of action of acetylsalicylic acid is well understood. It inhibits platelet cyclooxygenase and vascular endothelium, which is involved in the metabolism of arachidonic acid during the formation of thromboxane A2 (platelet aggregate and vasoconstrictor) and prostacyclin (disaggregant and vasodilator). ASA, inhibiting cyclooxygenase-1, inhibits platelet aggregation and blood clot formation in vessels through the blockade of the synthesis of thromboxane A2 (TAX2) in platelets from arachidonic acid. Along with this mechanism, ASA also has other unique properties that distinguish it from other disaggregants: the ability to inhibit the formation of fibrin by inhibiting the formation of thrombin and block lysine in fibrinogen molecules, as well as activate fibrinolysis by releasing plasminogen activators and “loosening” fibrin fibers.

To date, the results of more than 100 randomized trials are known, according to which taking high-risk aspirin by patients reduces the risk of vascular death by ~ 15%, non-fatal vascular events by ~ 30% (Patrono C, *et al*., 2005, Antithrombotic Trialists' Collaboration, 2002) The effectiveness of the use of acetylsalicylic acid for primary and secondary prevention of fatal complications of lesions of arteries of various vascular pools has been confirmed by a large number of controlled clinical studies

[9]. An analysis of the results showed that the administration of ASA in patients with a stable course of cardiovascular disease reduces the risk of all cardiovascular events by 21%, the risk of MI by 26%, the risk of stroke by 25% and the risk of all deaths by 13%; with unstable angina pectoris leads to a decrease in death and myocardial infarction by more than 50% [6].

At the same time, far from all patients, aspirin effectively suppresses platelet function. There was evidence that - in a third of patients, aspirin does not work [10]. According to the data (RG Kiss, 2002, WH Chen, 2004, JW Eikelboom, 2002, PA Gum, 2001), 35% of people have a reduced anti-aggregation response to aspirin use, and 19% of the patients did not show any effect of aspirin on aggregation platelet count. This phenomenon, called aspirin resistance (AR), dictates the need for a differentiated approach to the prevention and treatment of coronary heart disease.

Aspirin resistance is the inability of ASA to prevent the development of thrombotic complications, the basis of which is the inability to inhibit the synthesis of TxA2, as well as the reduction of platelet aggregation, revealed by the data of certain laboratory tests [11, 12]. The development of strokes, myocardial infarction, and other thrombotic complications in patients who have been taking ASA for a long time is called clinical aspirin resistance [13]. Laboratory or biochemical aspirin resistance is also distinguished - the inability of ASA to suppress platelet aggregation due to insufficient inhibition of thromboxane production, detected by functional tests [14, 15, 16]. A correlation was noted between laboratory signs of aspirin resistance and the clinical course of IHD. About 70-75% of non-fatal and 80-85% of fatal events are not prevented by taking aspirin, as well as other drugs used for the secondary prevention of IHD (statins, p-blockers, ACE inhibitors) (Hennekens CH. Elal. 2004). In such patients, increased platelet activity remains, despite ongoing antiplatelet therapy, which is associated with the risk of recurring cardiovascular events (Matetzky S, *et al*., 2004; Bonello L, *et al*., Working Group on High On-Treatment Platelet Reactivity, 2010).

The first data showing a decrease in the effectiveness of aspirin in some patients were obtained among patients with cerebrovascular disease: approximately a quarter achieved partial suppression of platelet aggregation, in a third of patients aspirin resistance develops after a long time, even despite an increase in the dose of aspirin (Patrono 2001). Therefore, it is believed that aspirin resistance is associated with a deterioration in the clinical prognosis of the disease. Thus, the HOPE and CHARISMA studies demonstrated that higher levels of 11-dehydro-thromboxane B2 in the urine (TxA2 metabolite and potential aspirin insensitivity biomarker) corresponded to an increased risk of cardiovascular catastrophes [6].

Currently, the most likely causes of aspirin resistance are

- Increased formation of metabolites of arachidonic acid along the lipoxygenase pathway, leading to inhibition of prostacyclin synthesis in endothelial cells, despite a decrease in thromboxane A2 production;
- Low patient adherence to aspirin treatment (in 2% of patients) or inadequate dosage;
- Cyclooxygenase gene polymorphism leading to the synthesis of an aspirin-sensitive or aspirin-resistant isoform of the enzyme;
- Polymorphism of the GP IIb / IIIa glycoprotein gene, causing the synthesis of glycoproteins with increased affinity for fibrinogen [17, 18];
- Endothelial dysfunction, accompanied by an increase in the activity of von Willebrand factor and a decrease in the level of prostacyclin [19];
- Hypercholesterolemia, increasing the rigidity of platelet membranes and degrading sensitivity of glycoprotein receptors [20];
- The combined use of non-steroidal anti-inflammatory drugs (NSAIDs) and aspirin (due to changes in the spatial configuration of the active center of COX-1) [21];
- Metabolic syndrome, that up to 30% of patients with MS are insensitive to aspirin [22, 23, 24, 25];
- Chronic hyperglycemia is the intensification of glycation of platelet proteins and coagulation factors that can interfere with acetylation processes and, thus, lead to an inadequate anti-aggregation effect of aspirin [26]
- Clinical features: female, old age, the prevalence of atherosclerosis, arterial hypertension, diabetes mellitus, obesity, infection / inflammation, heart failure, smoking, obstructive pulmonary disease, hyperuricemia, severe physical exertion and stress [27, 28, 29, 30].
- Currently, standardized techniques are actively being developed that can predict the effectiveness of ASA [11].

Methods for the study of platelet aggregation ability.

1. Quality

- Qualitative express-method of visual assessment on a glass slide according to A.S. Shitikova;
- High-quality test method according to R.M. Biggs
- Hemolysate-aggregation test according to Z.S. Barkagan, B.F. Arkhipov and V. M. Kuchersky;

2. Quantitative

- The Bourd and O'Brien Gold Standard Turbidimetric Optical Method
- The fluctuation method according to Z.A Gabbasov
- Impedance aggregatometry
- Luminescent aggregometry

Qualitative changes in the methodology for the study of platelets began around the middle of the 20th century. An important stage was the emergence of methods for the isolation of platelets isolated from other blood cells, and then from plasma components. The main methodological breakthrough in the study of platelet physiology occurred in the early 1960s, when two scientists from the UK - Bourne and O'Brien independently developed a simple optical method for measuring platelet aggregation [31]. This is still the most widely used test for detecting and diagnosing platelet function defects using commercially available aggregometers.

The effectiveness and safety of antiplatelet therapy in the early and long-term after a vascular event can be evaluated as a clinical analysis and as laboratory methods, which include the study of spontaneous platelet aggregation.

Spontaneous platelet aggregation (CAT) is the process of the formation of microaggregates, initiated by stirring a suspension of platelets without the addition of exogenous inducers. Most of the methods for studying spontaneous platelet aggregation can be

divided according to the principle of their implementation into two main groups:

1. optical (measuring the optical density of a platelet suspension);
2. visual (direct morphological assessment of aggregated platelets or a change in their number).

Both the presence of platelet aggregates in the test plasma or whole blood and the aggregation activity of platelets in response to non-specific stimuli (prolonged rotation in a centrifuge, shaking) are evaluated. Sometimes the presence of spontaneous platelet aggregation is assessed by the degree of their disaggregation. The most common method for assessing both induced and spontaneous platelet aggregation is the Born turbodimetric method [32], based on the study of changes in the optical density of the plasma.

The study of spontaneous platelet aggregation using laser aggregometers.

The method was proposed in 1989 by Z.A. Gabbasov *et al*. [33], based on the analysis of fluctuations in light transmission (FSP) caused by a random change in the number of particles in the optical channel. The advantage of this method is that the relative dispersion of such fluctuations is proportional to the average size of the aggregates and is used to study the kinetics of aggregation. The method is highly sensitive, which makes it suitable for the study of spontaneous aggregation, aggregation under the action of low concentrations of inducers, as well as aggregation of subcellular particles and macromolecules. The disadvantage of this method is that the aggregation index reflects only a relative increase in the average radius of the aggregates and is equal to zero in the absence of aggregation. This method is used in optical aggregometry using a 230-LA laser analyzer (NPF Biola) with computer processing using the AGGR program. Solutions of adenosine diphosphate (ADP) with final concentrations of 10 and 5 μg / ml are used as aggregation inducers. The presence of a release phase along the aggregation curve while taking ASA was considered the presence of AAP (Fig. 1).

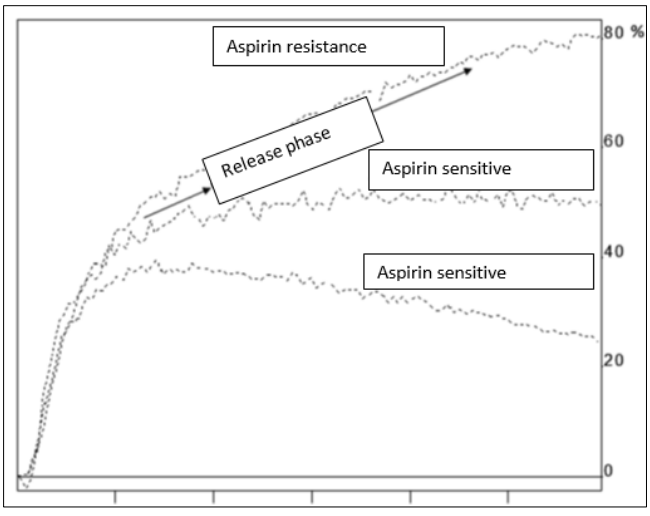

Fig 1: Platelet aggregation curves with the addition of ADP in high concentrations in patients resistant and sensitive to ASA.

Aggregate parameters. For a quantitative description of aggregation, apply such parameters as:

1. Degree of aggregation - is estimated by the maximum amplitude of the aggregatogram, which corresponds to the maximum increase in resistance on the electrode after making the inductor;
2. Aggregation rate - estimated by the amplitude of the aggregate for 1 min after the start of aggregation;
3. Delay time - estimated by the time in seconds elapsed after the addition of the inductor and before the start of aggregation registration;
4. The area under the aggregation curve is the product of the amplitude and the speed of its achievement.

In addition, there are other methods - impedance aggregation of whole blood, PFA-100, VerifyNow, thromboelastography.

Microscopic (visual) CAT research methods.

Light microscopy of sediment. When centrifuging a platelet-rich plasma, a precipitate is obtained to determine the ratio of the number of separately lying platelets and their aggregates, consisting of 3-5 or more cells. Normal platelet aggregates are not detected.

The PAT I method is based on microscopic examination of platelet-rich plasma. Aggregates are visible in pathology, while normal platelet accumulations are absent. Atomic force microscopy (AFM). This method is based on morphological and functional analysis of platelets with the release of adhesion stages (platelets have extended pseudopodia), release and aggregation reactions (platelets lose granules and look like flattened "platelet shadows").

Method N.I. Tarasova. With this method, platelet loss from whole citrate blood is taken into account after 3 minutes of agitation at a speed of 90-100 times in 1 min. With an increased tendency to aggregation, the difference in platelet count increases. Normally, it does not exceed 20%.

K.K. Method Wu and J.C. Hoak modified S.K. Bowry. This method is based on the calculation of platelets from venous blood in a solution containing EDTA and formalin (solution A) and only EDTA (solution B). There is no CAT in the venous blood of healthy people.

Other research methods for CAT

- Scanning flow cytometry method. In this method, for the assessment of CAT using monoclonal antibodies, levels of activated glycoproteins (GP Ib and GP IIb / IIIa), platelet factor 4 and β-thromboglobulin, or the isolation of L- and P-selectin are recorded;
- The method of recording platelet loss is based on determining the percentage of platelet count before and after shaking. The severity of CAT is judged by the level of platelet reduction. CAT and induced platelet aggregation (IAT) are investigated by impedance aggregometry. The method is based on determining the thickness of the layer of cells and the resistance at the electrode, which increase in proportion to the intensity of aggregation.

In the study of IAT, agents that are not alien to the body in chemical composition and can cause thrombosis are used as an

inducer substance. The components of the vascular wall are used as inducers: adenosine diphosphate (ADP), ristocetin (ristomycin), collagen, serotonin, arachidonic acid, adrenaline, thrombin [34].

A common problem for all of the above laboratory methods for assessing the effectiveness of ASA is the lack of standardization and generally accepted reference intervals. This led to a lack of consensus on the optimal method for quantifying AR and the feasibility of such a study in practice, which requires further study of the evidence regarding the predictive and diagnostic accuracy of the tests [35, 36, 37, 38].

Speaking about the problem of resistance to acetylsalicylic acid, we now have more questions than answers. Large multicenter studies and standardization of methods for diagnosing ASK resistance are required.

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