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Cardioprotection: Current Status of the Problem

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Cardiovascular diseases (CVD) have long been recognized by the world community as a problem that has reached the scale of a pandemic [4]. Scientific epidemiological studies both in Russia and around the world constantly demonstrate the global prevalence of major CVDs among the population of different age groups, in particular ischemic heart disease (IHD) and myocardial infarction, recording a high proportion of mortality and disability from these diseases.

According to WHO estimates, in 2016, 56.8 million people died in the world, and the share of non-communicable diseases in the overall structure of causes of death was 71%, compared with 60% in 2000 and 11% at the beginning of the 20th century. Of the 10 leading causes of death in high-income countries, 9 are noncommunicable diseases [13]. Despite a marked downward trend in CVD mortality in high-income countries since the early 1980s, CVD remains the leading cause of death and disability in the world.

In low- and middle-income countries, CVD mortality is more than three quarters of all deaths. Mortality from CVD reaches a critical level in 10 former USSR countries, exceeding 350 cases per 100 thousand population [22]. The number of deaths from CVD in the world in 2016 amounted to 17.9 million people, that is, every third case out of 10 [40].

At the same time, the cause of death of 8.8 million people was coronary heart disease, and 6.2 million - stroke. Experts predict that the burden of CVD

on the world will continue to grow [9]. First of all, this growth will be observed in economically developed countries with a high level of income, which is due to the aging of the population [5,23].

According to available data, in Russia, the economic damage from CVDs in 2016 amounted to 2.7 trillion rubles, which is equivalent to 3.2% of GDP. In the structure of damage among all diseases of the circulatory system, ischemic heart disease ranked first, the financial burden of ischemic heart disease was over 1 trillion rubles [1].

Myocardial infarction (MI) is one of the most important forms of ischemic heart disease. The world community has long recognized cardiovascular diseases (CVD) as a problem that has reached a pandemic scale. Scientific epidemiological studies in Russia and worldwide continuously demonstrate the global prevalence of major CVDs among the population of different age groups, particularly ischemic heart disease (IHD) and myocardial infarction, recording a high proportion of mortality disability from these diseases [30].

The 10 leading causes of death in high-income countries, 9 are non-communicable diseases [36]. Despite a marked downward trend in CVD mortality in high-income countries since the early 1980s, CVD remains the leading cause of death and disability globally. In low- and middle-income countries, CVD mortality is more than three-quarters of all deaths. Mortality from CVD reaches a critical level in 10 CIS countries, exceeding 350 cases per 100 thousand population [2].

The number of deaths from CVD in the world in 2016 amounted to 17.9 million people, that is, every third case out of 10. Simultaneously, the cause of death of 8.8 million people was coronary heart disease and 6.2 million - stroke. Experts predict that the burden of CVD on the world as a whole will continue to grow. First of all, this growth will be observed in economically developed countries with a high level of income due to the aging of the population [27].

According to available estimates, in Russia, the economic damage from CVDs in 2016 amounted to 2.7 trillion rubles, which is equivalent to 3.2% of GDP. In the structure of damage among all circulatory system diseases, ischemic heart disease ranked first; the financial burden of ischemic heart disease was over 1 trillion rubles [3,29]. Myocardial infarction (MI) is a basic form of ischemic heart disease for public health, characterized by high mortality [7,10]. More than 15 million new myocardial infarction cases are noted in the world every year [32]. The problem of high mortality from acute myocardial infarction of the working-age population in most countries is especially urgent. There is no doubt about the concern of repeated MI.

Several researchers have shown that repeated MI (RIM) is characterized by even higher mortality rates in patients compared with primary MI, in which an increase in the availability of timely high-tech treatment tactics plays an important role, as a result of which the proportion of patients who survived after

primary MI, and, consequently, the number of patients with recurrent myocardial infarction increases [6]. In Russia, as in the rest of the world, cardiovascular diseases (CVD) are the leading cause of death [19].

Simultaneously, CVDs are associated with significant socio-economic losses due to the expenditure of health care resources to provide medical care to patients and failures in the economy due to the death of people of working age [28]. In economically developed countries, one of the first stages of justifying the feasibility of introducing preventive interventions and programs is to demonstrate the current economic damage from CVD; this data is used to determine prevention investment. For example, the economic damage from CVD in the United States is estimated at $ 304.6 billion per year [8,12]; a similar indicator in Europe in 2005 amounted to 169 billion euros [38].

Having analyzed the above-mentioned statistical indicators, it is worth noting that the prevention of cardiovascular diseases is a popular field of modern medicine, in particular preventive cardiology. Therefore, the development of the therapeutic potential of cardioprotection looks like a rather promising task [35].

According to modern preventive cardiology concepts, over the past decades, the idea of risk factors has become firmly established in health care, clinical medicine, and public consciousness. Risk factors are factors of the body's external and internal environment, specific individual characteristics, and lifestyle features that contribute to an increase in the likelihood of developing the disease, its progression, and unfavorable outcome. Risk factors are any measurable signs of an individual that predict the possibility of developing the clinically significant disease. This definition of a risk factor is used in the early stages of the disease's study, when the etiology and pathogenesis are not precisely established [16]. This broad definition is broad and does not necessarily imply a causal relationship. Influenced by the environmental factor (environmental characteristics, tobacco smoking), an adjustable variable (blood pressure level, serum cholesterol concentration), depending on the environmental factor (lipid intake with food), or its genetic variant (a defect in low-density lipoprotein receptors - LDL), another disease (hypothyroidism, arterial hypertension or diabetes mellitus) or early or preclinical manifestation of coronary heart disease (phenotypic signs, abnormalities detected by echocardiographic examination, electrocardiographic data) [25].

It is noteworthy that all risk factors have a negative effect on the heart to one degree or another. For example, tobacco smoking through the nicotine contained in it has a vasoconstrictor effect on the coronary arteries, thereby reducing myocardial perfusion. In the context of the above, the role of cardioprotection is also emphasized [37].

Cardioprotection is a complex of pharmacological measures aimed at both normalizing cardiovascular homeostasis and preventing myocardioalteration and necrosis. In the modern pharmaceutical market, there are a large

number of different drugs with cardioprotective activity. However, the only drug recommended by the European Society of Cardiology is trimetazidine [11,24]. It is noteworthy that this drug acts at the cellular level to stabilize myocardial metabolism.

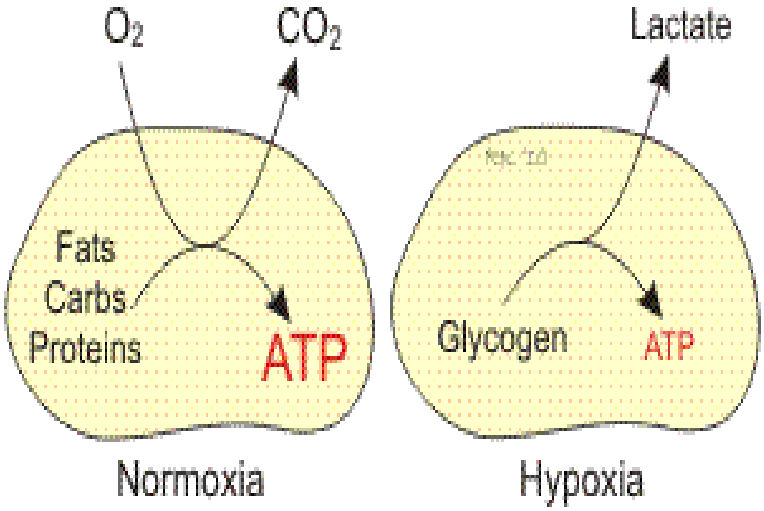

Fig. 1. Plasticity of Myocardial Metabolism[21]

The myocardium is an energy-dependent tissue. Since it requires about 6 kilograms of ATP per day [15]. To maintain an efficient energy supply, striated, cardiac muscle has an advanced coordinated ATP-producing system. There are two mechanisms for maintaining the required amount of ATP in the human body: production and accumulation. The accumulation is not suitable for the heart due to its unique anatomy - most of the cytoplasm consists of myofibrils. According to this fact, in an adult's heart, we observe low concentrations of ATP and many ATP hydrolases. Complete resynthesis of the entire volume of ATP takes only 10 seconds in a normal myocardium [39]. Most of the energy resources (~ 70%) are used for compression, and the rest are used for the operation of the ion pump (K, Na, Ca ATPase pumps). This system is well coordinated to help maintain normal flow: energy substrates and ions [33].

On average, the heart consumes about 20 grams of carbohydrates, 30 grams of free fat acids (FFA), and triglycerides (TG). These substrates are oxidized to 35 liters of oxygen produce ATP from ADP [17].

Oxidative phosphorylation of FFA provides about 60% of all ATP produced, while the oxidation of glucose, lactate, and other carbohydrates produces about 30% of all high-energy compounds. In understanding the myocardium's metabolic characteristics, changes in heart metabolism form the basis for the development of various heart diseases. It is the metabolism-stabilizing effect of Trimetazidine that predicts its effectiveness. [34]

Trimetazidine is an inhibitor of 3-ketoacyls-CoA thiolase. By directly

affecting cardiomyocytes, it optimizes their metabolism and function. Supports myocardial contractility, prevents a decrease in the content of intracellular ATP and creatine phosphate [14]. Under conditions of acidosis, it normalizes membrane ion channels' functioning, prevents the accumulation of calcium and sodium ions in cardiomyocytes, and normalizes the intracellular content of potassium ions. Trimetazidine reduces intracellular acidosis and increased phosphate levels caused by myocardial ischemia and reperfusion [26].

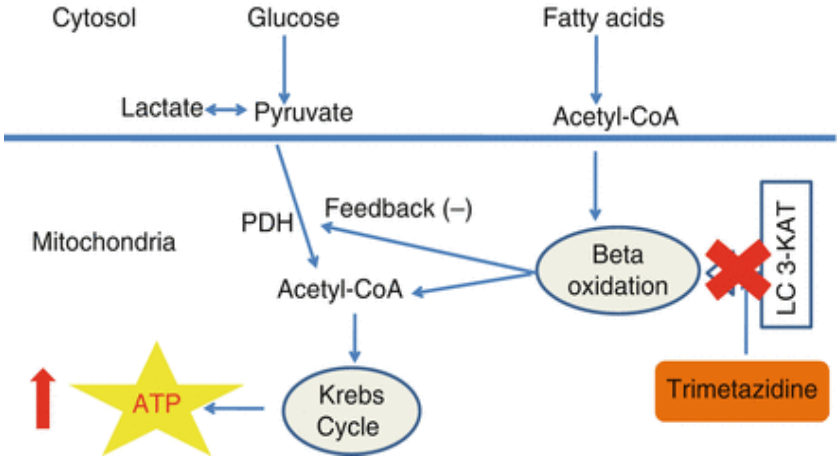

Fig. 2. Molecular mechanisms of Trimetazidine driven cardioprotection[21]

It prevents the damaging action of free radicals (modifies SPOL-induced damage), preserves the integrity of cell membranes, prevents the activation of neutrophils in the ischemic zone, increases the electric potential duration, reduces the release of creatine phosphokinase from cells and the severity of ischemic myocardial damage [31]. With stable angina pectoris, Trimetazidine reduces the frequency of attacks (the consumption of nitrates decreases); after 2 weeks of treatment, exercise tolerance increases, and sharp fluctuations in blood pressure decrease. Recommended daily dose: 40-60 mg / day, frequency of administration 2-3 times/day [18]. The most pronounced therapeutic effect of Trimetazidine was observed in combination with β-blockers. The drug is contraindicated in end-stage renal and hepatic insufficiency [21]. The antianginal and antiischemic efficacy of the combination of β-AB with Trimetazidine are significantly higher than β-AB with prolonged nitrates. Thus, we see that Trimetazidine stabilizes myocardial metabolism and can be used in diseases in the pathophysiological mechanisms of which there [20]:

1) violation of myocardial vascularization (for example, in various forms of ischemic heart disease),

2) disorders of myocardial metabolism (for example, in metabolic cardiomyopathy, anthracycline cardiomyopathy, toxicity, etc.),

3) various rhythm conduction disturbances as a modifier of the developed ischemia.

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Кардиопротекция: современное положение проблемы

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На сегодняшний день факт геометрического роста заболеваний сердечно-сосудистой системы является не решенной задачей современной медицины, решение которой является ургентным и требует организации координированных мероприятий, направленных на повышение как качества жизни, так и прогноза среди пациентов кардиологического профиля. В силу чего изучение молекулярных механизмов фармакодинамики кардиопротекторных препаратов выглядит принципиально важным. В настоящей статье приведены современные мировые данные, отображающие эпидемиологическую картину распространённости сердечно-сосудистых заболеваний. Более того, описываются молекулярные механизмы одобренного со стороны Европейского кардиологического общества препарата триметазидина, широко применяемого в реальной клинической практике в качестве стабилизатора дискоординации интрамиокардиального гомеостаза.

Սրտապաշտպանություն. խնդրի ընթացիկ կարգավիճակը

Ա.Բ. Բաղդասարյան, Ի.Մ. Բիկով, Ն.Վ.Սուլաշվիլի, Օ.Դ. Օստրոումովա, Ա.Վ. Ազնաուրյան

Մինչ օրս սիրտ-անոթային համակարգի հիվանդությունների երկրաչափական աճի փաստը ժամանակակից բժշկության չլուծված խնդիրներից է, որի լուծումը հրատապ է և պահանջում է համակարգված միջոցառումների կազմակերպում՝ ուղղված ինչպես կյանքի որակի բարելավմանը, այնպես էլ սրտի հիվանդությունների կանխատեսմանը:

Հետևաբար՝ սրտապաշտպանական դեղերի ֆարմակոդինամիկայի մոլեկուլային մեխանիզմների ուսումնասիրությունը սկզբունքորեն կարևոր է թվում: Այս հոդվածը ներկայացնում է ժամանակակից աշխարհի տվյալները, որոնք արտացոլում են սիրտ-անոթային հիվանդությունների տարածվածության համաճարակաբանական պատկերը: Ավելին, նկարագրված են Trimetazidin-է թմրամիջոցների մոլեկուլային մեխանիզմները, որոնք հաստատված են Եվրոպայի սրտաբանական հասարակության կողմից, որոնք լայնորեն օգտագործվում են իրական

կլինիկական պրակտիկայում՝ որպես ներսրտային հոմեոստազի անհամաձայնեցման կայունացուցիչ:

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