UDC 612.172.173
DOI:10.54503/0514-7484-2022-62.2-14

Trimeatazidine: Effective Protector of Heart and Vessels

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Key words: cardiotoxicity, trimetazidine, doxorubicin, cyclophosphamide, chemotherapy

Trimetazidine is a cardioprotective drug that normalizes intramyocardial metabolism and stabilizes the ionic potential of cardiomyocyte membranes [17]. The drug directly influences cardiomyocytes and brain neurons and optimizes their metabolism and function. The cytoprotective effect is based on increasing energy potential, oxidative decarboxylation activation, and rationalization of oxygen consumption (increased glycolysis and blockade of fatty acid oxidation).

Trimetazidine maintains myocardial contractility, prevents a decrease in the intracellular content of adenosine triphosphoric acid (ATP) and phosphocreatine. Under acidosis conditions, it normalizes the functioning of membrane ion channels, prevents the accumulation of calciumand sodium ions in cardiomyocytes, and normalizes the intracellular content of potassium ions. Also, trimetazidine reduces intracellular acidosis and elevated phosphate levels. It prevents the heart from the damaging action of free radicals, preserves the integrity of cell membranes, modifies the activation of neutrophils in the ischemic zone, increases the duration of the electrical potential, reduces the release of creatine phosphokinase (CPK) from cells, and thus the severity of ischemic myocardial damage.

Trimetazidine reduces the angina attacks frequency, reduces the demand for nitrates administration. Also, it increases exercise tolerance and contributes to stabile normal blood pressure (BP) achievement.

The myocardium is a highly energy-consuming and energy-independent morphophysiological structure. In the cell, we separate 2 ways of energy supplying regulation-production and accumulation, in the case of the myocardium, energy accumulation is onerous due to the well-developed myofibrillar apparatus of the cardiomyocytes' cytoplasm [11]. Consequently,

only energy generation is possible in the myocardium, and therefore a relatively low content and a high rate of ATP hydrolysis are determined in heart tissue [4]. It is known that a complete turnover of the ATP pool occurs within 10 s. Considering that more than 95% of ATP molecules are synthesized due to oxidative phosphorylation, however, this mechanism of intramyocardial homeostasis is disturbed in heart failure [2].

The regulation of myocardial metabolism is associated with the concentration of gases in arterial blood, hormone levels, coronary blood flow, inotropic state, and the state of the heart tissue itself [10]. The tricarboxylic acid cycle is a source of acetyl-CoA, resulting from the decarboxylation of pyruvate and β-oxidation of fatty acids. Reducing equivalents (NADH and FADH) supply electrons to the electron transport chain, which, in fact, leads to the formation of ATP (due to oxidative phosphorylation) [8]. In a healthy heart, the intensification of the above reactions is determined by the need for external energy generated by the myocardium and the rate of ATP hydrolysis.

It should be noted that there is a stoichiometric relationship between the rate of carbohydrate oxidation, NADH and FADH reduction, electron flow through the electron transport chain, oxygen consumption, oxidative phospho-relation, ATP hydrolysis, actin-myosin interaction, and myocardial contractility [3,5] (Fig.). Thus, an increase in contractility leads to a simultaneous rise in all the listed components of the system.

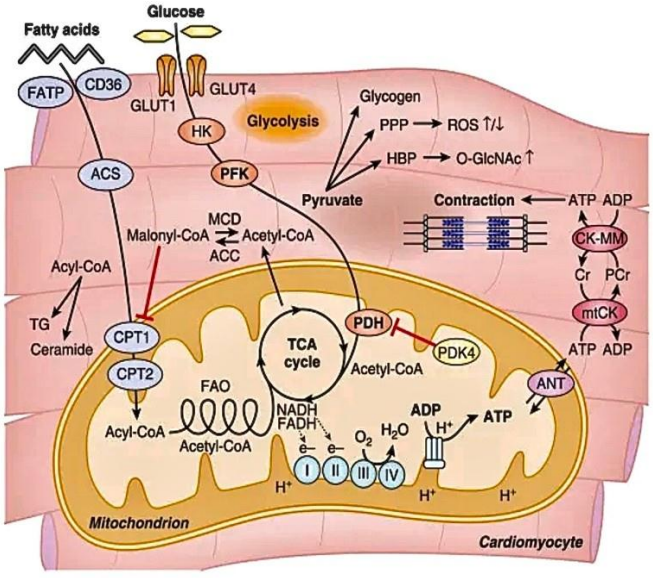

Fig. Biochemical aspect of trimetazidine action [5]

Long-chain free fatty acids (FFA), glucose, glycogen, lactate, pyruvate, as well as ketone bodies and amino acid metabolites, can act as a substrate for intramyocardial ATP production. Such a heterogeneous spectrum of substances

provides certain flexibility of myocardial metabolism; hence the following concepts follow [1]:

1.Myocardial metabolism is adaptive to changes in the internal and external environment. However, in HF, the degree of adaptability decreases significantly.

2.Myocardial metabolism is a self-regulating process; this is explained by the fact that the intermediate links of the tricarboxylic acid cycle are mediators that control the main pathway of energy production.

3.Metabolites can also provide a plastic function.

Thus, myocardial metabolism is a complexly organized functional and biochemical system that ensures the myocardium's coordinative functioning, ensuring its contractile activity and the operation of ion pumps. Therefore, the study of the mechanisms of maintaining normal myocardial metabolism in various pathological conditions looks like a very promising direction.

Currently, trimetazidine is the only cardioprotective medication included in clinical guidelines of noted cardiological societies, such as the European Society of Cardiology and the Russian Society of Cardiology. Trimetazidine is recommended for patients with stable angina [18]. Moreover, a growing body of clinical trial results proves the efficacy of trimetazidine in patients with CHF, including those with diabetes [6].

Trimetazidine, a piperazine compound is widely used in modern clinical practice by cardiologists and internists. This drug belongs to the group of FFA β-oxidation inhibitors [7]. It is known that the FFA oxidation releases a large amount of energy, but this process requires increased oxygen consumption [9]. A shift in metabolism during ischemia towards β-oxidation of FFA is associated with an even more significant increase in myocardial oxygen demand. In contrast, glucose metabolism decreases, which leads to the accumulation of lactate and, in extreme cases, to the development of metabolic acidosis [12]. Thus, trimetazidine selectively inhibits long-chain 3-ketoacyl coenzyme A thiolase (LC 3-KAT), the final enzyme in the FFAβ-oxidation pathway, thereby increasing the rate of glucose metabolism [15].

Trimetazidine also increases pyruvate dehydrogenase activity, restoring glucose oxidation and glycolysis balance during ischemia. This leads to a decrease in oxygen consumption during the synthesis of adenosine-5'-triphosphate (ATP), a limited increase in intracellular acidosis, and a decrease in calcium ions' accumulation in the cytoplasm cardiomyocytes. Correction of energy deficiency leads to stabilization of the plasma membrane and membrane potential [16].

Another mechanism of action of trimetazidine that may be important for patients with CSD, including patients with CHF, is the direct inhibition of cardiac fibrosis, trimetazidine reduces collagen accumulation and CTGF expression in cardiac fibroblasts, as well as NADPH oxidase activity and ROS production, compared with placebo [18].

Data obtained from an immense spectrum of experimental and clinical studies conducted among experimental animals and chronic heart failure patients demonstrated that trimetazidine has cardioprotective efficacy and is also a more unified drug than nifedipine and propranolol because trimetazidine doesn't possess any influence on hemodynamic parameters.

Trimetazidine also exhibits a mitochondrioprotective effect [2], limits ROS generation within cells, and suppresses the infiltration of myocardial tissue by neutrophils. Statistically significant data were also obtained regarding trimetazidine-mediated stimulation of the mir-21 molecule, which modifies the intensification of proapoptotic death of cardiomyocytes by inhibiting the Bax/Bcl-2 and caspase-3 genes.

Summing up the above, it is worth noting that despite the multifaceted study of the problem of cardiotoxicity of chemotherapy drugs, it is far from being finally resolved. The use of trimetazidine in doxorubicin and cyclophosphamide-induced disruption of the functioning of the cardiovascular system, due to the multi-directionality of its pharmacodynamics, can become a very promising direction in the prevention of cardiotoxicity caused by the AC-mode of chemotherapy.

Accepted 23.03.22

Триметазидин: эффективный протектор сердца и сосудов

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Триметазидин, соединение пиперазина, широко применяемое в современной клинической практике кардиологами и терапевтами. Данный препарат относится к группе ингибиторов β-окисления свободных жирных кислот. Известно, что при окислении жирных кислот выделяется большое количество энергии, однако данный процесс требует повышенного потребления кислорода. При ишемии происходит сдвиг метаболизма в сторону β-окисления свободных жирных кислот, что связано с еще большим ростом потребности миокарда в кислороде, в то время как метаболизм глюкозы снижается, что приводит к накоплению лактата и, в крайнем случае, к развитию метаболического ацидоза. Таким образом, триметазидин, селективно ингибируя длинноцепочечную 3-кетоацил-кофермент А тиолазу (LC 3-KAT), которая является конечным фермен-том в пути β-окисления свободных жирных кислот, увеличивает тем самым скорость метаболизма глюкозы.

Տրիմետազիդին. սրտի և անոթների արդյունավետ պաշտպան

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Հ.Վ. Երանոսյան

Տրիմետազիդին պիպերազինային միացությունը լայնորեն օգտագործվում է ժամանակակից կլինիկական պրակտիկայում սրտաբանների և ինտերնիստների կողմից: Այս դեղամիջոցը պատկանում է ազատ ճարպաթթուների β-օքսիդացման ինհիբիտորների խմբին: Հայտնի է, որ ճարպաթթուների օքսիդացումից ազատվում է մեծ քանակությամբ էներգիա, սակայն այս գործընթացը պահանջում է թթվածնի սպառման ավելացում: Իշեմիայի ժամանակ տեղի է ունենում նյութափոխանակության տեղաշարժ դեպի ազատ ճարպաթթուների β-օքսիդացում, ինչը կապված է սրտամկանի թթվածնի պահանջարկի էլ ավելի մեծ աճի հետ, մինչդեռ գլյուկոզայի նյութափոխանակությունը նվազում է, ինչը հանգեցնում է լակտատի կուտակման և ծայրահեղ դեպքերում՝ մետաբոլիկ ացիդոզի զարգացման:

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