Possibilities of traditional medicine in complex correction secondary mitochondrial dysfunction resulting from acute coronary syndrome

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Summary

The review discusses the features of the pathogenesis of acute coronary syndrome (ACS), leading to the development of secondary mitochondrial dysfunction. Methods of laboratory diagnostics of mitochondrial dysfunction, as well as the possibility of drug treatment with traditional medicine in patients with acute coronary syndrome, are discussed in detail.

In recent decades, all over the world, much attention has been paid to the mechanisms of development and principles of treatment of acute coronary syndrome (ACS).

Acute coronary syndrome - any group of clinical signs orsymptoms suggestive of acute myocardial infarction (AMI) or unstable angina pectoris (NS). Includes AMI, ST-segment elevation myocardial infarction (MI), non-ST-segment elevation MI, MI diagnosed by enzyme changes, biomarkers, late ECG signs, and NS. The term appeared in connection with the need to choose treatment tactics before the final diagnosis of the listed conditions. It is used to refer to patients at the first contact with them and implies the need for treatment (management) as patients with MI or NS [1].

Despite the obvious progress of modern medicine in understanding the processes of the pathogenesis of ACS, some of its aspects, from our point of view, need to be supplemented from the point of view of metabolic processes occurring in the mitochondria of affected cardiomyocytes. It should be noted that over the past few decades in medicine, the so-called "metabolic" direction has been intensively developing, which aims at theoretical and applied analysis of metabolic processes at various levels, as a basis or background for many diseases. The ideas about the role of cellular metabolism disorders in cardiovascular pathology are especially actively formed. Metabolism, both at the level of the whole organism and at the level of organs and tissues, is a diverse complex of processes, organized in the most complicated way and providing vital activity of living matter. The key link in this complex is the mitochondria, a general-purpose organelle that performs vital functions for every cell. Taking this into account, it becomes clear that disorders of cellular metabolism, which are based on mitochondrial insufficiency, lead to a wide range of clinical manifestations. These manifestations depend on the degree of involvement in the pathological process of various organs and tissues, including the cardiovascular system - from moderate (functional diseases) to pronounced organic lesions which are based on mitochondrial insufficiency, lead to a wide range of clinical manifestations. These manifestations depend on the degree of involvement in the pathological process of various organs and tissues, including the cardiovascular system - from moderate (functional diseases) to pronounced organic lesions which are based on mitochondrial insufficiency, lead to a wide range of clinical manifestations. These manifestations depend on the degree of involvement in the pathological process of various organs and tissues, including the cardiovascular system - from moderate (functional diseases) to pronounced organic lesions

coronary bed and myocardium (ischemic cardiopathy) [2, 3].

The main role of mitochondria is to provide cells with energy. Energy is generated by ATP molecules in the biochemical cycles of cellular respiration. The severity of the pathological process in a particular organ is associated with the degree of dependence of its tissue elements on aerobic respiration. The main biochemical processes in mitochondria are the tricarboxylic acid cycle, fatty acid oxidation, carnitine cycle, electron transport in the respiratory chain, and oxidative phosphorylation [4].

Mitochondrial dysfunction is a typical pathological process that occurs in various pathologies caused by various pathogenic factors. It has no etiological and nosological specificity and is a private concept in relation to any specific disease, being included in it as one of its elements and mechanisms. At the moment, it is customary to distinguish two types of mitochondrial dysfunction: primary, as a result of a congenital genetic defect, and secondary, arising from various acquired diseases [2, 3].

Based on the foregoing, the complex mechanism of ACS development should be considered taking into account the development of myocardial hypoxia and, as a consequence, mitochondrial dysfunction.

In essence, all manifestations of ACS are caused by an imbalance between myocardial oxygen demand and its delivery [6]. The prevalence of oxygen demand leads to its lack in the myocardium, i.e. to myocardial hypoxia. This is primarily reflected in the metabolism in cardiomyocytes in the form of a disruption in the functioning of the energy-producing organelles of the cell - mitochondria. In conditions of a lack of oxygen, the work of the most energetically efficient aerobic pathway of glucose oxidation is sharply slowed down, in which the tricarboxylic acid (TCA) cycle and the pyruvate-dehydrogenase reaction play a key role in the conjugation of glycolysis and CTA. Both of these biochemical cascades occur in the mitochondrial matrix and as a result, substrates are formed that are oxidized in the mitochondrial respiratory chain,

As a result of inhibition of aerobic oxidation of glucose, a forced restructuring of energy production to the anaerobic mechanism occurs: glycolytic breakdown of glucose is activated.

Anaerobic glycolysis is a complex enzymatic process of glucose breakdown that occurs without oxygen consumption, the end product of which is lactic acid. In the process of glycolysis, adenosine triphosphoric acid (ATP) is formed.

Several enzymes play a major role in the glycolysis process. These include lactate dehydrogenase (LDH) and alpha-glycerophosphate dehydrogenase(--GFDG) [7, 6].

LDH acts in the last stage of glycolysis, which occurs in anaerobic

conditions and accompanied by the recovery of lactate from pyruvate. Most of the enzyme, loosely bound to cellular structures, is found in the cytoplasmic matrix, a smaller part of it is firmly attached to mitochondrial membranes [4, 9, 10, 11].

Under conditions of hypoxia and inhibition of the tricarboxylic acid cycle, the conversion of pyruvic acid (PVA) to acetyl-CoA in the pyruvate dehydrogenase reaction (PDR) does not occur, and all the accumulated pyruvate is converted to lactate under the action of LDH. Thus, under conditions of hypoxia, lactic acid accumulates and intracellular acidosis develops.

--GFDH provides a shuttle mechanism between glycolysis and cycle Krebs. The essence of this mechanism is the transfer of reducing equivalents from the cytosol to mitochondria [9]. Inhibition of aerobic oxidation of glucose leads to uncoupling of glycolysis and the tricarboxylic acid cycle due to inhibition of the pyruvate-dehydrogenase reaction. As a result, the key substrate, acetyl-CoA, ceases to enter the TCA. The function of its main supplier is assumed by beta-oxidation of free fatty acids (FFA) [7].

FFA cannot undergo any biochemical transformations, including oxidation, until they are activated. Fatty acid activation occurs on the outer surface of the mitochondrial membrane with the participation of ATP, coenzyme A, and Mg2 + ions. The reaction is catalyzed by the enzyme acyl-CoA synthetase [5]. Carnitine is the carrier of long-chain activated fatty acids across the inner mitochondrial membrane. The reaction proceeds with the participation of a specific cytoplasmic enzyme, carnitine acyltransferase [7]. The process of fatty acid oxidation in the mitochondria of the cell includes several sequential enzymatic reactions, as a result of which there is a sequential cleavage of acetyl-CoA molecules followed by their oxidation in the Krebs cycle with the formation of ATP [11]. One of the key enzymes of this enzymatic cascade is long-chain 3-ketoacyl-CoA-thiolase (3-CAT) [5]. As already indicated, this pathway of ATP formation requires high oxygen consumption and, under ischemic conditions, turns out to be metabolically disadvantageous. In addition, an excess of FFA and acetyl-CoA inhibits PDR and leads to further uncoupling of the processes of glycolysis, oxidative decarboxylation, and CTA. The accumulation of FFA in the cytoplasm has a damaging effect on cell membranes, including the membrane structures of mitochondria, disrupting their function [12]. oxidative decarboxylation and CTA. The accumulation of FFA in the cytoplasm has a damaging effect on cell membranes, including the membrane structures of mitochondria, disrupting their function [12]. oxidative decarboxylation and CTA. The accumulation of FFA in the cytoplasm has a damaging effect on cell membranes, including the membrane structures of mitochondria, disrupting their function [12].

Inhibition of oxidative phosphorylation in the inner membrane of mitochondria under ischemic conditions and its uncoupling, as a consequence of the "calcium paradox", leads to a decrease in the activity of the key enzyme of energy metabolism, succinate dehydrogenase.

The above mechanisms lead first to electrophysiological disorders, to diastolic, and then to systolic myocardial dysfunction, and only then to the occurrence of chest pain. This sequence of changes is called the "ischemic cascade" [13]. Obviously, an anginal attack is its final stage, in fact, the "tip of the iceberg", at the base of which there are arisen due to perfusion disorders.

changes in myocardial metabolism [5] and, first of all, mitochondrial dysfunction, which in this case is of a secondary, acquired character.

In light of the above, a natural question arises about the methods of diagnosing mitochondrial dysfunction in patients with ACS and the degree of its severity.

Currently, there are no clear differential diagnostic criteria for mitochondrial dysfunction due to the absence of a significant difference in the value of biochemical parameters of metabolism in various pathologies. Determination of the concentration of lactate and pyruvate, as well as their ratio in peripheral blood, the study of organic acids in urine, determination of the content of fatty acids and peroxidation products in the blood can be used only as indicative criteria, which is unacceptable in ACS. Biochemical determination of the levels of carnitine in the blood and mitochondrial enzymes in various tissues can be of great help, although recent studies are rarely carried out in our country due to their high cost [3].

Sufficiently homogeneous skeletal muscle tissue is an ideal model for the morphological diagnosis of hereditary mitochondrial diseases. However, the morphological method is practically not applicable in patients with ACS [2, 3].

The comparative simplicity and low invasiveness of taking and processing blood explains the interest in the cytochemical analysis of mitochondrial activity in peripheral blood cells for the diagnosis of mitochondrial disorders. Relatively recently, a significant correlation was found between the cytochemical indicators of the activity of mitochondrial enzymes and the indicators of metabolic dysfunction in skeletal muscle. Thus, in many patients with mitochondrial insufficiency, a diagnostic biopsy can be replaced by a cytochemical analysis of formed elements (primarily, lymphocytes). Currently, available methods for determining the activity of SDH, LDH and GPDH have been developed [3].

Changes in the metabolism of cardiomyocytes during ischemia can be considered as the point of application of drug exposure, in particular, with the help of drugs that can directly affect the processes occurring in mitochondria [5].

To date, a number of antianginal drugs have been created that directly affect metabolic processes in the mitochondria of cardiomyocytes, which are called "myocardial cytoprotectors". These include trimetazidine, ranolazine, etomoxir, dichloroacetate, L-carnitine. However, only one of these drugs - trimetazidine - is a drug with proven antianginal efficacy in randomized trials, with a well-known mechanism of action. Trimetazidine is included in Russian, European and American recommendations for the treatment of coronary heart disease as an antianginal agent [6, 14].

The mechanism of action of trimetazidine has been finally deciphered for today. The drug selectively inhibits long-chain 3-ketoacyl-CoA-thiolase (3-CAT), a key enzyme of FFA beta-oxidation [15]. By inhibiting beta oxidation

FFA, trimetazidine provides an increase in the activity of the key enzyme of glucose oxidation - pyruvate dehydrogenase. This leads to a metabolic "shift" from FFA oxidation to glucose oxidation [16]. As a result, ATP resynthesis increases under ischemic conditions, and the conjugation of glycolysis and oxidative decarboxylation is restored [17]. The activity of the lactate dehydrogenase reaction decreases. Reducing the amount of lactate and free fatty acids reduces cellular acidosis [18], prevents excessive accumulation of calcium ions [20] and blocks the development of the so-called "calcium paradox" and, as a result, prevents not only functional, but also structural damage to mitochondria. The activity of the Krebs cycle and the mitochondrial respiratory chain is restored, which is manifested by an increase in the activity of all respiratory ensembles (complexes), including, succinate dehydrogenated complex. Trimetazidine also enhances the exchange of phospholipids of cell membranes, which leads to a decrease in the content of FFA and prevents their adverse effect on the function of cardiomyocytes [21].

Thus, it can be assumed that, by optimizing the production of energy by mitochondria, trimetazidine helps to reduce the severity of mitochondrial dysfunction not only in chronic, but also in acute ischemia underlying acute coronary syndrome.

At the same time, in addition to the drugs officially recommended for use for the treatment of ACS and its consequences (trimetazidine, B-blockers, angiotensin-converting enzyme inhibitors, antiplatelet agents, fibrinolytics, anticoagulants, etc.), it is of interest to use homeopathic (natural) medicines in the treatment of ACS, such as Cor suis compositum N and Cralonin.

Based on the pathogenesis of the individual components included in Corsuis compositum N, indications for its appointment are coronary circulation disorders after myocardial infarction, weakness of the heart muscle, heart failure, obliterating endoarteritis, arterial hypertension, gastrocardiac syndrome, cardiac arrhythmia, angina pectoris, sports heart and other disorders heart function.

With the help of the heart and liver extracts contained in the preparation, molecular bases are created for the restoration of disturbed functions of organs and an antihomotoxic effect is exerted according to the principle of similarity. Herbal ingredients tone up blood circulation and contribute to the normalization of impaired blood circulation, and Glonoinum and other components regulate the blood supply to the heart muscle and relieve the effects of myocardial damage (this is also facilitated by the citric acid cycle catalysts contained in the preparation) Acidum sarcolacticum and g-strophanthin act with a tendency to heart attack, inhibiting oxidation processes in accordance with the principles of similarity and inverse effect in areas of the heart muscle with poor blood supply. [22]

Based on the homeopathic components of the drug Kralonin compositum, which are included in its composition, it is indicated for cardiovascular diseases, the senile heart, the consequences of damage to the heart muscle, neurogenic

heart disorders, ischemic heart pain (angina pectoris) [22].

At the same time, there have been no studies describing the clinical significance of the use of homeopathic medicines in the complex therapy of ACS.

Thus, summarizing the above data, we can state that further serious study of the role of mitochondrial dysfunction in the pathogenesis of acute coronary syndrome is necessary, as well as the possibilities of diagnosing its presence and severity, which will allow developing a strategy for the subsequent correction of secondary mitochondrial disorders using standard therapy in combination with trimetazidine and homeopathic composites.

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Kulikov, K.G. Possibilities of traditional medicine in the complex correction of secondary mitochondrial dysfunction that developed as a result of acute coronary syndrome / K.G. Kulikov // Traditional medicine. - 2007. - No. 1 (8). - P.27-31.

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