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**ORIGINAL ARTICLE**

# Cardioprotective Signaling: Amino Acids as Mediators of Energy

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## ABSTRACT

*The objectives of the study were as follows: to study the features of catabolism/utilization of most endogenous amino acids of the heart under conditions of experimental ischemia and myocardial hypoxia; to clarify the relationship of these changes with the energy state of the myocardium, glycolysis and the tricarboxylic acid cycle; to investigate myocardial metabolism of glutamic acid, aspartic acid, glutamine, asparagine, alanine and ammonia using the coronary arteriovenous difference method in patients with ischemic heart disease; to study the effect of exogenous glutamic acid, aspartic acids and arginine on metabolism and contractile function of the heart during experimental ischemia/hypoxia and subsequent reperfusion/reoxygenation; to evaluate in clinical studies the feasibility of using exogenous glutamic acid to reduce metabolic and functional disorders of the ischemic heart.*

***Keywords:*** ***Amino acids, Cardiac metabolism, Myocardial ischemia***

## 1. INTRODUCTION

Studying changes in myocardial metabolism during ischemia and reperfusion and finding ways to reduce metabolic and functional damage to the ischemic heart are fundamental tasks in cardiology. In recent years, interest has increased in a less-studied, yet vitally important area of myocardial metabolism: amino acid and ammonia metabolism.

This is due to the fact that during myocardial ischemia, the role of certain amino acids in energy supply to the heart may increase. Experimental studies under these conditions have found increased rates of degradation/utilization of glutamic and aspartic acids and the formation of alanine and ammonia . In patients with coronary heart disease, a significant increase in myocardial glutamic acid extraction and the release of alanine and ammonia into the bloodstream has been found compared to these values in healthy individuals .

It is assumed that these shifts in the metabolism of key amino acids are associated with an increase in substrate phosphorylation in mitochondria at the level of succinate , compensating for the inhibition of oxidative phosphorylation. On the other hand, the metabolism of glutamate and aspartate is associated with the malate-aspartate shuttle, which transports reducing equivalents of cytoplasmic NADH into the mitochondria , and, thus, with the utilization of glucose, the main energy substrate of the ischemic myocardium. The undoubtedly important role of glutamic acid, its precursors - arginine and ornithine, as well as aspartic acid in the regulation of myocardial metabolism is indicated by their ability to maintain cardiac contractile function at a higher level during experimental ischemia and reperfusion .

These facts indicate a relationship between amino acid catabolism and the heart's energy status. However, the metabolic pathways for the degradation of most amino acids and their contribution to energy metabolism in the ischemic myocardium remain poorly understood. The sources of ammonia formation remain unclear, and amino acids may be one of them.

Clearly, to gain a deeper understanding of the biochemical changes occurring in the ischemic heart and to develop new approaches to its metabolic protection based on this knowledge, it is necessary to understand the role of amino acid catabolism in the regulation of myocardial energy production. Therefore, the aim of this study was to investigate the metabolism of key

endogenous P amino acids in the heart during impaired energy production and the effects of a number of exogenous amino acids on the metabolism and function of the ischemic myocardium.

The objectives of the study were as follows: to study the features of catabolism/utilization of most endogenous amino acids of the heart under conditions of experimental ischemia and myocardial hypoxia; to clarify the relationship of these changes with the energy state of the myocardium, glycolysis and the tricarboxylic acid cycle; to investigate myocardial metabolism of glutamic acid, aspartic acid, glutamine, asparagine, alanine and ammonia using the coronary arteriovenous difference method in patients with ischemic heart disease; to study the effect of exogenous glutamic acid, aspartic acids and arginine on metabolism and contractile function of the heart during experimental ischemia/hypoxia and subsequent reperfusion/reoxygenation;- to evaluate in clinical studies the feasibility of using exogenous glutamic acid to reduce metabolic and functional disorders of the ischemic heart.

1. In the myocardium of animals and humans, during ischemia and hypoxia, the rate of catabolism of only two endogenous amino acids, glutamate and aspartate, increases, leading to a significant decrease in their intracellular content. The rate of degradation of isoleucine, valine, leucine, methionine, proline, arginine, and lysine decreases, while that of serine, histidine, threonine, glycine, phenylalanine, and tyrosine remains unchanged. Using inhibitor analysis , precursors have been shown to be the end products of glutamate and aspartate degradation. Alanine is formed from glycolytic pyruvate by cytoplasmic alanine and aspartate aminotransferases, and succinate is formed by the oxidation of α-ketoglutarate and NADH-dependent reduction of fumarate.

2. Glutamate degradation in the ischemic myocardium is catalyzed by cytoplasmic alanine aminotransferase and mitochondrial aspartate aminotransferase, and aspartate degradation is catalyzed by cytoplasmic aspartate aminotransferase. Mitochondrial glutamate concentration decreases proportionally to the decrease in the mitochondrial respiration rate in state 3 and the matrix adenine nucleotide content and an increase in the NADH/NAD* ratio; the glutamate/aspartate ratio in the mitochondrial cytosol and heart positively

correlates with the NADH/NAD+ and lactate/pyruvate ratios in the tissue, respectively. Thus, changes in compartmentalization of both amino acids reflect impaired transfer of reducing equivalents of NADH from the cytosol to the mitochondria and inhibition of oxidative phosphorylation.

3. Glutamate and aspartate catabolism via transaminases is linked to glycolysis and the formation of ATP and GTP in reactions coupled with succinate synthesis. The content of both amino acids and one glutamate in ischemic myocardium positively correlates with the content of ATP, total creatine, adenine nucleotide pool, and the adenylate charge ratio. The rate of alanine and succinate elimination from the ischemic heart positively correlates with a decrease in ATP content and decreases with an increase in the tissue ATP/ADP and phosphocreatine/creatine ratios during reperfusion. This means that changes in the content of glutamate and aspartate in the heart and the rate of elimination of their breakdown products can be used to assess the energy state of ischemic myocardium.

4. Using isolated non-aerated cardiac mitochondria, it was shown that the ATP yield in reactions catalyzed by succinyl thiokinase and fumarate reductase increases when both energy-producing pathways are coupled with substrates of mitochondrial aspartate aminotransferase (glutamate and oxaloacetate) or intermediate products of glutamate and aspartate catabolism (malate and α-ketoglutarate). This effect was reproduced in isolated hypoxic and ischemic hearts using exogenous glutamate, aspartate, and α-ketoglutarate. An increase in ATP and adenine nucleotide content in the heart occurred without an increase in oxygen consumption and glycolytic flux and was combined with an increase in succinate production. This proves that amino acids are capable of improving the energy state of the ischemic heart by stimulating anaerobic energy production in the mitochondria.

cardiomyocytes and, by exploiting the metabolic shifts caused by ischemia or reperfusion, improve the energy state and function of the ischemic heart. The ability of exogenous glutamic acid to reduce ischemic damage to the human heart indicates potential for its clinical use in various forms of myocardial energy production disorders.

***Citation:***

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