

## **Insufficiency of Cardioprotection at Adaptation to Chronic Hypoxia and at Remote Postconditioning in Young and Aged Rats with Metabolic Syndrome, the Role of Metabolic Disorders or Opioid Signaling**

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**Abstract :** Background: Techniques of adaptation to hypoxia and remote postconditioning (RPost) have great prospects for use in the clinic. However, recent studies have shown low efficacy of remote postconditioning in patients with AMI. We hypothesize that the reasons for this inefficiency may be metabolic disorders, which are very common, especially in patients with cardiovascular disease, and age of patients. The purpose of the study was to reveal the effectiveness of adaptation to chronic hypoxia and RPost. To determine the possible relationship between the decrease in the effectiveness of projective impacts and disorders of carbohydrate and lipid metabolism. Design: The study was carried out on Wistar rats 60 day old. MetS was induced by high-carbohydrate, high-fat diet (HCHFD). Modeling MS led to the formation of obesity, hypertension, impaired lipid and carbohydrate metabolism, hyperleptinemia, and moderate stress. Groups with adaptation to chronic hypoxia were subjected to hypoxia for 21 days at 12% O<sub>2</sub> and 0.3% CO<sub>2</sub> after complete of HCHFD. All animals were subjected to 45 min coronary occlusion and 120 min reperfusion. Groups with RPost, immediately after the end of ischemia, tourniquets were applied to the hind limbs in the area of the hip joint (3 times in the mode of 5 min ischemia, 5 min reperfusion). Results: RPost led to a twofold reduction of infarct size in rats with intact metabolism ( $p < 0.0001$ ), while in rats with MetS, a decrease in infarct size during RPost was 25 % ( $p = 0.00003$ ). A direct correlation was found between of infarct size during RPost and the serum leptin level of rats with MetC ( $r = 0.85$ ). The presented data suggested that a decrease in the efficiency of remote postconditioning in rats with diet-induced metabolic syndrome depends on serum leptin. Chronic hypoxia resulted in a 38% reduced in infarct size in metabolically intact rats. The decrease of cardioprotection was observed in rats with chronic hypoxia and MetS. Infarct size showed a direct correlation with impaired glucose tolerance (AUC, glucose tolerance test,  $r = 0.034$ ) and serum triglyceride levels ( $r = 0.39$ ). Our study showed the dependence of cardioprotection in rats with metabolic syndrome during chronic hypoxia and DPost on opioids in the blood serum and myocardium, protein kinase C and NO synthase activity. Conclusion: The results obtained showed that the infarct-limiting efficiency of adaptation to hypoxia and remote postconditioning is reduced or completely absent in animals with metabolic syndrome. The increase in the infarction, in this case, directly depends on the disturbances in carbohydrate. lipid metabolism and opioids signaling. Funding: Investigation of effectiveness of chronic hypoxia at the metabolic syndrome was carried out within the support of Russian Science Foundation Grant 22-15-00048. Studies of the mechanisms of arterial hypertension in induced metabolic syndrome were carried out within the framework of the state assignment (122020300042-4). The work was performed using the Center for Collective Use "Medical Genomics".

**Keywords :** chronic hypoxia, opioids, remote postconditioning, metabolic syndrome

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