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Application of Ischemic Postconditioning in Disease Treatment

Xinyi Sui[1,*,a], Ziqi An[1], Zhongwei Liu[1], Yutong Fan[1], Shiyao Liu[1], Menghan Li[1]

[1]School of Chinese Medical Sciences University, Shenyang 110000, China.

[a]601492891@qq.com

Abstract

Ischemic postconditioning Can inhibit neutrophil activation, Inhibition of oxygen free radical accumulation during reperfusion,Prolonged adenosine clearance time, reduced calcium overload,Protect protein kinase cell signals transduction pathway, reduce cell autophagy, inhibit cell apoptosis,Inhibition of astrocyte scar formation and other ways to reduce ischemia-reperfusion injury, protect the heart, brain and other important organs, has a strong clinical feasibility and practical value.This article mainly reviews the protective mechanism, treatment methods and clinical application of ischemic postconditioning protective mechanisms.

Keywords

Ischemic postconditioning, Remote ischemic postconditioning.

1. Protective mechanisms of ischemic postconditioning

At present, many studies have shown that the protective mechanism of ischemic postconditioning is closely related to neutrophils, oxygen free radicals, adenosine, internal calcium overload, protein kinase cell signal transduction pathways, autophagy, apoptosis, brain astrocyte scar formation and so on.

1.1 Neutrophils

Whether ischemic postconditioning protective mechanisms can play a role is closely related to neutrophils. When ischemia-reperfusion injury occurs, neutrophils can be massively aggregated and activated. Protease, collagenase and other active substances are released, and the structure of vascular endothelial cells is damaged and the damage is increased. The application of ischemic postconditioning can inhibit the activation process of neutrophils and effectively protect human vascular wall and vascular endothelial cells.

1.2 Oxygen radical

Cells that acquire oxygen through respiration bind 98% of the oxygen obtained to the fat present in the organelles of the body. It combines with glucose and converts into energy to meet the normal physiological needs of cell activities, another 2% of oxygen is converted to oxygen free radicals in the body. Because this substance is very active, it can interact with almost all kinds of substances, causing a series of destructive chain reactions to human cells, and reduce the body's oxidative defense system clearance capacity.ischemic postconditioning can prevent ischemia-reperfusion injury by regulating oxygen free radicals. The application of ischemic postconditioning can reduce the generation of oxygen free radicals after interventional surgery and accelerate the recovery process of patients after surgery.

1.3 Adenosine

Adenosine is widely found in human cells and has certain physiological effects on the cardiovascular system and many other systems and tissues of the body. Adenosine is an important intermediate for

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the synthesis of adenosine triphosphate (ATP), adenine, adenylate, and arabinosine. After ischemia, appropriate treatment can prolong the clearance time of adenosine, alleviate cell damage and improve the prognosis of patients.

1.4 Internal calcium overload

Some harmful factors may cause calcium dysfunction and disturbance of calcium and phosphorus distribution in the calcium balance system, causes abnormal elevation of intracellular calcium concentration, i.e. calcium overload. Calcium overload 15 can cause the impairment of oxidative phosphorylation process in mitochondria, the decrease of mitochondrial membrane potential level, and the decrease of ATP content in tissue cells, as well as the functional activation of intracytoplasmic phospholipases, proteases, etc., can promote and lead to irreversible cell damage. Initial calpain activation leads to an influx of extracellular Ca2+ through nifedipine-sensitive calcium channels, followed by transfer to the cell membrane, causing Cl-influx and cell death. The results suggest that IPO opens mitochondrial AT P-sensitive potassium channel (mitoKATP) and mitochondrial permeability transition pore (mPTP), mPTP is the main terminal effector of the protective pathway, and IPostC finally opens mitoKATP channel activation through multiple cascade reactions, control the change of mitochondrial matrix volume, reduce mitochondrial membrane potential, reduce Ca2+ influx, reduce calcium overload, thus effectively prevent the opening of mPTP, maintain the normal homeostasis of mitochondrial membrane potential and matrix metabolism, and play a protective role[1].

1.5 Protein Kinase Cell Signal Transduction Pathway

Chemise postconditioning regulates the expression of cell Fibulin-5 through the P13K/AKT signaling pathway, leading to increased expression of fibulin-5, and over expression of Fibulin-5 can effectively alleviate the damage caused by cerebral ischemia-reperfusion.

1.6 Relevant role of autophagy

LC3II is a self-aggregating protein during the formation of autophagy, and the amount of this protein is used to react to autophagy. The expression of LC3II began to increase at 6 h after ischemia-reperfusion, and the time of expression enhancement was delayed compared with that in the reperfusion group after ischemic postconditioning treatment. Studies have found that both ischemic cerebral infarction and ischemia-reperfusion can inhibit the expression of autophagy-related[2] gene 5 (Atg5), an important protein for cell degradation and circulation, and autophagy-related gene 7 (Atg7), which is essential for the induction of autophagy.

1.7 Apoptosis

Apoptosis is a programmed cell death. Mitogen activated protein kinases (MAPK) signaling pathway plays an important role in regulating cell death, apoptosis and survival. MAPK cascade activation is the center of many kinds of signal pathways. It is a kind of important molecules that receive the signals converted and transmitted by membrane receptors and bring them into the nucleus. It plays a key role in many cell proliferation related signal pathways. MAPK was still in the non stimulated cells. After the cells were stimulated by ischemia-reperfusion, MAPK was activated by receiving the activation signals of MKK and mkkk, which showed gradual phosphorylation. After ischemia, stimulation can significantly reduce MAPK level and protect damaged tissue cells.

1.8 Scar formation of astrocytes

Cerebral ischemia leads to the activation of overexpression and proliferation of astrocytes, which leads to the formation of scar of astrocytes. Due to the change of molecular structure of astrocytes, astrocytes have been transformed from vegetative neurons to neurotoxic neurons, resulting in serious neuronal damage. [3]

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2. Treatment

2.1 Ischemic postconditioning

At present, ischemic postconditioning has been widely concerned. It can be used to treat some patients with acute myocardial infarction and ischemic stroke. Post ischemic postconditioning refers to repeated transient ischemia-reperfusion cycles of the occluded artery several time after myocardial or neuron ischemia, and then reopening the artery for continuous reperfusion, so as to enhance the tolerance of cells to long-term ischemia, reduce apoptosis and damage, to reduce the infarct area. The concept of post ischemic adaptation was first proposed by Zhao et al. Zhao occluded the left anterior descending (LAD) for 60 minutes in anesthetized open chest dogs, and then reperfusion for 3 hours. In the control group (n = 10), there was no intervention. In the experimental group (n = 10), 30 second reperfusion and 30 second LAD occlusion were performed before 3 hours of reperfusion. Then the edema and neutrophil peroxidase level of ischemic myocardium were measured to determine the degree of myocardial injury. However, clinical use of invasive myocardial ischemia is very limited, it is difficult to carry out in clinical treatment, and there are few clinical trials of ischemic postconditioning.

2.2 Remote ischemic postconditioning

Both remote ischemic postconditioning (RPC) and ischemic postconditioning can reduce the ischemia-reperfusion injury and thus achieve the protective effect. Moreover, because of the characteristics of remote ischemia-reperfusion, it is easier to carry out clinical promotion. Some scholars used the mouse model of coronary artery occlusion and reperfusion to carry out the experiment of blocking and recanalization of renal artery for a single time of 5 minutes. The research found that it can significantly reduce the myocardial ischemia-reperfusion injury. This result proved for the first time that the remote ischemic postconditioning also has the treatment effect similar to the ischemic postconditioning. The protective mechanism of remote ischemic postconditioning can be divided into neural mechanism, humoral mechanism and systemic response. Nerve mechanism refers to the ischemic stimulation of the radial nerve and the ulnar nerve in the process of upper limb vascular occlusion, which is transmitted to the heart or brain and other important ischemic organs along with nerve conduction. The humoral mechanism is to produce nitric oxide, bradykinin, endogenous opioids, capsaicin, adenosine, endogenous cannabinoids and other substances in the process of remote ischemia. With the extension of time, these substances will have a protective effect, especially for chronic ischemia. Systemic response is that hypoxia and ischemia affect the lymphatic system, and then affect the immune regulation and anti-inflammatory response.

Hu et al. Also found that there was no overlapping effect of ischemic postconditioning and post remoteischemic postconditioning on myocardial protection of acute myocardial infarction, however, Yang et al. Found that the superposition of the two can produce more significant myocardial protection in the rabbit model in vitro. Therefore, this result still needs to be further confirmed by a large number of clinical studies. Remote ischemic postconditioning is to reduce the ischemia-reperfusion injury of important organs through the intervention of short-term non lethal ischemia-reperfusion injury on remote organs, avoid the risk of direct ischemic operation on the heart, brain and other important organs sensitive to ischemia, and provide the possibility for the clinical treatment of ischemic postconditioning.

3. Clinical application

3.1 Ischemic stroke

Ischemic stroke is due to the ischemia of cerebral artery, which presents a series of symptoms and diseases. The clinical symptoms of stroke are due to the limited and comprehensive ischemia of brain tissue caused by the disorder of cerebral blood circulation and the corresponding death of nerve tissue. Because of its high morbidity and mortality, it has become the number one killer of human health.

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Therefore, how to effectively treat ischemic stroke is an important research direction of cerebrovascular diseases.

（1） Che et al. Randomly divided 30 patients with post ischemic stroke treated by intravenous thrombolysis into the experimental group (15 cases) and the control group (15 cases). The experimental group received immediate adaptive treatment after 6 hours of intravenous thrombolysis, The cuff was tied to the upper arms of the subjects with the remote ischemic postconditioning physical therapy instrument and pressurized. After 5 minutes, the cuff was deflated and maintained for 5 minutes and circulated for 5 times. One cycle was conducted on the first day, twice a day in the following six days. The control group was given routine treatment without any other intervention. In the experimental group, all participants (15 cases) tolerated the whole process of positioning adaptation. By 9 participants (60.0%), although some needle like erythema appeared in the upper part of the upper arm, there was no skin pallor, edema, pain or tenderness at the distal end of the radial artery. There was no significant difference in systolic pressure, diastolic pressure and heart rate between the two groups. There was no significant adverse effect on vital signs. NIHSS score of the adaptive group was significantly lower than that of the control group at 30 days. Therefore, the results of this experiment show that the adaptation after remote ischemia is safe and effective for patients with acute ischemic stroke after intravenous thrombolysis.

（2）Zhao et al. Carried out the experiment of adaptation after remote ischemia in patients with acute ischemic stroke who had been treated with intravenous thrombectomy for 6 hours. The results showed that the prognosis of patients in the experimental group was preferable to that in the control group, and the patients were well tolerated. This study further proves that there are fewer adaptive adverse reactions and stronger protective effects after remote ischemia.

（3）Wei et al. Randomly divided 100 patients with symptomatic intracranial atherosclerotic stenosis into an experimental group (50 cases) and control group (50 cases). According to the analysis and evaluation of global and local cerebral hemodynamics, the scores of patients in the experimental group were significantly higher than those in the control group. This also fully shows that the remote ischemic adaptation can dramatically improve the prognosis of patients with cerebral ischemic stroke.

3.2 Acute myocardial infarction

(1) In 2005, staat, P, et al. Conducted a clinical study in the background of dog experiment of Zhao, ZQ. 30 patients who received coronary angioplasty due to progressive acute myocardial infarction contributed to the study. Staat, P after the patients were divided into groups, the experimental group was treated with direct stent placement for reperfusion, while the control group was not treated with intervention. The infarct area was assessed by measuring the total release of creatine kinase within 72 hours. Compared with the control group, the area under the creatine kinase release curve was significantly reduced in the post-treatment, with an average of 326984 + / - 48779 (any unit) and an average of 208984 +/ - 26576 (36%). This suggests that adaptation after ischemia during acute myocardial infarction can protect the heart and streamline of myocardial infarction.

(2) Some scholars have found that adaptation after ischemia can reduce the number of acute renal injury and major adverse cardiac events (MACE) for one year. In addition, six months after myocardial infarction, SPECT imaging showed that the infarct area of the adaptive group was significantly lower than that of the control group. It can be observed that the adaptive reduction of myocardial infarct area after ischemia is persistent. Mewlon et al. Showed that post ischemic adaptation can reduce the no reflow or microvascular occlusion (MVO) in STEMI patients.

(3) It is known that drugs that can activate the risk pathway can be used as a treatment for myocardial reperfusion in patients with acute myocardial infarction. The "risk" pathway[4]is a group of survival promoting protein kinases (including Akt and ERK1) that are specifically activated during myocardial reperfusion and have strong cardiac protective function/ 2) It provides a pharmacological target suitable for heart protection. When it is given specially during myocardial reperfusion, it can reduce the size of myocardial infarction by activating risk pathway, so that the clinical outcome of the patient

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group can be improved. The cardiac protection phenomenon of ischemic pre adaptation and post adaptation also recruits the risk pathway, so that the pharmacological agents targeting the risk pathway can be used as drug simulants during myocardial reperfusion. Hausenloy, DJ found that adaptive cardioprotection after ischemia also recruited risk pathway, which can improve myocardial injury in patients with acute myocardial infarction.

(4) In 2018, botker, he et al. Studied the effect of acute intervention combined with post ischemic adaptation on the prognosis of patients with ST elevation myocardial infarction. Studies have shown that postischemic adaptation can reduce ischemia-reperfusion injury and make a significant contribution to the final infarct area, mortality and post infarct heart failure. It is worth noting that not only after acute ischemia-reperfusion events (such as acute myocardial infarction and cardiac surgery), but also in patients with heart failure, post ischemic adaptation has some effect.

(5) In 2019, 122 STEMI patients will randomly be divided into two groups (n = 65) and control group (n = 57). The control group only received stent implantation, and the adaptive group opened blood vessels 1min after ischemia and inflated them by an angioplasty balloon for 4 cycles repeatedly. 30 S / is bleeding for 30s. This experiment again verified the long-term beneficial effect of post ischemic adaptation on left ventricular remodeling and reduction of myocardial infarction area, and especially proposed that post ischemic adaptation is particularly suitable for patients with microvascular occlusion, and there is no significant adverse event before and after the whole post ischemic adaptation operation.

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