Review Article

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Protection of multiple ischemic organs by controlled reperfusion

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Abstract:

Reperfusion injury (RI) is a harmful complication that takes place during recanalization treatment of ischemic organs. Currently, there are no efficacious treatments for protecting the organs against RI. Therefore, it is necessary to discover new strategies to prevent RI. As a novel intervention technique, controlled reperfusion has promising effects on protecting multiple organs from RI, and it is done by adjusting physical parameters of blood flow or chemical compositions of the reperfusion liquid. In this brief review, the status of various controlled reperfusion methods is presented, as well as their application in the protection of ischemic organs.

Keywords:

Controlled reperfusion, organ protection, reperfusion injury

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Introduction

Reperfusion injury (RI) is a complicated pathological process that is initiated by the recanalization of blocked blood vessels through the course of thrombolysis or thrombectomy, which leads to serious tissue damage and organ dysfunction.[1] The mechanism of RI is still not clear, but it is believed to be associated with increased reactive oxygen species, reductive antioxidant enzymes and growing inflammatory infiltration (e.g., the accumulation of neutrophils coming from the blood flow after a long time of ischemia).[2] RI has the potential to damage tissues and organs such as the heart, brain, lung, kidney, and small intestine. For instance, it usually occurs after coronary artery bypass grafting for coronary heart disease,[3] thrombolysis for stroke patients,[4] lung transplant,[5] aneurysm,[6] and surgeries of the small intestine[7] or extremities.[8] Existing therapies of RI are mainly pharmacologic administration such as free-radical scavengers,[9] calcium ion antagonists, apoptosis inhibitors, and nonpharmacologic protective strategies such as cardiopulmonary resuscitation.[10] The mechanism of the existing pharmacologic options is mainly reduction of reactive oxygen species and calcium, recovery of mitochondrial function. However, the side effect of drugs is inevitable, and the evaluation of these treatment methods is still under exploration whose potential clinical application should be evaluated in future clinical trials. Recently, with the developing research on the pathogenesis and therapeutic methods of RI, controlled reperfusion is proposed through the manipulation of physical parameters (infusion pressure, flow rate, temperature, etc.) and chemical compositions (ion content, drugs, acid-base balance, etc.). Among all the methods of controlled reperfusion, many studies suggested that ischemic postconditioning is a promising treatment strategy.[11]

The Basic Concept of Controlled Reperfusion

Basic concept

The concept of controlled reperfusion was first proposed in vascular surgery in the

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1960s.[12] Revascularization after aortic ischemia-induced RI. To lower the incidence of RI, controlled reperfusion was conducted by adjusting the physical parameters (infusion pressure, flow rate, temperature) as well as chemical compositions [ion content, drugs, acid-base balance, shown in Table 1].

Condition

The conditions of controlled reperfusion include physical parameters (reperfusion pressure, flow rate, temperature, etc.) as well as chemical compositions (ion content, drugs, acid-base balance, etc.). These interventions are promising methods of organ protection in clinical practice.[17]

Control of physical parameters

The adjustment of flow rate was mainly conducted by a slow and gradual supply of blood to the ischemic area to avoid damage of tissue resulting from abrupt reperfusion of blood. This adjustment could also improve the functional recovery of the nervous system. A study demonstrated that high flow rate reperfusion such as 18 ml/kg/min did not relieve cerebral RI.[13] Researchers found that the higher the flow rate was, the less cerebral blood flow would be. A high flow rate may cause brain edema without glycometabolic improvement (no significant difference in glucose uptake and utilization of brain). This could lead to major brain damage, and therefore, it is vital to control the time and velocity of the perfusate in the brain.

Avolio *et al*. pointed out that high-flow-rate reperfusion leads to damage of the cerebral small vessels and diseases, similar to stroke and cognitive impairment, etc.[14] If the blood pressure, as a result of reperfusion, is limited to 80-100 mmHg, then it will not only reduce the production of superoxide radical, but it will also avoid vascular endothelial injury. As characterized by Vinten-Johansen,[15] low-pressure reperfusion and ischemic postconditioning were related to controlled reperfusion, which induced less morphological damage and led to quicker functional recovery of the nervous system.

Controlled reperfusion has a buffer effect in the regulation of blood flow, and it is widely applied in many fields. For instance, lowering the initial reperfusion pressure improves functional and metabolic recovery in the rat model of ischemic myocardium; reducing reperfusion flow rate relieves edema and muscle injury in the pig model of ischemic skeletal muscle.[19] It is known that aortic surgery needs cardiac arrest, so measures are taken

Table 1: Selected studies of controlled reperfusion in reperfusion injury models

Condition	Method	Animal model/human	Result	Benefit
Physical parameters				
Blood flow rate[13,14]	Rapid infusion rate: 18 ml/kg/min	Extracorporeal circulation model of norwegian landrace breed	Decreased cerebral blood flow and reduced brain edema	Ensure blood supply, relieve edema, and benefit the recovery of neurological function after ischemia
		Rat model of calcified carotid artery	Cerebral small vessel damage, stroke, cognitive disorder	
Blood pressure[15]	Low-pressure perfusion	Rat model of cardiac perfusion	Reduced superoxide radical concentration and vascular endothelial injury	Reduce morphological damage and recover postischemic function
Temperature of the perfusate[12]	Hypothermia	Yorkshire pig model of subrenal aorta occlusion	Inhibited metabolism, reduced organ damage, improved internal environment to an optimal state	Hypothermia reduces tissue metabolism to provide local protection of ischemic viscera
Chemical compositions				
Ion content[16]	Decrease calcium and potassium ion content, include magnesium ion to the perfusate	/	Reduced structural damage to the tissue	Reduce the need for oxygen in cells
Drugs[17,18]	Calcium ion antagonists, vasodilatory agents and antioxidant	/	/	Reduced pathological tissue damage
	PTX	Sprague-Dawley rat cardiomyocyte model of hypoxic damage	Reduced adverse reaction after reperfusion	Maintain the normal structure of cellular microtubules, reduce tissue damage caused by hypoxia to reduce myocardial RI
Acid-base balance[16]	/	/	/	Adjust pH value of blood to maintain optimal cell metabolism

PTX: Paclitaxel, RI: Reperfusion injury

to protect the important organs from ischemia. Tissue metabolism is usually reduced through hypothermia, which relieves organic damage and results in the best restored internal environment.[12]

Control of chemical compositions

Besides physical parameters, the other essential component of controlled reperfusion is chemical composition. The change of reperfusion liquid composition such as blood-crystalloid solution, composed of glutamate, glucose, NaCl *et al*. rather than highly oxygenated pure blood, reduces the pathological damage caused by reperfusion. In addition, we may also adjust ion content or the pH of the extracellular fluid to maintain homeostasis.

First, we should ensure materials including glucose and amino acid supply during ischemia. Second, controlling the type and concentration of ions by reducing calcium or adding magnesium can avoid calcium overload. Furthermore, some chemicals such as calcium ion antagonists, vasodilatory agents, and antioxidants may alleviate pathological tissue damage.[15] A promising method to reduce myocardial RI was put forward by Guo.[18] He found that Paclitaxel (PTX) reduced RI by maintaining the normal structure of cellular microtubules and helping mitigate the tissue damage caused by hypoxia. Therefore, the addition of moderate PTX to reperfusion composition is beneficial to decrease the adverse reactions after reperfusion.

It is also desirable to limit leukocyte infiltration to adjust the pH of blood to reach the best metabolic status and to use mannitol to restrain cell edema, as studied by Gerald.[20] However, another research reduced calcium concentration by accelerating sodium-calcium exchange so that sodium overload increased blood pressure by water-sodium retention.[21] This was not the most favorable outcome, so the clinical benefit of changing chemical compositions of perfusate is still controversial.

Research and Development of Controlled Reperfusion

Protection in ischemic cerebrovascular disease

As a vital field, cerebral controlled reperfusion is a new strategy of reperfusion, which emphasizes the perfusion time and perfusate volume during the treatment of RI. One-time infusion is changed into the controlled infusion. In addition, it is effective to reduce cerebral edema and cell apoptosis, as well as to reduce infarct size and improve neural functional recovery, and then improve the prognosis of ischemic stroke. Researchers found that moderate to severe leukoaraiosis significantly increases the risk of intracerebral haemorrhage.[22] Controlled reperfusion reduces hemorrhagic transformation together with white matter lesions in RI in acute ischemic stroke. Nevertheless, the key to relieve RI is putting these theories into practice.

A pilot animal study was conducted in 2018 by using a middle cerebral artery occlusion (MCAO) rat model to carry out controlled reperfusion by controlling the blood flow, which may reduce oxygen radicals as well as calcium overload. Xu divided 42 rats into Gradual Flow Restoration (GFR) group and Rapid Flow Restoration (RFR) group.[23] Each group contained 14 rats with respective 15, 30, 60 min of MCAO. The crux of GFR is increasing cerebral blood flow (CBF) to 40%–49% of the baseline value in the first 2 min, 60%–69% in the next 2 min, and gradually reaching the baseline value in 5 min. The main criteria of RFR are 80% CBF of baseline value in 30 s. The results show significant differences in the mean neural system severity score, median infarct ratio, mean apoptosis rate of nerve cells, and mean histopathological anomaly score, of which GFR is better than RFR. Specifically, the 30-min and 60-min groups show pronounced benefits. Thus, the authors conclude that GFR is more effective in relieving cerebral RI than RFR, of which 60 min of reperfusion is more protective.

Zhang divided adult gerbils into a complete reperfusion group and a gradual reperfusion group at random.[24] The latter was divided into ¼ and ½ CBF baseline reperfusion. After 10 min of reperfusion, they found that the complete reperfusion group had the worst damage to the hippocampus and the most severe neurocyte apoptosis, and the lowest neurological scores. The gradual reperfusion group showed significantly reduced neurological damage and decreased infarct areas. Ji *et al*. came up with an alternative method of neuroprotection for ischemic stroke, which perfused cold normal saline to the internal carotid discontinuously.[25] Ji's team used 85 MCAO Sprague-Dawley rats with the reperfusion rate of 15 ml/h for 30 min, followed by a 20-min rest interval, and then repeated the cycle three times. This study confirmed the safety and effectiveness of the controlled target hypothermia for neuroprotection.

In large animal studies, researchers mainly use the pig model [Figure 1] and carry out controlled reperfusion by blood flow volume and velocity. Allen *et al*. induced transient cerebral ischemia for 30 s and then conducted reperfusion for 5 min to the model.[26] The researchers found that the low reperfusion group of 450 cc/min had a better outcome than the high reperfusion group of 750 cc/min in reducing oxygen consumption, cerebral edema, and infarct areas. However, if the blood flow is lower than 450 cc/min, it may cause irreversible damage to the brain. Therefore, it is necessary to make sure that the minimum value is achieved to improve patients' prognosis.

Clinical applications of controlled reperfusion have not been reported. From animal experiments, we can see GFR is more helpful to 30 or 60 min of MCAO rats than 15 min. Thus, the outcome of GFR may depend on the timing of revascularization of acute occlusion of intracranial arteries and a late onset may yield a better effect. One possible protection mechanism of GFR in reducing cerebral RI is the inhibition of calcium overload via decreasing the production of calcium to avoid neurocyte apoptosis.[17] The study may provide some insights into the treatment of ischemic stroke patients because it does not require extra medical apparatus or drugs. It is predicted that GFR combined with thrombectomy might be effective in preventing cerebral RI and improving prognosis, which needs to be confirmed by further research.[27] Above all, controlled reperfusion plays a vital role in neural protection by reducing cerebral RI, which is potentially applicable to clinical practice.

Protection in other organs

We also find several studies of controlled reperfusion in other organs besides the brain. Many researchers studied the protection of controlled reperfusion on using animal models through the control of blood flow volume within the organs such as the stomach,[28] hind limbs,[29] lung,[30] kidney[31] *et al*. [Table 2]. They find that GFR relieves RI and protects ischemic tissues from the sudden recovery of blood supply. Furthermore, controlled reperfusion is widely applied in the myocardium,[32] skeletal muscle,[29] cremaster[20] *et al*.

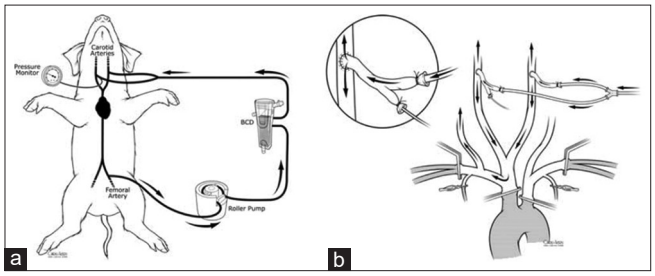

Figure 1: (a) Yorkshire-Duroc Pig model of cerebral perfusion system and (b) model of isolate brain perfusion[26]

Protection Mechanism of Controlled Reperfusion

Physical parameters

In the control of blood flow rate and pressure, Haldenwang *et al*. claim that high blood flow volume increases vascular resistance and hydrostatic pressure, which results in vascular endothelial dysfunction and even encephala edema.[33] On the contrary, controlled reperfusion avoids this problem, and it plays a vital role in maintaining intracellular pH values and ATP levels. Controlled reperfusion provides a gradual oxygen supply, in which the ischemic tissues have a certain process of adaption with less damage and quicker recovery. One possible mechanism is that GFR slows down the production of oxygen radicals to the benefit of an organic clearance mechanism. Zhang *et al*. hypothesized that controlled reperfusion was a type of ischemic postconditioning.[32] He explained that a gradual infusion, rather than opening up blood vessels immediately after ischemia, leads to ischemic damage at a lesser extent. The result indicated cardiac protection in reducing markers of myocardial damage such as creatine kinase, myocardial infarction areas, and apoptotic index. Moreover, he compared the three patterns of ischemic postconditioning, gradually increasing reperfusion, constant reperfusion, and gradually reduced reperfusion, which all provided better protection effects on the heart compared to the control group. Among them, gradually increased reperfusion has the best cardio-protection effect. Another mechanism for this beneficial effect is decreased inflammatory responses. For instance, Jancsó *et al*. detected less leukocyte radical production in the controlled reperfusion group [Figure 2].[12]

Table 2: Studies of controlled reperfusion in other organs

Organs	Model	Condition	Method	Result	Possible mechanism
Stomach[28]	Cat	Blood pressure	Abdominal arterial pressure rises 10 mmHg every 10 min	Blood loss caused by vascular injury is less than the control group	GFR relieved RI and protect ischemic tissues from the sudden recovery of blood supply
Hind limbs[29]	Rat	Blood flow rate	After 150 min, the next 30 s, 60 s, 90 s, 120 s respectively perfuse 1/4, 1/2, 3/4, and 1 of baseline CBF	Malonyl dialdehyde and myeloperoxidase are lower than the control group	In the process of GFR, transient acidification restrains the accumulation of neutrophils and reduces the production of superoxide radicals, therefore eases RI
Lung[30]	Rabbit	Blood flow rate	At first, the reperfusion rate is 60 ml/min, lasting for 5 min, and then the rate is changed to 120 ml/min, lasting for 25 min	Pulmonary artery pressure, arterial oxygenation, and indicators of pulmonary edema are improved	Pulmonary artery hypertension destroys vascular endothelium mechanically. Controlled reperfusion eases RI by reducing the gradient of arterial pressure
Kidney[31]	Rat	Blood flow rate	Clamps open the renal artery gradually	Levels of MDA and MPO are the lower and renal injury is less than the control group	High blood flow rate produces more ATP and oxygen, and then speeds up inflammation reaction as well as cellular apoptosis followed by organic injury

CBF: Cerebral blood flow, MPO: Myeloperoxidase, MDA: Malondialdehyde, RI: Reperfusion injury, ATP: Adenosine tri-phosphate, GFR: Gradual flow restoration

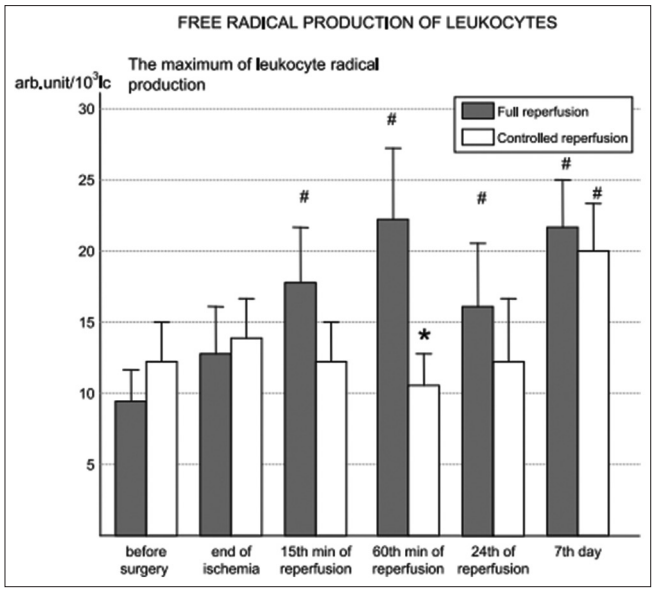

Figure 2: Changes in the maximum of leukocyte radical production in the experimental groups during the examined perioperative period. (#$P < 0.05$ vs. before surgery; *$P < 0.05$ vs. non-conditioned group)[12]

In the control of temperature, research showed that hypothermia treatment on the brain tissue makes it more tolerant to ischemia by reducing energy consumption. Local hypothermia is induced by infusing cold perfusate via the internal carotid, which contributed to the relief of neurological impairment for stroke patients [Figure 3].[34]

Chemical compositions

Oxygen radicals are important inducers of RI,[35] which are delivered with the oxygen into the ischemic area after the revascularization of the blood vessels. Therefore, to avoid the sudden outbreak of oxygen radicals, one study proposed perfusing hypoxic blood into the vessel during reperfusion. Researchers found that the vascular damage was less in this case than in the control group, which indicated that as a main source of RI, oxygen radicals could be reduced by controlled reperfusion. It can also relieve the destruction of the blood-brain barrier and inhibit the activation of immune inflammation.[36] Furthermore, controlled reperfusion is available by adjusting ion content to reduce calcium ion overload.[37,38]

Conclusion

Controlled reperfusion has been proven to be an effective approach to relieve RI. Research protects heart, brain, and other vital organs. It mainly consists of adjusting physical parameters of blood flow or chemical compositions of the reperfusion liquid. Therein, the control of blood flow volume is widely studied and put into practice. Patients with acute ischemic stroke are likely to benefit from controlled reperfusion. We propose that a new form of controlled reperfusion, especially gradual enlargement

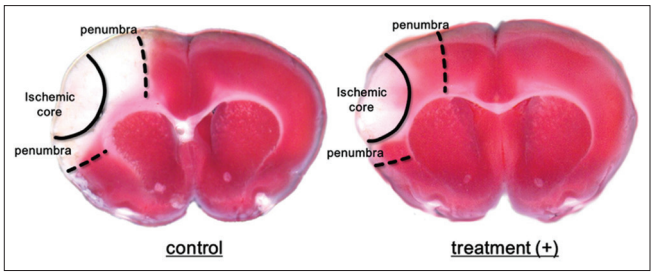

Figure 3: A representative image for examination of the ischemic core and penumbra between hypothermia (treatment) group and control group[34]

of the inner diameter of the blood vessel, may relieve RI of acute ischemic stroke.

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Conflicts of interest

Prof. Xunming Ji is Editor-in-Chief, Prof. Yuchuan Ding is an Associate Editor of *Brain Circulation*. The article was subject to the journal's standard procedures, with peer review handled independently of them and their research groups.

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