Journal of Surgery
Cao Z. J Surg 8: 1777
www.doi.org/10.29011/2575-9760.001777
www.gavinpublishers.com
Short Commentry

From Molecule and Cell to Whole Body Recovery after Warm Ishemia - the Techniques from Organex Perfusion to Emergency Preversation Resusicitation

Zhongping Cao*

Department of Anesthesia, The special characteristic medicine center of Chinese People Armed Police Force, Tianjin 300162, China

*Corresponding author: Zhongping Cao, Department of Anesthesia, The special characteristic medicine center of Chinese People Armed Police Force, Chenlin road, 220, Dongli district, Tianjin, China

Citation: Cao Z (2023) From Molecule and Cell to Whole Body Recovery after Warm Ishemia - the Techniques from Organex Perfusion to Emergency Preversation Resusicitation. J Surg 8: 1777 DOI: 10.29011/2575-9760.001777

Received Date: 28 March, 2023; **Accepted Date:** 31 March, 2023; **Published Date:** 03 April, 2023

Abstract

In the field of organ transplantation and cardiac arrest resuscitation, reducing warm ischemia and reperfusion injury and protecting the function of tissues and organs as much as possible has always been the research hotspot. The OrganEx system published in Nature of 2022 and emergency protective resuscitation of cardiac arrest in severe traumatic hemorrhagic shock have successfully applied the hypothermic technique of extracorporeal circulation, these methods recovered the function of molecular cells and even the whole function of organs, which brings us some enlightenment and future imagination.

Keywords: Cardiac arrest; Damage control resuscitation; Emergency protective resuscitation; Hypothermic cardiopulmonary bypass; Ischemia-reperfusion injury

In the field of organ transplantation and cardiac arrest resuscitation, it is of great significance for functional recovery of transplanted organs and resuscitation of important organs such as heart and brain to minimize the injury of warm ischemia and reperfusion, to prolong the time of warm ischemia and to protect the function of tissues and organs. In recent years, the academic circles have done a lot of work for the organ warm ischemia protection, the most groundbreaking research is the ORGANEX system published in Nature in 2022, and emergency preservation resuscitation of cardiac arrest in severe traumatic hemorrhagic shock. The former achieved the function of molecular cells and even the whole organ recovery after 1 hour of warm ischemia due to cardiac arrest in pigs, and which is combined the technology of cardiopulmonary bypass with anti-ischemia-reperfusion drugs. The latter emphasized organ protection by emergency hypothermia perfusion after cardiac arrest, deep hypothermic circulatory arrest, wound repair, and cardiopulmonary bypass perfusion to achieve complete recovery of the body and brain function. [1-4] Both of them have successfully applied the cryogenic technology of extracorporeal circulation. What inspiration and imagine can they bring us?

Organex Perfusion System

The OrganEx system integrated the methods of hypothermia, dialysis, oxygenation and a variety of drugs perfusion, which effectively protected and partially restored the functions of heart, liver and kidney, but failed to restore the functions of brain. The study is of great significance for organ transplantation, clinical rehabilitation and ischemic disease research. [2] The pre-filling fluid is a mixture of crystalline fluid, oxygen-carrier and blood, with a variety of drugs that are beneficial to cellular and molecular repair while against damage, such as oxygen-carrying agents, NO synthase inhibitors, necroptosis inhibitors, ketone bodies, antioxidants, neuroprotectants, nerve inhibitors, pan-caspas enzyme inhibitors, antibiotics, anti-inflammatory agents, antihistamines and so on. By inducing ventricular fibrillation and

then 1 hour after warm ischemia in pigs, the authors used an OrganEx hypothermic (28□) perfusion system to protect tissue integrity, reduce cell death, and restore the molecular and cellular functions of multiple organs, which can even restore circulation and correct metabolic imbalance.[2] Single-nucleus transcriptomic analysis showed enhanced expression of genes that inhibit cell apoptosis, cell damage, inflammatory mediators, and promote cell repair processes (Figure 1) [2].

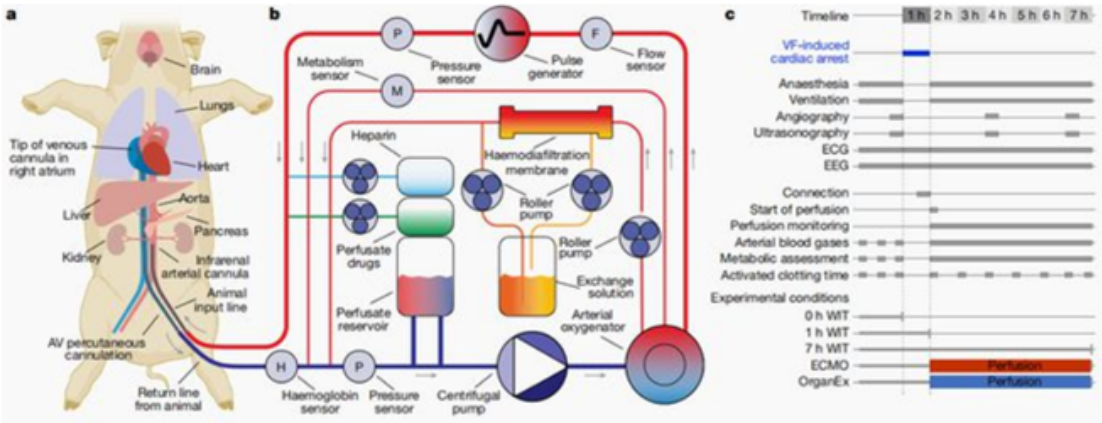

Figure 1: OrganEx technology and workflow.

Emergency Preservation Resuscitation (Epr)

The ventricular fibrillation and warm ischemia animal mode of OrganEx perfusion system is made in anesthetized female porcine, which is more difference from the clinical cases of cardiac arrest caused by uncontrolled hemorrhagic shock, with symptoms of hypothermia, acidosis and coagulopathy. Compared with the study of molecular cell and tissue organ function, in recent years, the clinical emergency treatment has evolved from damage control resuscitation to emergency preservation resuscitation and from animal experiment to clinical experiment for the patients with severe traumatic and hemorrhagic shock with cardiac arrest. [3] In the EPR, the descending aorta is blocked as soon as possible (within 5 minutes of cardiac arrest) in cases with temporary uncontrolled bleeding and tissue damage, Selective Aortic Arch Perfusion (SAAP) is performed with 0-4℃normal saline at high speed (2-5 L/min), while drained from the vena cava or right atrium. The temperature is lowered rapidly at 2-3℃/min. The temperature of the tympanic membrane is lowered to 10℃, and that of the rectum to 30℃, so as to buy one hour for final hemostatic and tissue repair. After that, the patient is transferred to cardiopulmonary bypass and slowly rewarmed at 0.5℃/min with blood products transfusion, till the body including brain function complete recovery (Figure 2) [3,4].

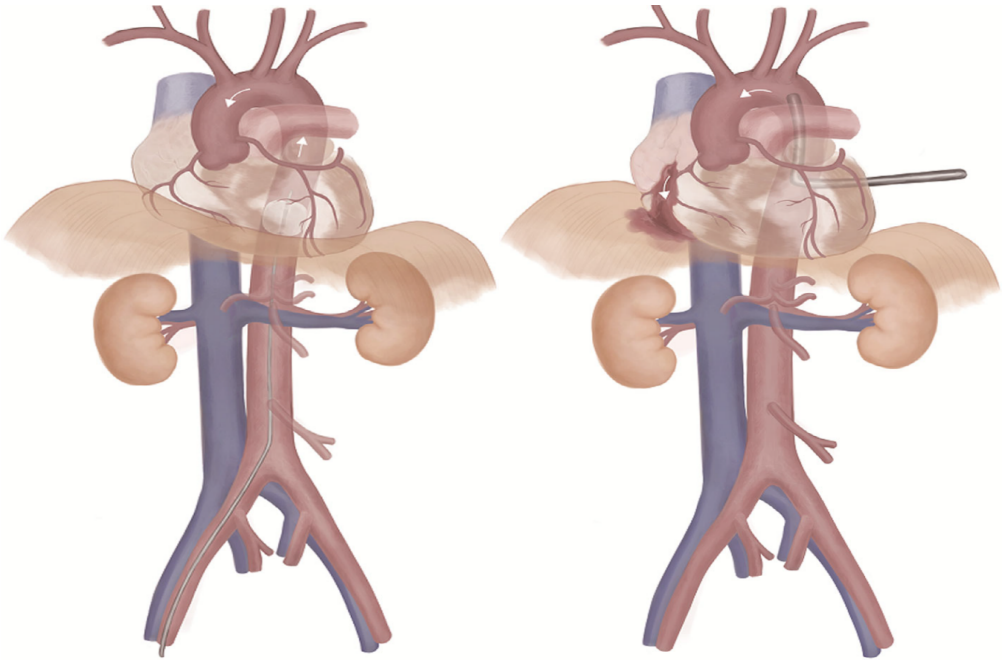

Figure 2: Selective aortic perfusion and emergency preservation resuscitation.

Thermoregulation

Severe multiple trauma combined with hemorrhagic shock is characterized by severe pathophysiological disorders and metabolic abnormalities with a lethal triad of metabolic acidosis, hypothermia and traumatic coagulation. Hemorrhage and loss of body fluid can lead to decreased tissue perfusion, which can replace aerobic metabolism of cells with anaerobic metabolism and glucose hydrolysis, and result in lactic acidosis. Hypovolemia and hypoperfusion result in contraction of peripheral circulation and a decrease in body temperature. [1,3,5] Hypothermia secondary to hemorrhagic shock is often an independent risk factor for death. Metabolic acidosis and hypothermia can jointly aggravate the coagulation dysfunction, while thrombocytopenia and consumptive coagulation disorder can lead to further bleeding in patients with severe trauma and accelerate the process of shock. Lethal triad acidosis, hypothermia and coagulation dysfunction interact and promote each other, and when they do, death is imminent [1,3,5].

However, the above-mentioned organ perfusion and cardiocerebral deep hypothermia perfusion protection, whether at the cellular and molecular level or the overall recovery including brain function, all of these experiments have properly applied hypothermia protection technology. Hypothermia effectively reduces tissue metabolism and increases hypoxia tolerance, which is an active process. Studies show that mild therapeutic hypothermia (32-34℃) after cardiac arrest reduces oxidative stress, cell apoptosis, autophagy and inflammatory reaction, which is conducive to the recovery of neural function. While the hypothermia occured in hemorrhagic shock reflects the severe trauma of the body, the decompensation of tissue and organ functions, and the disorder of temperature regulation, which is a passive process [6,7].

Future Research Direction

In these experiments, moderate hypothermia was used in OrganEx system, while deep hypothermia was used in emergency protection resuscitation. The way of hypothermia perfusion management mode and method of controlling temperature in resuscitation still need to be explored, the effects of hypothermia on cardiac function, coagulation function, immune function and drug metabolism still need to be further studied. [1,8] In the systemic hypothermic perfusion experiments, tissues and organs function can recover and even brain function can recover, untill now, it remain unclear whether the organ protective pre-filling fluid, including extracellular and intracellular fluids, synthetic red blood cells, fluorocarbon, and other oxygen-carryier fluids, can better protect the function of tissues and cells, even the function of nervous system, to prolong the time for wound repair in tissues and organs. [1,3] It still need to be explored whether antioxidants, anti-apoptotic agents and other agents in the organEx system can reduce ischemia-reperfusion injury and prolong the tissue repair time during emergency preservation and resuscitation. Based on

future clinical or basic research, it should be certified the effects of anti-injury, anti-oxidation, anti-inflammation, anti-apoptosis, membrane stabilizing agents, free radical scavengers, anti-reperfusion injury drugs, energy substrates, hemostatic drugs in the hypothermic perfusion resuscitation [2,3].

In mechanism research of molecular biology, the effects of hypothermic perfusion resuscitation on cell gene transcription, inflammatory mediators expression, free radical production, oxidative damage, apoptosis damage need to be further explored, especially in the central nervous system including the neuron, neuroglia and microglia cells. [4,8] In the future, we should not only protect the function of molecule and cell at the micro-level, but also protect the brain function at the macro-level in the treatment of ischemia and reperfusion injury [2-4].

Funding Source: This work was supported by the National Natural Science Foundation of China (81270560).

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