Transformation of Mechanical Perfusion Technique of Isolated Liver Based on Factor Analysis

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Abstract: In different stages of organ preservation, evaluation and repair, there are different modes of in vitro liver perfusion technology. At present, the commercialized technology focuses on the modes of hypothermic machine perfusion (HMP), subhypothermic machine perfusion (SNMP) and normothermic machine perfusion (NMP).

1. Introduction

Based on the technical analysis of four commercial equipment, it is found that there is no equipment in the market that can meet all perfusion modes and different mode combinations[1]. At the same time, combined with the characteristics of each stage of organ perfusion mode and the clinical physiological characteristics of liver, we developed a full-functional product to meet the clinical research and application of all isolated liver perfusion.

2. Research Progress on Transformation of mechanical perfusion technology of isolated liver

2.1 Perfusion principle

The ideal cold preservation time of liver in vitro is less than 8 h. in clinic, 12-15 h is generally used as the selection standard for donor liver[2]. The principle of using machine perfusion (MP) to preserve liver is to use mechanical pump to continuously pump blood or preservation solution, nutrient substrate, liver function auxiliary repair drugs into perfused organs through the system[3]. At the same time, oxygenator, microthrombotic filter, dialyzer and other extracorporeal circulation consumables can be selected according to the perfusion mode. According to the perfusion temperature, it can be divided into HMP (4-6 ℃), SNMP (20-30 ℃) and NMP (37 ℃)[4].

2.2 Perfusion mode and intervention time

According to the clinical purpose of isolated liver perfusion (preservation, activity evaluation, repair, intervention treatment), different perfusion modes can be selected[5]. So far, there are various research directions and clinical applications of liver perfusion. Different perfusion temperatures (hypothermia, mild hypothermia, sub normal temperature and normal temperature) can be used to treat the isolated liver, prolong the preservation time before transplantation, evaluate the liver function (blood gas, Biochemistry), repair liver function (bile generation, lactate and glucose metabolism), and improve the liver function by the length of perfusion time Nowadays, many liver perfusion models have been extended to different stages of liver transplantation: ① static cold storage (SCS), which remains the gold standard. ② Before liver transplantation, especially in extended criteria donors (ECD) or longer cold ischemia time. ③ There was a period of SCS before liver transplantation. ④ After the liver was harvested, there was ischemia of donor after cardiac death (DCD) before SCS. ⑤ The whole preservation stage from liver acquisition to transplantation. ⑥ Then HMP, SNMP and NMP were implemented[6-8].

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2.2.1 HMP

Cold preservation is based on the principle of reducing aerobic metabolism. On this basis, HMP can keep the low aerobic metabolism environment of organs, remove the waste inside the liver, wash the liver congestion, thrombus and provide metabolic substrate through continuous 4-6 ℃ perfusion, so as to prolong the preservation and improve the internal environment of the liver. The commercial cold perfusion equipment and animal experiments were performed with portal pulse pressure of 3-5 mmHg (1 mmHg = 0.133 kPa) and hepatic arterial pressure of 20-30 mmHg. Besides the above technical parameters, other parameters such as temperature and oxygen selection and control have a great influence on the effect of low temperature perfusion system.

2.2.2 SNMP

The perfusion temperature of SNMP is 20-30 ℃. The perfusion fluid provides metabolic nutrients and oxygen for the liver. The liver activity is evaluated by the blood gas and biochemical parameters of the perfusion fluid, which promotes the synthesis of ATP by isolated hepatocytes and the recovery of liver physiological function. The sub normal temperature mechanical perfusion system is mainly composed of power unit, circulation unit, organ unit, temperature control unit and oxygenation unit. Generally, NMP equipment can be directly used for SNMP, with hepatic artery perfusion controlled at 60 mmHg and static pulse pressure controlled at 2-6 mmHg.

2.2.3 NMP

The biggest characteristic of NMP is that the perfusion temperature is consistent with the body temperature. In order to restore the energy reserve of donor organs and maintain the normal metabolism of organs, the physiological environment was simulated and the temperature of the system was maintained at 32-37 ℃. The main system parameters involved in NMP include temperature, pressure, flow and so on[9]. The temperature depends on the physiological temperature of the liver. The pressure parameters include portal vein pressure and hepatic artery pressure. The centrifugal pump pipeline system is used to simulate the pressure corresponding to the physiological value of the body. The portal vein perfusion pressure is 4-8 mmHg and the hepatic artery perfusion pressure is 60-80 mmHg.

3. Commercial products of isolated liver perfusion equipment

3.1 Lifeport Liver Transporter

James guarrera team used the low-temperature mechanical perfusion equipment of organ recovery systems for clinical application, and confirmed the clinical application effectiveness of the liver cold perfusion transport device, which can effectively reduce the early primary graft failure after liver transplantation. In 2015, the team transplanted the abandoned donor liver to the recipient after low-temperature mechanical perfusion, and the operation was successful, which confirmed that the device can improve the marginal donor liver and abandoned donor liver. The device is in the clinical experimental stage. It is used to operate with the liver to precisely control the perfusion of hepatic artery and portal vein. Two safety mechanisms support the preservation of liver, dynamic cold perfusion and static cold storage.

3.2 Liver Assist: Liver Assist

The liver perfusion machine is developed by the medical center of Groningen University in the Netherlands. It uses two sets of extracorporeal circulation systems to supply blood to the hepatic artery and portal vein. The equipment controls the perfusion pressure and automatically regulates the blood flow through intrahepatic resistance. The two-way membranous pulmonary circulation allows the two pulse independent oxygenation, which can be adjusted to the blood gas value close to human physiology. The temperature can be set according to the desired MP type (the minimum temperature is set at 10 ℃), and the liver can be mechanically perfused at low temperature, sub normal temperature and normal temperature.

3.3 OrganOX

Organoxmetra is a portable normothermic liver perfusion system, which is equipped with battery and automatic oxygen supply system. Its advantage is that it can be applied to the normothermic perfusion of donor liver for up to 24 hours. It can provide the information of liver hemodynamics (blood pressure, flow), synthesis and metabolism at the same time of perfusion. It is equipped with CDI 500 continuous blood gas analysis system, blood glucose analyzer, blood glucose analyzer, etc Microinjection pump can maintain normal metabolism through real-time blood gas analysis, promote donor liver regeneration and repair, and assist clinicians to evaluate the suitability of organ transplantation.

3.4 Transmedics

Organ care system (OCs) of transmedics ™. It is a mobile perfusion and monitoring system, which can maintain organ activity in near physiological state. The system enables surgeons to better utilize and monitor organs between donors and recipients. It is composed of movable perfusion equipment and perfusion consumables. The mobile perfusion equipment includes wireless display screen, flow sensor, pressure sensor, blood gas sensor, centrifugal blood pump motor, gas cylinder, standby power supply and other components. The device displays various perfusion parameters and blood gas parameters, and can adjust the perfusion fluid parameters in real time through the micro injection pump. The perfusion fluid can be controlled at constant temperature through the temperature control device. At the same time, the wireless monitoring function is implanted to ensure that the perfusion platform can be obtained in the transfer between donor and recipient hospitals, and the product is in clinical trials. Its technical features are as follows: 1) open ring perfusion of vena cava, blood heating by electric heating, perfusion temperature constant 37 ℃; ② The two-way non independent hepatic perfusion pipeline, the pressure control perfusion of hepatic artery centrifugal pump, the flow control of portal vein centrifugal pump re regulating throttle valve, the two-way blood through the same membranous lung, blood perfusion parameters are the same; ③ The integrated car design and spare battery can realize the perfusion and transportation in different hospitals; ④ Wireless screen, which can separate the device from the monitoring screen, visual interface design, can track organ perfusion status, perfusion temperature, dual pulse flow, pressure, resistance index, blood gas, gas flow, micro injection pump control, electricity and other key data; ⑤ With WiFi function, the perfusion liver can be remotely monitored, consulted and adjusted; ⑥ Automatic gas transmission system and standby power supply are provided to avoid gas and power supply problems during filling.

4. Functions of a perfect equipment

Liver assist covers the perfusion requirements of HMP, SNMP and NMP for liver perfusion, but it does not consider the transport between the recipient and the donor hospital in the design. It is only suitable for repairing and evaluating perfusion in the recipient hospital or the donor hospital alone. At the same time, it lacks perfect perfusion configuration modules, such as micro injection pump, online continuous blood gas analysis, wireless remote monitoring, etc.

Organox and transpedics are well equipped and suitable for transfer and preservation between hospitals, but they have the following disadvantages: 1) single pump perfusion can not meet the physiological regulation function of human body by artificially adjusting the pressure and flow of portal vein; ② Only focus on the NMP field, but the situation of different liver is different, it should be able to meet the perfusion mode of other temperatures for the repair of marginal liver. In addition, there are other research directions in the field of isolated liver perfusion, such as gradient rewarming perfusion of liver, hepatic artery pulsation and constant pressure perfusion switching, portal vein constant pressure perfusion and constant current perfusion switching, and so on.

Therefore, a complete liver perfusion system in vitro should include the following functions: ① transport design of HMP, SNP and NMP to increase the preservation time and repair possibility of

liver; ② Hepatic artery and portal vein perfusion were controlled independently (automatic control of different mode switching) to meet physiological pressure and flow demand; ③ Online continuous blood gas analysis and injection pump configuration, quickly adjust perfusion fluid blood gas parameters; ④ Automatic ventilation system, according to the oxygen partial pressure, carbon dioxide partial pressure and oxygen saturation of blood gas, adjust the mixing proportion and overall flow of oxygen, air and carbon dioxide; ⑤ Remote monitoring function and big data server, expert consultation can obtain perfusion real-time parameters and historical curve through mobile app, evaluate the status of liver, and monitor the status during transportation; ⑥ Automatic perfusion program setting can meet the requirements of gradient rewarming perfusion (COPE mode), multi-mode perfusion mode switching (constant pressure, constant current, pulsation) and other automatic perfusion modes; ⑦ Dual membrane lung configuration can realize different oxygenation configuration of hepatic artery and portal vein to meet the physiological needs of liver; ⑧ The historical data of hepatic artery and portal vein flow and pressure were recorded and the perfusion trend map was formed. The bile production volume was recorded and the generation trend map was used to evaluate the vascular resistance index and bile synthesis function of the liver[10].

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