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OPTIMAL STRATEGIES FOR PREVENTION OF ISCHEMIA-REPERFUSION INJURY IN HEART TRANSPLANTATION WITH PROLONGED COLD ISCHEMIA TIME (REVIEW)

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The shortage of organs for transplant remains a major challenge in transplantology. Transporting donor organs over long distances increases cold ischemia time, which is a risk factor for ischemia-reperfusion injury (IRI). In the face of critical shortages, the method and timing of organ preservation are crucial in increasing the donor pool. This paper examines the approaches, benefits, and drawbacks of organ preservation techniques used around the world.

Keywords: cardioplegia, ischemia-reperfusion injury, heart transplantation, allograft.

INTRODUCTION

Gaps in the organization of organ donation currently remain the main problem of transplantology. Using unclaimed organs from distant locations is one solution to the critical organ shortage. he lengthy distances between donor bases and transplant facilities in interregional interactions, the predominant use of service vehicles or commercial aircraft for organ transportation, and the absence of "green corridors" are the hallmarks of the Russian organ donation system. As a consequence, long transportation and logistical challenges prolong the cold ischemia time [1].

Cardiac graft quality is inversely proportional to cold ischemia time, and the recommended maximum cold ischemia time for a donor heart is 240 minutes [2, 3]. Exceeding this safe threshold increases the risk of postoperative allograft dysfunction and death. This becomes especially relevant in heart transplantation from expanded criteria donors, as such a heart is most sensitive to the effects of ischemia. At the same time, the number of suboptimal donors in Russia is gradually increasing. Heart transplantation with prolonged cold ischemia is most typical for European countries, where the proportion of heart transplantations with ischemic time of more than 4 hours is over 40% [4].

During ischemia, decreased oxygen availability causes a shift from fatty acid metabolism to anaerobic glycolysis. The resulting lactic acidosis causes the extracellular pH to drop to 6.0–6.5. Continued acidosis results in activation of several transmembrane ion channels and receptors, each contributing to calcium overload, metabolic dysfunction, and ultimately cell death [5].

Ischemia-reperfusion injury (IRI) is the primary cause of donor graft dysfunction after prolonged transportation. Given the prohibitive risk of IRI and primary graft dysfunction with cold ischemia lasting more than 4 hours, there is an obvious necessity to enhance myocardial protection, but there is no consensus on the effectiveness of a particular method of preservation in prolonged ischemia of donor heart.

Currently in Russia, the standard heart preservation method is perfusion with Custodiol solution followed by static storage in a thermal container with ice and coolants; however, this is not able to fully protect the organ under conditions of prolonged ischemia [6]. Metabolism during cold cardioplegia does not stop under ischemic conditions; energy supply of metabolic processes occurs in anaerobic conditions, which leads to lactate accumulation and cardiomyocyte acidification, and metabolic acidosis occurs. In addition, histidine, one of the main components of Custodiol, has demonstrated some cytotoxic effects [7]. On the other hand, uncontrolled reduction in graft temperature to critical values and uneven cooling of the heart leads to impaired transmembrane transport of electrolytes, formation of free radicals that damage cardiomyocytes, as well as the process of tissue crystallization. Brain death causes a cascade of hormonal changes, changes in catecholamine levels, and release of inflammatory mediators (IL-1, IL-6, IL-8), resulting in hypotension and organ hypoperfusion. Appropriate handling of a brain-dead donor (conditioning) prior to

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the withdrawal stage is equally critical because hypoperfusion and inflammatory response cause extra harm to the transplant even before IRI develops [2].

The increasing use of expanded criteria donors [1] – high inotropic therapy, over 55 years of age, myocardial hypertrophy, transmissible coronary atherosclerosis – also requires revision of the standard approach to heart transplant preservation.

Thus, the relevance of developing new strategies for graft transportation and preservation is obvious. Currently, various strategies have been described to further improve donor heart preservation results, including pharmacological, organizational and other methods that can significantly reduce IRI severity.

Analysis of known strategies for reducing the damaging effect of IRI during prolonged transportation of donor heart allows us to highlight several key aspects.

It is commonly known that when prolonged cold ischemia is anticipated, it is best to use hearts from young donors. An interesting observation was published by Kim et al [8]. When analyzing 43,304 heart transplantations, the scientists found that recipients of obese donor hearts experienced improved immediate and long-term outcomes when organ ischemic times exceeded 4 hours.

REPEATED INFUSION OF PRESERVATION SOLUTION

Several studies have shown that the use of repeated infusion of preservation solution (crystalloid, blood cardioplegia), which is given continuous retrograde or as terminal "hot shots", reduces organ ischemic injury, shortens intensive care stay, and improves early survival after transplantation [9]. The authors conclude that the technique is particularly relevant when using hearts from marginal donors and with prolonged cold graft ischemia. The history of research on the efficacy of repeated cardioplegia dates back to the 1990s, when the first prospective studies in this field were conducted.

Two studies used normothermic blood cardioplegia, administered immediately before the completion of aortic occlusion (terminal "hot shot") [10, 11]. The results of these studies showed that the use of blood cardioplegia was associated with a lower incidence of right ventricular failure, cardiac arrhythmias, and laboratory signs of ischemia (decreased levels of creatine kinase (CK), creatine kinase MB (CK-MB) in the early postoperative period. Twelve-year heart transplant outcomes demonstrated [12] that the use of blood cardioplegia is safe and results in comparable survival and prevalence of adverse events late after orthotopic heart transplantation. Encouraging results have also been obtained regarding the reduced incidence of chronic graft rejection and less prevalence of coronary artery disease in heart transplant patients after blood cardioplegia, but larger prospective studies in this area are needed to validate this hypothesis.

Two other studies used antegrade cold blood cardioplegia and an additional terminal "hot shot" with warm blood cardioplegic solution. Cold crystalloid cardioplegia was injected initially and cold blood cardioplegia (Buckberg) was infused every 30 minutes as soon as the graft arrived in the operating room [13]. No surface cooling was used. Warm blood cardioplegic reperfusion was administered before removal of the aortic clamp. Mean ischemic time was 158 minutes. The post-transplant need for catecholamines was tenfold lower in patients with warm blood cardioplegia reperfusion. Also, cytologic examination of the graft (after 7 days) showed a lower degree of ischemic lesions in this group of patients.

Some studies have been devoted to the use of continuous retrograde normothermic blood cardioplegia during donor heart implantation [14–16]. The results of these studies revealed that continuous normothermic blood cardioplegia can lead to less ischemic injury according to myocardial pathohistologic examination, while lower CK, CK-MB levels, more frequent recovery of spontaneous sinus rhythm, and lower duration of inotropic therapy were observed in groups using continuous blood cardioplegia technique.

A single-center retrospective study in Switzerland compared orthotopic heart transplant outcomes with (37 patients) and without additional cardioplegia (41 patients) [17]. The myocardial preservation protocol was standardized and included the infusion under low pressure of 2000 ml cold (4–8 °C) Celsior solution. In the study group, an additional single antegrade coronary infusion of 100 ml cardioplegic solution (Cardioplexol™, Laboratorium Dr G. Bichsel AG, Unterseen, Switzerland) was administered immediately before graft implantation. Cardioplexol™ is a ready-to-use solution based on potassium, magnesium, procaine and xylitol. The study group showed more frequent spontaneous restoration of sinus rhythm after aortic clamp removal and myocardial reperfusion, lower CK-MB/CK ratio, and shorter ICU and hospital stays.

Regarding immediate transplant outcomes, an analysis of available publications is favorable to the use of repeated or extra infusions of preservation solution, particularly when the preservation time is more than 240 minutes.

ISCHEMIC PRECONDITIONING AND POSTCONDITIONING

Because pharmacologic and ischemic preconditioning activate mitochondrial ATP-sensitive potassium channels, they may be useful cardioprotective methods [18]. Mozaffari et al. argue that the protective effect of ischemic preconditioning and postconditioning is linked to reduced IRI through regulation of the phosphatidylinositol-3 kinase (PI3K)/Akt pathway, which, in turn, leads to phosphorylation and inactivation of glycogen synthase

kinase-3β (GSK-3β), culminating in inhibition of the mitochondrial permeability transition pore. There have also been descriptions of mitochondrial KATP channels, which when activated, can confer cardioprotection.

The effect of preconditioning was demonstrated in a study on sheep orthotopic heart transplantation models. Preconditioning was achieved with brief (5 seconds) aortic occlusion followed by 10 minutes of reperfusion. The heart was then arrested with 1 liter of antegrade crystalloid cardioplegia, explanted, and placed in a transport cooler. Next, the heart was transplanted into a recipient sheep. The total ischemic time was 2 hours. The study showed that a single episode of preconditioning significantly reduced myocardial stunning and increased ATP level in tissues [19].

In another study, remote ischemic conditioning was used immediately after anesthesia induction (preconditioning) and 20 minutes after aortic declamping (postconditioning) [20]. The technique itself consists of applying four cycles of 5-min ischemia and 5-min reperfusion on the right upper limb by a cuff inflated to 200 mmHg, then the cuff was deflated. Patients in the control group underwent false cuffing of the right upper arm without inflation. Serum cardiac troponin I level was determined preoperatively and at 3, 6, 12, 24 hours after aortic declamping.

In summary, remote ischemic preconditioning and postconditioning reduced myocardial injury 6 hours after aortic clamping, but there was no evidence that this method could improve clinical outcomes. Preconditioning and postconditioning techniques in cardiac transplantation have been shown to reduce the severity of myocardial injury as measured by laboratory parameters, but no significant effect on clinical outcomes has been found. Available reports are based on a small number of patients, on retrospective analysis. A detailed study of the mechanism of the technique and further trials are needed.

PRESERVATION SOLUTIONS

As mentioned above, the standard cardiac preservation method is perfusion of the heart with a preservation solution followed by static storage in a refrigerator with ice and coolants. Despite notable disadvantages of HTK (Custodiol) solution, it remains the main preservation solution used in Russia both in heart transplantation and in cardiac surgery involving prolonged myocardial ischemia.

There are currently more than 167 different cardiac preservation solutions for heart transplantation. The most commonly used are histidine-tryptophan-ketoglutarate (HTK) solution, University of Wisconsin (UW) solution, and Celsior solution [21]. Due to the small number of heart transplants performed, there is a lack of high-quality randomized clinical trials to determine the effect of preservation fluids on graft function and survival. Such studies often lack the capacity to determine optimal regimens for the use of these preservation solutions.

Experimental studies provide conflicting results regarding the efficacy of different preservation solutions in preserving cardiac function during routine transportation with ice and coolants. According to some studies that compared UW with Celsior solution [22], UW demonstrated better survival at 30 and 90 days after transplantation. Recipients receiving suboptimal allografts, defined as donor age >50 years or ischemic duration >4 hours, had significantly increased mortality at 30 days and 1 year. The UW solution was also associated with better survival compared with the HTK solution. When HTK was compared with Celsior solution, there was no statistical difference in donor heart dysfunction and in-hospital mortality, with a mean ischemic time of 187.9 ± 52.6 minutes [23]. However, in multivariate analysis, a combination of recipient and donor age ≥60 years, intraoperative biventricular failure, and prior cardiac surgery were predictors of in-hospital mortality.

Four-hour preservation of porcine heart grafts obtained from beating and non-beating donor animals in Somah resulted in better cardiomyocyte and endothelial cell viability and higher expression levels of myocardial and endothelial proteins compared with controls. Better cardioprotection was observed after 5-hour preservation of porcine heart at about 21 °C compared to Celsior and UW.

The new Custodiol-N solution is an intracellular preservation solution that differs from HTK by its lower concentration of histidine, addition of amino acids glycine, alanine and arginine, N-acetyl-histidine partially replacing histidine, and aspartate and lactobionate replacing chloride. The superiority of Custodiol-N over HTK has been demonstrated in a rat model of heterotopic heart transplantation [24, 25]. Also, Custodiol-N showed significant benefit in a heart transplantation model in dogs after prolonged preservation for 8 and 12 hours. After heart transplantation in animals from the control group using conventional HTK, in no case was it possible to wean off from artificial circulation; in the Custodiol-N group, all animals were withdrawn from artificial circulation with stable hemodynamics [26]. According to the authors, the iron chelator LK614 played a key role in this mechanism by reducing the chelatable iron content in the myocardium. Thus, Custodiol-N, UW, Somah look preferable to conventional HTK with respect to long-term preservation.

A detailed analysis was performed by Minasyan et al. In their opinion, the possible methods of improving preservation methods in prolonged ischemia are by optimizing the composition of the preservation solution (PS), adding various active components to the PS (enhancing the buffer capacity and colloidal components), using polarizing PS, constant perfusion of donor heart, and low-temperature preservation [27]. The theory of

low-temperature preservation (<less than 0 degrees Celsius) using cryoprotectant protein looks interesting, considering some contradiction with the concept used in the Paragonix system [28]. However, standard cold transportation of donor hearts in a container with ice has several disadvantages, in particular, the lack of organ temperature control. A study on 186 organs showed that the average temperature of organs during transportation fell below +2 °C, and then below ±0 °C after 6 hours of transportation [29]. Preservation at this temperature may cause injury to the donor heart, especially if prolonged. It is known that there is damage to cardiomyocyte structures at a temperature <2 °C, irreversible diastolic dysfunction occurs at <1 °C, and protein denaturation at <0 °C.

The SherpaPak Cardiac Transport System (CTS) (Paragonix Technologies, MA, USA) has been developed, which involves uniform cooling with constant temperature from 4 °C to 8 °C, excluding any environmental influence, which prevents the risk of cold injury to the organ and further irreversible changes in myocardial cells. A decrease in post-heart transplant in-hospital mortality was demonstrated in a study group (Paragonix preservation) compared to standard "ice" preservation [30]. The Paragonix SherpaPak™ Cardiac Transport System demonstrates excellent results compared to standard cold preservation. It is necessary to study the system for cardiac preservation of >4 hours.

NORMOTHERMIC MACHINE PERFUSION OF DONOR HEART

The most promising technology for long transportation of donor organs is machine perfusion. Currently, the device for normothermic machine perfusion (NMP) of the heart manufactured by TransMedics Inc. (Andover, Massachusetts, USA) has the greatest clinical experience [31]. The prospective multicenter randomized PROCEED II study compared the NMP system with standard heart storage on ice. The 30-day patient survival rate was 94% in the machine perfusion group with a mean organ ischemia time of 5.4 hours and 97% in the control group. Short-term clinical results showed that the TransMedics Inc. organ care system was non-inferior to storing the graft in a refrigerator. Further studies demonstrated no differences in two-year survival or serious cardiac-related adverse events between the two groups [32].

In expanded criteria donors, the use of TransMedics Inc. normothermic perfusion systems has demonstrated a significant advantage over refrigerated allografts. The EXPAND-Heart study showed that expanded criteria hearts using NMP had a 30-day survival rate of 94% and a 6-month survival rate of 88%. The incidence of severe primary graft dysfunction was 11% [33]. There is also evidence of successful heart transplantation with an ischemia time of 611 minutes, which was performed using a normothermic myocardial perfusion system [34]. According to a study conducted in the USA, this machine perfusion system was more cost-effective than standard refrigerated graft storage [35]. The use of a normothermic perfusion system seems to be the most preferable and physiologic way to preserve the donor heart. The TransMedics system demonstrates good results for short- and long-distance transportation. The disadvantages of the system are determined by its weight/size characteristics and operating features, but its primary limiting factor is its exorbitant cost. Currently, normothermic cardiac perfusion is not used in Russia.

TECHNOLOGY OF THE FUTURE

Proton-activated acid-sensing ion channels (ASIC1a) are known to play a key role in IRI. Redd et al. demonstrated in an experimental rat model that the use of pharmacologic ASIC1a inhibitors derived from the venom of the Australian spider Hadronyche infensa (Hi1a) improves functional recovery of isolated rodent hearts after prolonged hypothermic ischemia. To evaluate the cardioprotective effect of ASIC1a inhibition in a donor heart preservation model, the scientists added a pharmacologic Hi1a inhibitor to Celsior solution, with an ischemia time of 8 hours. Coronary blood flow was then restored, and cardiac function assessed. Compared to the control group, hearts preserved with Hi1a supplementation showed a significant improvement in the recovery of aortic flow and cardiac output. These findings demonstrate that Hi1a has high cardioprotective activity against IRI in a clinically relevant model of donor heart preservation under long-term cold storage [5].

CONCLUSION

A detailed understanding of the pathophysiology of IRI and a fundamental approach are necessary when looking for an optimal method of preserving donor heart with prolonged cold ischemia. Available reports on this problem, with presumed prolonged cold ischemia, require that donors without associated risk factors be used, that any loss of time during transportation be avoided, and that repeated infusions of the preservative solution or blood cardioplegia be performed. There is an obvious urgent need to develop new Russian-made preserving solutions and to come up with new organ perfusion techniques.

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