DOI: https://doi.org/10.51922/2616-633X.2024.8.1.2181

PRACTICAL APPLICATIONS OF HEMOGLOBIN-BASED OXYGEN CARRIERS IN ORGAN TRANSPLANTATION

Qinqi Wang[1,2], Liana Shestakova[3], Irina Kolesnik[4], Jianxun Ding[5,*], Tianmeng Sun[6,*], Wenliang Li[1,2], Youry Ostrovsky[3], Yury Aliakseyeu[7]

School of Chemical and Environmental Engineering, Changchun University of Science and Technology, Changchun, 130022, China[1]
Redpharm (Beijing) Biotech Limited, Beijing, 100176, China[2]
Belarusian Republican Scientific and Practical Center of Cardiology, 110 B R.Luxemburg Str., Minsk, 220036, Belarus[3]
Institute of Physical Organic Chemistry of National Academy of Sciences of Belarus, 13 Surganov Str., Minsk, 220072, Belarus[4]
Key Laboratory of Polymer Ecomaterials, Changchun Institute of Applied Chemistry, Chinese Academy of Sciences, Changchun, 130022, China[5]
Key Laboratory of Organ Regeneration and Transplantation of Ministry of Education, Institute of Immunology, The First Hospital, Jilin University, Changchun, 130061, China[6]
Belarusian "Innovative International Center for Scientific, Educational and Commercial Cooperation "Delo", Minsk, Belarus[7]
Corresponding author: Wenliang Li, Ostrovsky Youry
Email: shestakova@hotmail.com

УДК 616-089.843:615.384

Key words: *organ transplantation, artificial oxygen carriers, HBOCs.*

FOR REFERENCES. Qinqi Wang, Liana Shestakova, Irina Kolesnik, Jianxun Ding, Tianmeng Sun, Wenliang Li, Youry Ostrovsky, Yury Aliakseyeu. Practical applications of hemoglobin-based oxygen carriers in organ transplantation. *Neotlozhnaya kardiologiya i kardiovaskulyarnye riski* [Emergency cardiology and cardiovascular risks], 2024, vol. 8, no. 1, pp. 2181–2186.

In recent years, much attention has been paid to the excellent oxygen transport properties of Hemoglobin-based oxygen carriers (HBOCs), which deliver oxygen to organs and tissues via arterial blood by binding oxygen and carbon dioxide via venous blood back to the lungs for respiratory elimination from the body. Studies have shown that HBOCs, which are characterized by low immunogenicity, little risk of hemolytic reaction, low viscosity, and enhanced diffusive oxygen transport, can show excellent results in clinical applications in the field of organ transplantation. Early HBOCs generations had a short intravascular circulation life-time, could cause vasospastic and toxic side effects induced by free hemoglobin circulation. Polymerization of hemoglobin molecules significantly increased the size of acellular hemoglobin, thus minimizing the extravasation and prolonging their half-life in intravascular circulation, and was considered to be the key factor in mitigating the vasoconstriction effects.

The aim of this paper is to provide an in-depth review of the current status of research and application of HBOCs in organ transplantation, as well as to look forward to their future application in this field.

ВОЗМОЖНОСТИ ПРАКТИЧЕСКОГО ПРИМЕНЕНИЯ ПЕРЕНОСЧИКОВ КИСЛОРОДА НА ОСНОВЕ ПОЛИМЕРИЗОВАННОГО ГЕМОГЛОБИНА В ОРГАННОЙ ТРАНСПЛАНТАЦИИ

Циньци Ван[1,2], Л.Г. Шестакова[3], И.А. Колесник[4], Цзяньсюнь Дин[5], Тяньмэнь Сунь[6], Вэньлян Ли[1,2], Ю.П. Островский[3], Ю.Г. Алексеев[7]

Школа химической и экологической инженерии, Чанчуньский университет науки и технологий, Чанчунь, 130022, Китай[1]
Редфарм (Пекин) Биотех Лимитед, Пекин, 100176, Китай[2]
Государственное учреждение «Республиканский научно-практический центр «Кардиология», г. Минск, Беларусь[3]
Государственное научное учреждение «Институт физико-органической химии Национальной академии наук Беларуси», г. Минск, Беларусь[4]
Главная лаборатория полимерных экоматериалов, Чанчуньский институт прикладной химии, Китайская академия наук, Чанчунь, 130022, Китай[5]
Главная лаборатория регенерации и трансплантации органов Министерства образования, Институт иммунологии, Первая больница, Университет Цзилинь, Чанчунь, 130061, Китай[6]
Общество с ограниченной ответственностью «Инновационный международный центр научно-образовательного и коммерческого сотрудничества «Дело», г. Минск, Беларусь[7]

Ключевые слова: *трансплантация органов; переносчики кислорода на основе гемоглобина, HBOCs.*

ДЛЯ ЦИТИРОВАНИЯ. Циньци Ван, Л.Г. Шестакова, И.А. Колесник, Цзяньсюнь Дин, Тяньмэнь Сунь, Вэньлян Ли, Ю.П. Островский, Ю.Г. Алексеев. Возможности практического применения переносчиков кислорода на основе полимеризованного гемоглобина в органной трансплантации. *Неотложная кардиология и кардиоваскулярные риски*, 2024, Т. 8, № 1, С. 2181–2186.

В последние годы большое внимание уделяется кислородно-транспортным свойствам переносчиков кислорода на основе гемоглобина (HBOCs), которые способны связывать кислород в легких и доставлять его к органам и тканям через артериальную кровь для обеспечения тканевого дыхания. Исследования показали, что HBOCs, характеризующиеся низкой иммуногенностью, малым риском гемолитической реакции, низкой вязкостью и улучшенным диффузионным переносом кислорода, могут показать хорошие результаты при клиническом применении в области трансплантации органов. Ранние поколения HBOCs имели короткое время внутрисосудистой циркуляции из-за нестойкости тетрамера гемоглобина, вызывали побочные вазоспастические эффекты и токсичность, обусловленную свободным гемоглобином. Полимеризация молекул гемоглобина стабилизировала тетрамер путем сшивания димеров внеклеточного гемоглобина, тем самым минимизируя экстравазацию и продлевая период внутрисосудистой циркуляции. Полимеризация глютаральдегидом считается ключевым фактором в смягчении вазоконстрикторных эффектов внеклеточного гемоглобина.

Цель данной статьи – дать подробный обзор современного состояния исследований и применения переносчиков кислорода на основе гемоглобина (HBOCs) в трансплантации органов, а также заглянуть в будущее их использования в этой области.

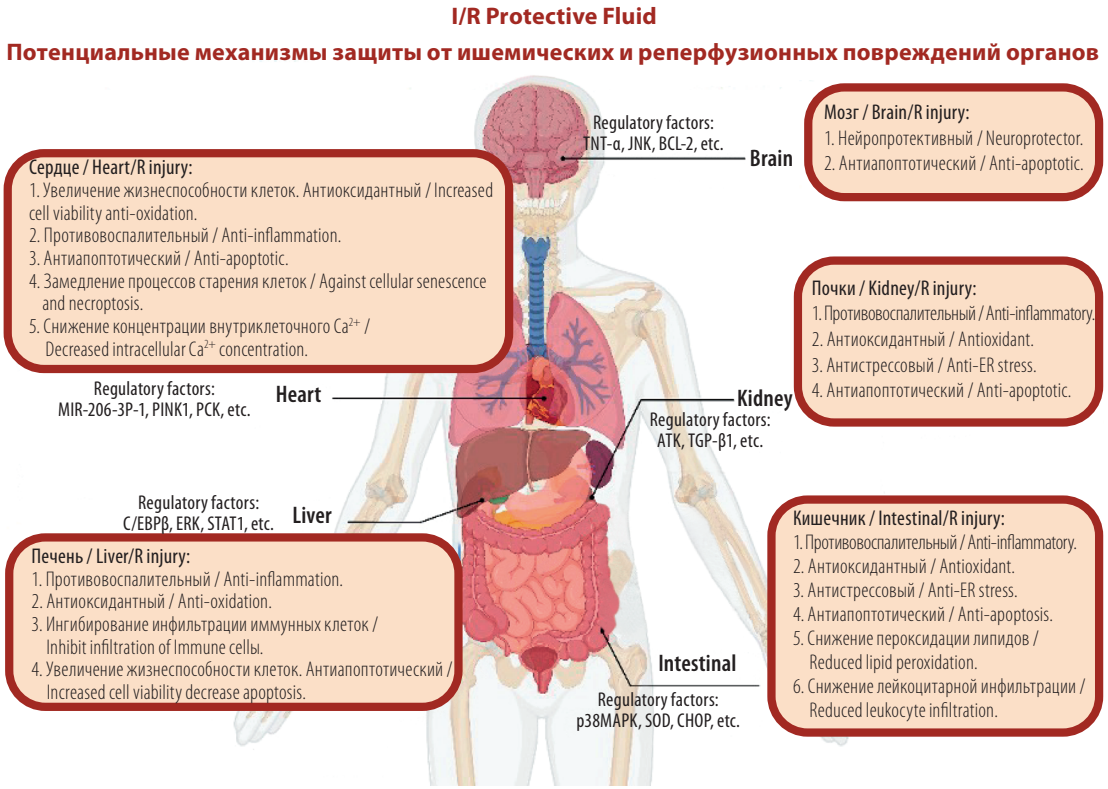
Introduction

The number of new organ failure patients in China and the United States is as high as 300,000 and 120,000 per year respectively, and worryingly, less than 20,000 and 40,000 patients are available for organ transplantation, which is a huge gap between supply and demand that leads to life-threatening situations for hundreds of thousands of patients with organ failure while waiting for donor organs [1]. Currently, organ transplantation is considered as one of the most effective means of treating end-stage organ failure. However, the global organ shortage has become a common challenge limiting the development of organ transplantation [2].

Donor organ preservation and post-transplantation Ischemic Reperfusion Injury (IRI) are important factors affecting the prognosis of organ transplantation. In order to effectively protect transplanted organs, various types of preservation fluids have been developed, such as Collins fluid, University of Wisconsin preservation fluid (UW fluid), histidine-tryptophan-ketoglutarate fluid (HTK fluid), etc, and the introduction of these fluids has promoted the rapid development of organ preservation technology [3]. As shown in Figure, ischemia-reperfusion protective fluid has a protective effect against ischemia-reperfusion injury in many vital organs. IRI is inhibited or attenuated by regulating different key signaling pathways and genes in several organs, including heart, liver, brain and kidneys. However, these preservation fluids themselves lack oxygen-carrying and oxygen-releasing functions and fail to provide essential oxygen to ischemic and hypoxic tissues. HBOCs, as a class of artificial blood substitutes, are widely used in preclinical and some clinical studies as oxygen-carrying products made by cross-linking or polymerization of hemoglobin of animal or human origin. Chemically polymerized or modified HBOCs have a long half-life, are less likely to cause kidney damage, can effectively release oxygen to tissues at low temperatures and low pH, have a long shelf life, and do not require crossmatching [5]. In addition, HBOCs are non-toxic, easy to store, inexpensive, and can be mass-produced, possessing potential value and prospects for industrial research and development [4]. In the field of cardiac surgery and organ transplantation, HBOCs potentially can be used not only for preservation of isolated organs, but also for cardiopulmonary bypass priming and myocardial protection, showing a wide range of application prospects [5]. The aim of this article is to detail the current research status and promising application prospects of HBOCs in various organ transplantation fields.

Heart transplantation

Currently, there are more than 8 million heart failure patients in mainland China, and the life expectancy of patients with end-stage heart failure is only 6–12 months [6]. End-stage heart failure is the main cause of cardiac death, and heart transplantation is considered to be the most effective treatment for end-stage heart failure, which can improve the condition of recipients, prolong the survival time of patients, and improve their quality of life [6]. However, the current effective time of cardiac cryopreservation is only 4–6 h. The longer the preservation time, the more severe the postoperative IRI is, and the greater the impact on the recovery of cardiac function, which may even lead to primary grafting failure, and myocardial IRI is an important factor affecting the recovery of grafted cardiac function and the development of the disease in the late transplantation period [7]. How to find more effective anti-myocardial ischemia methods, and thus prolong the preservation time limit of isolated hearts, improve the preservation effect of cardiac preservation solution, and reduce the IRI damage, has gradually become the focus of research. In order to meet the growing demand for treatment of patients waiting for transplantation, and remote patients can receive surgery within the donor heart preservation timeframe, prolonging the preservation time of isolated hearts and expanding the range of donor choices have become prominent issues [8]. The oxygen-carrying and oxygen-releasing capacity of HBOCs is less affected by temperature than that of blood, and they can



Note: I/R Protective fluid - ischemia-reperfusion protective fluid

Figure. Mechanisms of Ischemia-reperfusion protective fluids reducing organ damage

Рисунок. Потенциальные механизмы защиты от ишемических и реперфузионных повреждений органов

still supply oxygen efficiently to oxygen-depleted tissues and organs at low temperatures [6], which is conducive to prolonging the preservation time and improving the preservation effect of the heart [7].

Some researchers used New Zealand rabbit hearts to conduct related studies, and the results showed that the left ventricular function of hearts perfused with 3% HBOCs was better than that of hearts perfused with ordinary preservation solution [9], some researchers have explored that HBOCs greatly improved the contractile function of the heart, and reduced the area of myocardial infarction, necrosis, and apoptosis of cardiomyocytes. Langendorff's isolated heart perfusion method was also used to observe the changes in cardiac function of rat hearts preserved in St. Thomas' fluid containing HBOCs for 8 h and then reperfused for 120 min. The results showed that the preserved fluid containing HBOCs enhanced the rate of change in myocardium and improved left ventricular pressures during reperfusion, reduced the content of creatine kinase and lactate dehydrogenase in the coronary effluent and reduced the percentage of myocardial infarct area demonstrating a significant protective effect of HBOCs on IRI in isolated rat hearts after 8 h of cryostatic preservation [10]. The delayed protective effect of bovine HBOCs for rabbit isolated hearts has also been investigated. Bovine HBOCs were added to St Thomas II fluid and left ventricular developmental pressure and adenosine triphosphate (ATP) content of the hearts were examined after perfusion at room temperature, and the results showed that bovine HBOCs could significantly improve the preservation of the hearts [11]. In conclusion, HBOCs are expected to be able to effectively prevent myocardial injury during in vitro preservation of the heart, reduce the area of myocardial infarction, and improve the basic function of the heart in order to prolong the time of in vitro preservation of the heart.

During direct cardiac surgery, IRI inevitably occurs in cardiomyocytes [10]. Myocardial protection has always been the focus of cardiac surgery with a cardiopulmonary bypass, and good myocardial protection is not only a guarantee of smooth operation, but also an important influence on the patient's postoperative recovery and prognosis [12]. Poor myocardial protection is one of the main causes of low cardiac output syndrome and patients death after cardiac surgery. As an important part of intraoperative myocardial protection, cardioprotective solution plays an important role in preservation myocardial structure, function and metabolism during surgery [13]. Similarly, ischemia-reperfusion-protective drugs reduce reperfusion injury in the postoperative period. There is a review of drugs in clinical trials for ischemia-reperfusion protection during organ transplantation (Table).

HBOCs are one-thousandth the size of red blood cells (RBCs), but have an oxygen-carrying capacity of 7–9 times that of RBCs [13]. Several

Table.
Summary of the ischemia-reperfusion protective drugs tested in organ transplantation

	Drug name	Type of surgery / organ	Clinical trial effect / phase	Mechanism of action
Cold ischemia-reperfusion	IDN-6556	Transplantation / liver	Lessened liver injury and apoptosis markers / II	Caspase inhibitor
	rPSGL-Ig	Transplantation / liver and kidney	Liver function improved, kidney function not improved / II	P-selectin inhibitor
	NAC	Transplantation / liver	Ameliorated graft failure / II	Antioxidant agent
Warm ischemia-reperfusion	sodium nitrite	Percutaneous coronary intervention / heart	Fewer deaths from arterial occlusion myocardial infarction / II	Anti-inflammatory
	atorvastatin	Percutaneous coronary intervention / heart	Myocardial infarction mitigation / II	Anti-inflammatory
	doxycycline	Percutaneous coronary intervention / heart	Reducing the area of myocardial infarction in the heart / II	Matrix metalloproteinases inhibitor
	delcasertib	Percutaneous coronary intervention / heart	No improvement in myocardial damage / II	Anti-apoptotic
	TRO40303	Percutaneous coronary intervention / heart	Experiments / II	Mitochondrial permeability transition pore inhibitor
	melatonin	Angioplasty / heart	Experiments / II	Antioxidant effect
	ethyl pyruvate	Coronary artery bypass graft / heart	No significant improvement effect / II	Anti-inflammatory
	cariporide	Coronary artery bypass graft / heart	Improves neurotoxicity and reduces myocardial ischaemia / III	Na^+ / H^+ inhibitor
	pexelizumab	Coronary artery bypass graft replacement / heart	Mortality from cardiovascular angiography without valve replacement does not show improvement / III	Inhibition of complement system
	MC-1	Cardiography / heart	No significant improvement in cardiovascular deaths / III	Antagonist of purinergic receptors

Таблица.
Исследования препаратов с целью защиты от ишемических и реперфузионных повреждений в хирургии и трансплантации органов

	Название препарата	Вид хирургического вмешательства / орган	Клинический эффект / фаза исследования	Механизм действия
Холодовая ишемия-реперфузия	IDN-6556	Трансплантация / печень	Снижение уровня повреждения печени и маркеров апоптоза / II	Ингибитор каспазы
	rPSGL-Ig	Трансплантация / печень и почки	Функция печени улучшена, функция почек не улучшена / II	Ингибитор P-селектина
	NAC	Трансплантация / печень	Реже случаи недостаточности трансплантата/II	Антиоксидантный эффект
Тепловая ишемия-реперфузия	Нитрит натрия	Чрескожное коронарное вмешательство / сердце	Снижение смертности от коронарной окклюзии и инфаркта миокарда/II	Противовоспалительный
	Аторвастатин	Чрескожное коронарное вмешательство / сердце	Смягчение последствий инфаркта миокарда/II	Противовоспалительный
	Доксициклин	Чрескожное коронарное вмешательство / сердце	Ограничение зоны инфаркта миокарда в сердце/II	Ингибитор матриксных металлопротеиназ
	Делкасертиб	Чрескожное коронарное вмешательство / сердце	Отсутствие эффекта (сохраняется повреждение миокарда)/II	Антиапоптотический
	TRO40303	Чрескожное коронарное вмешательство / сердце	Эксперимент/II	Ингибитор проницаемости митохондриальных мембран
	Мелатонин	Ангиопластика / сердце	Эксперимент/II	Антиоксидантный эффект
	Этил пируват	Коронарное шунтирование / сердце	Отсутствие значительного эффекта /II	Противовоспалительный
	Карипорид	Коронарное шунтирование / сердце	Снижение нейротоксичности и уменьшение ишемических повреждений миокарда/III	Na^+ / H^+ ингибитор
	Пекселизумаб	Коронарное шунтирование / сердце	Нет снижения смертности после коронарного шунтирования/III	Ингибитор системы комплемента
	MC-1	Чрескожное коронарное вмешательство / сердце	Нет снижения смертности от сердечно-сосудистой недостаточности/ III	Антагонист пуринергических рецепторов

studies have shown that HBOCs can reach the microcirculation areas which are inaccessible for RBCs to achieve. HBOCs can provide effective oxygenation, rapidly restore myocardial oxygenation after coronary embolism, reduce the area of myocardial infarction, maintain cardiac output, and protect the function of the left ventricle, and at the same time, reduce the myocardial IRI after coronary recanalization, which reflects the research value of its application in patients with cardiovascular diseases [10]. Relevant studies have pointed out that the use of HBOCs before myocardial ischemia and reperfusion can significantly reduce the degree of myocardial inflammation and IRI injury in canine myocardial membranes. Additionally, in the study of a model of severe myocardial ischemia caused by acute coronary artery stenosis, it was found that HBOCs can significantly reduce the area of infarction and improve myocardial viability.

Renal transplantation

Kidney transplantation is the treatment of choice for end-stage renal disease [14], and IRI is one of the most important factors affecting graft function in the early post-transplantation period and has a deleterious effect on long-term graft survival. HBOCs have been found to attenuate IRI during renal transplantation, effectively improving the quality and prolonging the preservation of donor kidneys [10]. Normothermic Machine Perfusion (NMP) provides a new platform for pre-transplant evaluation and repair of renal grafts. Maintaining the metabolic activity of preserved grafts at the physiological level requires an adequate delivery of oxygen, which is usually supplied by crystalloid solutions supplemented with RBCs. It has been demonstrated that HBOCs can be used as a substitute for RBCs in renal NMP preservation [15]. Vanessa Mallet et al. [16] added different doses of HBOCs to UW (University of Wisconsin) fluid and demonstrated that higher doses of HBOCs were more effective in terms of cell viability, metabolic activity, and cellular integrity as demonstrated by endothelial cells in vitro. In an in vivo porcine kidney autotransplantation model, UW fluid with added HBOCs was superior to UW fluid for kidney preservation. Jacques Kaminski et al. [17] used a porcine autotransplantation model to assess the potential benefit of HBOCs in static cold preservation and mechanical perfusion preservation for borderline kidney transplantation outcomes. In the static cold preservation group, there was no significant benefit during the first 2 weeks of follow up, but at 1- and 3-months normalized level of creatinine. And in the mechanically perfused group, HBOCs improved short-term and long-term renal function as well as tissue integrity, with no loss of function or tissue integrity recorded throughout follow-up. Studies have shown that HBOCs are good blood substitute for use as oxygen-carrying molecules for mechanical perfusion of isolated kidneys [18].

Liver Transplantation

Normothermic Machine Perfusion is a new technique to preserve liver grafts under near-physiological conditions and to maintain normal metabolic activity of the liver; however, NMP requires an oxygenated perfusion solution to maintain the oxygen supply requirements of the normothermic liver, and therefore RBCs are usually added for oxygenation purposes. It was found that the oxygen uptake of livers perfused with HBOCs was higher than that of the RBC group, suggesting that HBOCs can be used as an effective oxygen donor in the NMP perfusate in place of RBCs [19]. NMP can also be used to assess the viability of donor livers prior to transplantation, and some investigators have used HBOCs to perfuse discarded livers, which were compared to RBC or plasma-perfused livers in terms of ATP content and cumulative cholestasis. Results showed that HBOCs were used in the perfusion of liver with RBCs to maintain the liver normal metabolic activity [18]. Comparisons showed that HBOCs can be effectively used for ambient mechanical perfusion of livers without the use of human blood products, and some biomarkers of liver function and injury indicated better perfusion with HBOCs [19]. Plaats V.D. et al. [20] used HBOCs oxygen carriers for sub-ambient mechanical perfusion of livers in a porcine in situ liver transplantation model, where the livers were cold ischemic for 9 hours and then mechanically perfused and cold preserved. By comparing hematological, tissue and metabolic aspects of the liver, the results showed a significant increase in liver survival and a significant increase in bile production in subnormal temperature perfusion using HBOCs, which suggests that NMP using HBOCs solution significantly improves the conditions for liver preservation.

Lung Transplantation

Surgical treatment of lung transplantation is the only intervention that can improve the life expectancy of patients with idiopathic pulmonary fibrosis (IPF) [21], but post-transplantation is prone to complications such as IRI, primary graft dysfunction and so on, which seriously affects the prognosis of patients. Relevant studies have shown that the addition of HBOCs to the standard preservation fluid (Perfadex®) for cryostatic lung preservation significantly reduse long-term cold ischemic injury in lung transplants, resulting in a significant improvement in functional parameters of the donor lungs, a decrease in vascular resistance, and an increase in the donor lung oxygenation ratio [22].

Conclusion

In recent years, the shortage of donor hearts has seriously affected the development of heart transplantation, and the contradiction between supply and demand has become increasingly acute, so doctors and researchers have gradually turned their attention to xenotransplantation and borderline hearts. Although xenotransplantation has a certain significance of scientific exploration, it is still a very long way to cross over from animal experiments to clinical success, and the University of Maryland Medical Center in the United States released a news that David Bennett, a 57-year-old patient who had received the world's first porcine heart, died two months after the operation. The use of marginal hearts may become an important means of expanding the source of donor hearts, but in the case of marginal hearts, advanced preservation techniques and novel preservation fluids are required to maintain the availability of donor hearts, one of which is to mitigate ischemic and hypoxic damage during preservation of the donor heart. HBOCs may act as a direct oxygen donor by facilitating the diffusion of oxygen and the ability to carry or release oxygen efficiently, and increase the transfer of oxygen between RBCs as well as between RBCs and tissues. HBOCs are gradually applied to treat various ischemic-hypoxic situations, including myocardial infarction, aortic cross-clamping during cardiac surgery and organ transplantation.

The application of HBOCs in organ transplantation is expected to prolong the preservation time of transplanted organs and provide sufficient time to solve the problems caused by the mismatch difference between donors and recipients, as well as the problems caused by xenotransplantation; to reduce the risk of ischemic-hypoxic injuries, as well as alleviate the secondary injuries caused by reperfusion after transplantation; to reduce the phenomenon of organ wastage due to the limitation of preservation time and improve the utilization rate of transplanted organs. With the increasing number of organ transplants and the demand for prolonged organ preservation time, HBOCs have an important potential clinical application value.

Conflictof interest: none.

Конфликт интересов: не заявлен.

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Поступила: 22.04.2024