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The role of oxygenation in kidney and liver machine perfusion

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Abstract

Background*. Organ transplantation is the optimal decision for patients in the end stage of many diseases. Certain conditions are required for the transportation and preservation of a donor organ after explantation, including factors such as temperature, pressure, and preservative solution. All currently available methods of preservation of donor organs are aimed at maximizing the complete preservation of the functional state of the graft from the moment of its removal to implantation and reperfusion in the recipient's body.*

Aim. *The purpose of this review is to provide up-to-date information on the results of the studies performed in order to decide on the preferred method*

of organ preservation.

***Material and methods**. An analysis of literature sources in English and Russian from 2009 to 2023 on this topic was performed in the databases PubMed, MEDLINE, Google Scholar. The review highlights the results of preclinical (on animal models) and clinical studies, as well as achievements in the field of ex-vivo machine perfusion with an emphasis on machine hypothermic perfusion and modified oxygenated hypothermic machine perfusion, subnormothermic machine perfusion and machine normothermic perfusion.*

***Results**. The daily increase in the number of patients in need of organ transplantation delays the timely selection and search for a donor. Organ donation after cardiac death is a promising step in an attempt to overcome the disbalance between the number of patients and organs, but the risk of developing early graft damage increases. The criteria for selecting donors and donor organs are being expanded, as a result, elderly donors and not-optimal grafts are included, but they are less resistant to ischemic damage. In this connection, there is a need for long-term infusion support through machine perfusion.*

***Conclusion.** In recent years, research has focused on alternative preservation methods, studying hypothermic, subnormothermic and normothermic machine perfusion. The use of machine perfusion has become the most widespread among kidney transplants and has shown good results. Further development is expected in the field of studying and improving this method of organ preservation, which allows not only transporting, but also improving the functional state of the graft.*

Keywords: machine perfusion, oxygenated perfusion, hypothermic machine perfusion, transplantation,

Conflict of interests Authors declare no conflict of interest

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ALT, alanine aminotransferase
AST, aspartate aminotransferase
ATP, adenosine triphosphoric acid
HMP, hypothermic MP
MP, machine perfusion
NMP, normothermic MP
RCT, randomized clinical trial
SMP, subnormothermic MP

Introduction

Organ transplantation is the only radical method of treating chronic diseases in the end stage and with fulminant development [1]. Improvements in surgical technology have led to a rapid increase in the number of surgical interventions, and at the moment we can state that organ transplantation is a routine operation [2]. But this success has led to many more patients being placed on waiting lists than there are available donor organs. The growing gap between supply and demand has caused an increased mortality before organ transplantation. The issue of donor organ shortage has not been resolved yet [3, 4]. There is always an active search for new approaches and ways to preserve or heal those organs that would have previously been

considered unsuitable for transplantation. Expanding organ donor eligibility criteria is a promising step, with the main targets being non-heart-beating donors, older age group donors, and suboptimal graft. In GODT statistics, approximately 22% are non-heart-beating donors [5], but in these cases the grafts often have reduced functional reserve and are therefore less resistant to preservation and reperfusion injury. Possible difficulties such as graft ischemia, primary graft non-function and biliary complications come to the fore in case of liver transplantation [6]. To solve these problems, a number of authors present for discussion some methods of early diagnosis, treatment and prognosis of graft survival. One such method is machine perfusion (MP). It is likely that existing technologies will help to increase the pool of donor organs and, respectively, the number of transplantations [7].

There are many studies in the literature comparing protection against ischemic injury through the use of machine perfusion versus static cold preservation [8]. This technique allows one to assess and predict organ function, ensure perfusion of nutrients and oxygen, and, importantly, increase the time for transportation. The mechanism of the protective properties of machine perfusion is to reduce cellular metabolism, maintain stable temperature and pressure, and provide a constant supply of nutrients [9]. Adding oxygen to the perfusion solution provides protection against reperfusion injury. Moreover, the team of authors from Wuhan University also suggests improving organ viability through reducing vascular spasm. There may be a link with the maintenance and restoration of the physiological state of the vascular wall and pulsatile perfusion use. It is proposed to use machine perfusion with oxygen not only for transportation, but also for short-term (1–3 hours) treatment of the graft immediately before implantation [10]. The positive factor here is that there is no need to

transport the device itself. The protective effects of this method on the graft have been proven in a number of studies and provide a very attractive idea, but require further study [11].

The first clinical trials of hypothermic MP (HMP) were registered in 2010 in marginal donors with beating heart [12]. To date, there are 7 prospective clinical studies with the results demonstrating a 1-year HMP-treated graft survival varying from 80.6 to 97% [13].

Thus, MP provides a number of advantages, some of which are still awaiting confirmation and research. However, the essence of the MP method is to store the organ under conditions of controlled pressure and temperature, as well as filtration, recirculation of the solution, and oxygenation [1-4]. The modern device is small in size, portable, autonomous, which provides opportunities for transportation. According to the mechanism, it is a circuit for recirculating the perfusion solution, in controlled pressure and temperature. This continuous flow ensures better saturation of organ tissues with a preservative solution, as well as the delivery of oxygen and nutrients when necessary. In addition, there is the possibility of constant monitoring of biochemical parameters and a safe increase in storage time [15]. To determine viability and functional status during MP, various organ-specific parameters, such as the vascular resistance, elasticity, and pressure, can be assessed [16]. However, the predictive value still needs to be proven in future studies.

History

Since the beginning of the 20th century, there has been a search for a way to preserve the organ ex vivo. In 1935, A. Carrel, together with C.A. Lindbergh, became the inventors of the first available organ perfusion machine ensuring a maintained constant pressure and nutrient delivery [17].

There were technical shortcomings in Carrel's technique, such as a lack of sufficient oxygen supply, inability of temperature control, and the risk of infection. Interest in continuing research in this direction decreased for a short time, but subsequently, with the development of transplantation, this technique found its clinical application [18]. So, the first MP was introduced into clinical practice of kidney transplantation in the 1960s. Its main goal was to provide conditions to prolong organ transportation; donor plasma was used as a perfusion solution. However, with the discovery of static cold perfusion solution (UW Solution) by F. Belzer and J. Southard, which is a simpler and more reliable method of graft preservation, the need for machine perfusion decreased [19]. Static cold preservation is still an effective and safe method of organ transportation, which is used all over the world [20]. But due to the shortage of donor organs and the forced use of expanded criteria donor organs, the next step in the history of MP development included the attempts to use the device more for the treatment and diagnosis of any graft damage rather than for transportation [21]. Experimental studies demonstrated that MP helped to protect the organ from ischemic effects. The first clinical trial was described by J.V. Guarrera in 2009 with a sample size of 20 liver transplant recipients from non-heart-beating donors [25]. MP was performed for a mean of 4 hours; and during perfusion, liver enzymes were analyzed. The authors reported of no adverse events, such as a graft rejection or other serious organ dysfunctions; there were no vascular or biliary complications [23]. The procedure was considered a promising solution of problems with suboptimal donor organs requiring additional diagnosis. A follow-up study by P. Dutkowski et al. with median follow-up periods of 448, 528, and 1530 days for a non-heart-beating donor liver preserved by using oxygenated HMP, a non-heart-beating donor liver preserved by MP

without oxygen, and a liver from a brain-dead donor, respectively, demonstrated impressive results of using oxygenated MP [23]. The authors state that the effect of MP with oxygen depends on the oxygen saturation of the perfusate; and recent experimental studies in porcine livers using deoxygenated and oxygenated perfusion solutions have indicated this fact. However, at the control timepoints of the study mentioned above, the improvements were recorded in a number of biochemical and clinical parameters after a 1-year follow-up. The most reliable parameter for assessing the graft safety is biochemical markers [24]. Thus, the liver treated with hypothermic MP (HMP) with oxygen demonstrated less pronounced release of liver enzymes after reperfusion compared to non-perfused liver (peak alanine aminotransferase (ALT) 1239 versus 2065 U/L, peak aspartate aminotransferase (AST) 1808 versus 2848 U/L; peak bilirubin 44 mmol/L versus 109 mmol/L). And these patients showed less severe early graft dysfunction [25].

At present, after so many years of studying the MP subject, we can say that this method is a promising way to optimize the functioning of organs ex-vivo before implantation to the recipient; however, the full potential of the technique can be revealed in further clinical studies. The key goal of using MP is the organ ex vivo procurement under conditions of aerobic metabolism, which has an advantage over anaerobic static cold storage. Anaerobic metabolism, in turn, leads to thinning of cell membranes and an increased risk of damage to organ tissue [25, 26].

Growing interest in assessing the functional integrity of an organ and the success of reperfusion, including the graft acceptance, has led to new studies examining the importance of perfusion parameters for this purpose. According to the literature studied, there are several types of donor organ

MP, differing in temperature conditions and the presence or absence of solution oxygenation.

– HMP in the temperature range from 0º C to +10º C without oxygen saturation of the perfusate or with oxygen saturation (hypothermic oxygenated perfusion),

– mediathermic MP (MMP) from +10º C to +20ºC

– subnormothermic MP (SMP) from +20º C to +25ºC,

– normothermic MP (NMP) from +35º C to +38ºC.

Besides time and temperature of MP performance, the perfusate composition varies significantly between different techniques. NMP or SMP requires the presence of red blood cells or artificial oxygen carriers; the cold perfusion technologies depend on the amount of oxygen dissolved in the perfusate.

Hypothermic machine perfusion

More than several decades have passed in studying the effect of hypothermia on the graft preservation ex vivo and various models of this technique. HMP combines low temperature (0–10°C) and a colloid-containing preservative solution for the purpose to slow down cellular metabolism [27]. The device is a sealed sterile system, in which stable temperature and pressure are continuously maintained. There are many registered hypothermic machine perfusion platforms, such as the KidneyAssist Device (Organ Assist BV, Groningen, The Netherlands) and Airdrive (AD). Such systems consist of a disposable organ chamber, pump, oxygenator with an oxygen supply tank, battery and control panel, the entire system is contained in an ice box to provide a hypothermic state from -4ºC to 10º C for no more than 24 hours [27, 28]. The pump operates at a

controlled pressure of approximately 30 mm Hg with a pulse wave of about 60 beats/min. The device is portable, which means there are no difficulties in transporting the organ from one center to another where implantation is to be performed. Parameters such as temperature, vascular resistance, and pressure are recorded every minute. Clinical trials of kidney HMP device in animal models described a decrease in renal tubular damage, increased clearance, and less oxidative stress [28]. Comparative studies that included humans undergoing liver transplantation have shown lower levels of biochemical parameters, namely serum lactate, ALT, alkaline phosphatase, γ-glutamyltranpeptidase, prothrombin time, and total bilirubin, as well as the absence of biliary complications, and a reduction in hospital length of stay in patients. It should be noted that in any machine liver preservation at low temperatures, too high perfusion pressures must be strictly avoided to prevent endothelial stress with subsequent damage [28, 29].

A study analyzing more than 90,000 kidney transplants found that, HMP had a significant benefit compared with standard cold storage, particularly when preservation times are longer than 6 hours [31]. Despite the obvious advantages of this technique, there have been published a study reporting negative results of HMP. The study was conducted on porcine kidneys and described three groups: classic static cold perfusion, HMP for 18 hours, and HMP for 4 hours. The negative effects were the damage to endothelium and the development of edema; these effects depended on the perfusion duration and the pressure level. V. Gomez, using 93 kidney grafts, proved the connection between the pressure during perfusion and the subsequent functioning of the organ. Measurements were made using Doppler sonography [30]. Further studies should answer the question of how much this technique can restore suboptimal grafts.

Hypothermic machine perfusion with oxygen

The most suitable method of delivering oxygen is active oxygenation of the perfusate. In a number of studies, oxygen-perfused livers showed a lower release of liver enzymes compared to controls subjected to static conventional hypothermic storage for the similar storage period. The studies performed have demonstrated a decrease in metabolic rate in a hypothermic state with continuous oxygen consumption [30, 31]. For optimal recovery, and reperfusion injury reduction, the graft should be initially perfused at low temperatures to restore cellular homeostasis under a protective hypothermic effect. Authors from the Netherlands analyzed 10 transplantations involving hypothermic oxygenated machine perfusion (HOPE) and 20 patients from the control group. The perfusion fluid was oxygenated by membrane oxygenators at a flow rate of 500 mL/min of 100% oxygen, and the partial pressure was at least 450 mm Hg. [31]. The authors selected secondary endpoints: a 1-year graft survival, the technical safety of MP, microbiology testing of perfusion fluid, and serum markers of damage and hepatobiliary system function. Peak serum ALT levels at 1 week were lower in recipients of oxygen-preserved livers than in the control group. There were no significant differences in function, hospital length of stay, or postoperative complications. According to the results of the above study, the oxygenated MP is stated by the authors as a safe and feasible procedure that provides better preservation of liver grafts and leads to a decrease in ischemia-reperfusion injury and to the improvement of early graft function [32]. Another study led by M. Ravaioli showed how much the oxygenated HMP was effective and safe for both liver and kidney transplants. According to this technique, perfusion was undertaken in two stages: the first was washing with an oxygenated solution for 30–40 minutes, the second was recirculation

before implantation. A multicenter randomized clinical trial (RCT) is currently being conducted to study the properties and benefits of preimplantation MP after static hypothermic perfusion. But in the absence of other RCTs, the exact oxygen content necessary and sufficient for graft preservation still remains unknown [33, 34].

Subnormothermic machine perfusion

When the temperature of graft storage and transportation is within the range from +15º–+30º C, there is reliably no potential risk of damage associated with hypothermia, nor with the temperature changes during reperfusion after explantation. This hypothesis arose back in the 1990s, L. Brazil and his colleagues studied the preservation of canine kidney grafts at temperatures close to physiological ones. At a temperature of +32º C and a pressure of 35 mm Hg, the grafts were preserved for 4 to 7 hours, after which they were reimplanted. There was no rejection, and the renal function was preserved [36]. The authors considered subnormothermic perfusion to be a possible alternative to hypothermic preservation; however, clinical studies including humans have not yet been conducted to confirm this hypothesis so it is not yet possible to judge the feasibility and efficacy of this method. In 2014, D.P. Hoyer et al. investigated SMP in a porcine model. After 30 minutes of warm ischemia, renal grafts were procured and subjected to 7 hours of static cold preservation, oxygenated HMP or SMP. The perfusion pressure was 30 mm Hg for HMP, 40 mmHg for SMP. Evaluation using reperfusion device with blood perfusion showed significantly higher blood flow, urine output, and improved creatinine clearance for SMP-preserved grafts with higher structural integrity. In addition to standard technology, there is SMP with controlled oxygenated

rewarming [34]. This technique implies a gradual temperature increase over several hours with simultaneous oxygenated perfusion. A study conducted on laboratory animals showed better results when using SMP including controlled oxygenated rewarming compared to a standard SMP. The issues of the rate, and the temperature level increase remain unspecified, though there were pilot studies conducted on laboratory rat models, aimed to elucidate these issues. The authors found that rewarming above 20ºC gave no additional therapeutic effect, but there is still a need for further studies in larger size animals.

Normothermic machine perfusion

Continuous normothermic perfusion is performed at the temperature in the range from 35º C to 38º C, providing the graft with nutrients and oxygen. This technique has found its clinical application, although not as widespread as the previously described temperature regimes. NMP was first used in Spain for organs from non-heart-beating donors as a measure to prevent warm ischemic injury. The first study of NMP-treated liver transplantation was published by R. Rawikumar et al. in 2016 [33, 34]. The authors reported the safety and feasibility of this temperature regime as it allowed successful preservation of livers that would not have tolerated hypothermic preservation. The result was presented in a group of 20 patients and showed no significant differences from static cold storage. NMP implies the restoration of normal cellular processes while facilitating the assessment of viability. The obvious advantage of this particular method is based on the concept of preventing long periods of cooling that can cause cell damage. In the reported series of 6 patients who received liver grafts treated with NMP before implantation, no complications were observed and a significant

reduction in early allograft dysfunction was found compared to a control group in the study. Organ controlled rewarming may improve functional and structural integrity upon transplantation, likely by preserving cell membrane integrity and replenishing adenosine triphosphoric acid (ATP) stores. The role of ATP in liver graft survival has already been repeatedly proven by the presence of a correlation between a favourable transplant outcome and ATP levels. Another advantage of NMP is the possibility of testing the graft viability in a physiological environment and temperature. However, the basis for the positive effect of this technique still needs to be studied both on expanded criteria donor organs, and also on optimal grafts.

Discussion

The shortage of donor organs leads to the increased interest and search for the most suitable modality of preservation and transportation. The method of static hypothermic perfusion, which demonstrates stable results, prevails everywhere. Nevertheless, preservation of grafts using MP has a number of advantages over static cold preservation. The classic way to preserve the donor graft is a hypothermic state. At low temperatures, all vital processes slow down, which allows one to increase the time from explantation of the organ to its implantation. Since the origin of transplantation, the static cold preservation has been widely used and is still the most common method; however, MP has a number of advantages over this technique. Initially, MP was invented for a long-term organ preservation ex-vivo; later on it was forgotten for a short time, and in the recent years this technique has again attracted interest of the transplant community. Machine-assisted graft perfusion has been reimplemented into clinical practice, mainly for organs from non-heart-beating donors to prevent and predict

ischemic injury [35]. Despite the fact that the metabolic activity of the organ slows down under conditions of preservation, its vital activity does not stop completely; this leads to the need for an oxygen flow. Oxygenated hypothermic perfusion preserves the organ, additionally supporting its aerobic metabolism, which optimizes the preservation process [36]. The studies of HMP have found that the oxygen-supplemented perfusion, particularly, immediately before organ implantation to the recipient, improves the organ function and increases protection against injury in liver and kidney grafts. Namely, 1–2 hours of MP after static cold storage restores lost functions and prevents the development or replaces already formed areas of ischemic damage. Unanswered questions concerning oxygen perfusion still remain, but they may be answered by future clinical studies [37].

A rather interesting concept of preventing cold damage to the graft is reflected in the normothermic and subnormothermic MP modes [38]. However, these temperature regimes of perfusion showed the results not so impressive as the hypothermic one. The SMP technique with controlled oxygen rewarming is of interest from the transplant community, but there is not enough research on this topic to form a definite opinion.

The vast majority of clinical studies are retrospective evaluations of new preservation techniques, largely demonstrating their feasibility. Therefore, it is difficult to draw appropriate conclusions. Only one RCT was completed in 2018 [1]. In that study, the authors compared normothermic machine liver preservation with conventional cold storage and selected a peak AST level as the primary endpoint, which, however, is an ambiguous and non-exhaustive indicator of liver injury after transplantation.

Conclusion

This review summarizes the results of preclinical (animal models) and clinical studies and highlights advances in the field of ex vivo machine perfusion, with an emphasis on hypothermic machine perfusion and oxygen-supplemented hypothermic machine perfusion, subnormothermic machine perfusion, and normothermic machine perfusion. The review provides an up-to-date overview of the current published literature on the state of the art of machine perfusion and the preferred methods of its implementation. Various preservation strategies were compared to choose the most effective for the improvement of suboptimal grafts. Most authors agree that machine perfusion can reduce the risks of an early graft rejection and ischemia, as well as to diagnose damage and dysfunction at an early stage before organ implantation. Assessment of graft viability during hypothermic machine perfusion has been insufficiently studied, and data from large clinical trials are needed to determine its value as a tool for predicting transplant outcome.

There are also debates about the need for active oxygenation, such as that with an oxygenator in hypothermic conditions, although the ideal oxygen content is unknown.

Thus, the main purpose of machine perfusion is the graft evaluation and rehabilitation before surgery, giving the chance to improve the functional and structural integrity of organs, and, as a result, to increase the availability of transplantation. It is believed that the benefits of machine perfusion lie in the removal of toxic products and the supply of energy substrates. However, the optimal conditions for machine perfusion, such as temperature, perfusate solution, circuit characteristics and timing, are unknown. For this reason, further study of dynamic preservation methods is necessary. The optimal perfusion system still remains an unresolved

question that needs to be answered by future clinical studies. It seems likely that existing preservation technologies will need to be improved to meet the needs of the developing field of graft preservation and conditioning.

References

1. Ceresa CDL, Nasralla D, Coussios CC, Friend PJ. The case for normothermic machine perfusion in liver transplantation. *Liver Transpl.* 2018;24(2):269-275. PMID: 29272051 https://doi.org/10.1002/lt.25000

2. Dutkowski P, Polak WG, Muiesan P, Schlegel A, Verhoeven CJ, Scalera I, et al. First comparison of hypothermic oxygenated perfusion versus static cold storage of human donation after cardiac death liver transplants: an international-matched case analysis. *Ann Surg.* 2015;262(5):764–770. PMID: 26583664 https://doi.org/10.1097/SLA.0000000000001473

3. Ravaioli M, De Pace V, Angeletti A, Comai G, Vasuri F, Baldassarre M, et al. Hypothermic oxygenated new machine perfusion system in liver and kidney transplantation of extended criteria donors: first Italian clinical trial. *Sci Rep.* 2020;10(1):6063. Erratum in: Sci Rep. 2020;10(1):14658. PMID: 32269237 https://doi.org/10.1038/s41598-020-62979-9

4. Schlegel A, Muller X, Dutkowski P. Machine perfusion strategies in liver transplantation. *Hepatobiliary Surg Nutr*. 2019;8(5):490–501. PMID: 31673538 https://doi.org/10.21037/hbsn.2019.04.04

5. *Those [2023] data are based on the Global Observatory on Donation and Transplantation (GODT) data, produced by the WHO-ONT collaboration.* Available at: https://www.transplant-observatory.org/ [Accessed September 28, 2023].

6. Lüer B, Koetting M, Efferz P, Minor T. Role of oxygen during hypothermic machine perfusion preservation of the liver. *Transpl Int.* 2010;23(9):944–950. PMID: 20210932 https://doi.org/10.1111/j.1432-2277.2010.01067.x

7. Hamar M, Selzner M. Ex-vivo machine perfusion for kidney preservation. *Curr Opin Organ Transplant.* 2018;23(3):369–374. PMID: 29697462 https://doi.org/10.1097/MOT.0000000000000524

8. Schlegel AA, Kalisvaart M, Muiesan P. Machine perfusion in liver transplantation: an essential treatment or just an expensive toy? *Minerva Anestesiol.* 2018;84(2):236–245. PMID: 28726360 https://doi.org/10.23736/S0375-9393.17.12016-X

9. Jochmans I, Akhtar MZ, Nasralla D, Kocabayoglu P, Boffa C, Kaisar M, et al. Past, present, and future of dynamic kidney and liver preservation and resuscitation. *Am J Transplant.* 2016;16(9):2545–2555. PMID: 26946212 https://doi.org/10.23736/S0375-9393.17.12016-X10.1111/ajt.13778

10. Minor T, von Horn C, Paul A. Role of temperature in reconditioning and evaluation of cold preserved kidney and liver grafts. *Curr Opin Organ Transplant.* 2017;22(3):267–273. PMID: 28266940 https://doi.org/10.1097/MOT.0000000000000402

11. Hameed AM, Pleass HC, Wong G, Hawthorne WJ. Maximizing kidneys for transplantation using machine perfusion: from the past to the future: a comprehensive systematic review and meta-analysis. *Medicine (Baltimore).* 2016;95(40):e5083. PMID: 27749583 https://doi.org/10.1097/MD.0000000000005083

12. Gulyaev VA, Zhuravel SV, Novruzbekov MS, Olisov OD, Lutsyk KN, Minina MG, et al. Will the machine perfusion of the liver increase the number of donor organs suitable for transplantation? *Transplantologiya. The*

Russian Journal of Transplantation. 2018;10(4):308–326. (In Russ.). https://doi.org/10.23873/2074-0506-2018-10-4-308-326

13. Zhong Z, Lan J, Ye S, Liu Z, Fan L, Zhang Y, et al. Outcome improvement for hypothermic machine perfusion versus cold storage for kidneys from cardiac death donors. *Artif Organs.* 2017;41(7):647–653. PMID: 28703374 https://doi.org/10.1111/aor.12828

14. Guarrera JV, Henry SD, Samstein B, Odeh-Ramadan R, Kinkhabwala M, Goldstein MJ, et al. Hypothermic machine preservation in human liver transplantation: the first clinical series. *Am J Transplant.* 2010;10(2):372–381. PMID: 19958323 https://doi.org/10.1111/j.1600-6143.2009.02932.x

15. Schlegel A, Kron P, Dutkowski P. Hypothermic machine perfusion in liver transplantation. *Curr Opin Organ Transplant.* 2016;21(3):308–314. PMID: 26918882 https://doi.org/10.1097/MOT.0000000000000303

16. van Rijn R, Karimian N, Matton APM, Burlage LC, Westerkamp AC, van den Berg AP, et al. Dual hypothermic oxygenated machine perfusion in liver transplants donated after circulatory death. *Br J Surg.* 2017;104(7):907–917. PMID: 28394402 https://doi.org/10.1002/bjs.10515

17. Carrel A, Lindbergh CA. The culture of whole organs. *Science.* 1935;81:621–623. https://doi.org/10.1126/science.81.2112.621

18. Schlegel A, Muller X, Kalisvaart M, Muellhaupt B, Perera M, Isaac J, et al. Outcomes of liver transplantations from donation after circulatory death (DCD) treated by hypothermic oxygenated perfusion (HOPE) before implantation. *J Hepatol.* 2019;70(1):50–57. PMID: 30342115 https://doi.org/10.1016/j.jhep.2018.10.005

19. Hosgood SA, Saeb-Parsy K, Wilson C, Callaghan C, Collett D, Nicholson ML. Protocol of a randomised controlled, open-label trial of ex vivo normothermic perfusion versus static cold storage in donation after circulatory death renal transplantation. *BMJ Open.* 2017;7(1):e012237. PMID: 28115329 https://doi.org/10.1136/bmjopen-2016-012237

20. van Golen RF, Reiniers MJ, Vrisekoop N, Zuurbier CJ, Olthof PB, van Rheenen J, et al. The mechanisms and physiological relevance of glycocalyx degradation in hepatic ischemia/reperfusion injury. *Antioxid Redox Signal.* 2014;21(7):1098–1118. PMID: 24313895 https://doi.org/10.1089/ars.2013.5751

21. Iskender I, Cosgun T, Arni S, Trinkwitz M, Fehlings S, Cesarovic N, et al. Cytokine filtration modulates pulmonary metabolism and edema formation during ex vivo lung perfusion. *J Hear Lung Transplant.* 2017;S1053–2498(17)31802–31808. PMID: 28587802 https://doi.org/10.1016/j.healun.2017.05.021

22. Reiniers MJ, van Golen RF, van Gulik TM, Heger M. Reactive oxygen and nitrogen species in steatotic hepatocytes: a molecular perspective on the pathophysiology of ischemia-reperfusion injury in the fatty liver. *Antioxid Redox Signal.* 2014;21(7):1119–1142. PMID: 24294945 https://doi.org/10.1089/ars.2013.5486

23. Tang D, Kang R, Zeh HJ, Lotze MT. High-mobility group box 1, oxidative stress, and disease. *Antioxid Redox Signal.* 2011;14(7):1315–1335. PMID: 20969478 https://doi.org/10.1089/ars.2010.3356

24. Dutkowski P, Krug A, Krysiak M, Dünschede F, Seifert JK, Junginger T. Detection of mitochondrial electron chain carrier redox status by transhepatic light intensity during rat liver reperfusion. *Cryobiology.*

2003;47(2):125–142. PMID: 14580847 https://doi.org/10.1016/j.cryobiol.2003.08.004

25. Brockmann J, Reddy S, Coussios C, Pigott D, Guirriero D, Hughes D, et al. Normothermic perfusion: a new paradigm for organ preservation. *Ann Surg.* 2009;250(1):1–6. PMID: 19561463 https://doi.org/10.1097/SLA.0b013e3181a63c10

26. Schlegel A, Graf R, Clavien PA, Dutkowski P. Hypothermic oxygenated perfusion (HoPe) protects from biliary injury in a rodent model of DCD liver transplantation. *J Hepatol*. 2013;59(5):984-991. PMID: 23820408 https://doi.org/10.1016/j.jhep.2013.06.022

27. Mergental H, Perera MP, Laing RW, Muiesan P, Isaac JR, Smith A, et al. Transplantation of declined liver allografts following normothermic ex-situ evaluation. *Am J Transplant.* 2016;16(11):3235–3245. PMID: 27192971 https://doi.org/10.1111/ajt.13875

28. Hoyer DP, Gallinat A, Swoboda S, Wohlschlaeger J, Rauen U, Paul A, et al. Influence of oxygen concentration during hypothermic machine perfusion on porcine kidneys from donation after circulatory death. *Transplantation.* 2014;98(9):944–950. PMID: 25369373 https://doi.org/10.1097/TP.0000000000000379

29. Kaushik D, Roychoudhury A. Reactive oxygen species (ROS) and response of antioxidants as ROS-scavengers during environmental stress in plants. *Front Environ Sci.* 2014;2:53. https://doi.org/10.3389/fenvs.2014.00053

30. Monbaliu D, Vekemans K, De Vos R, Brassil J, Heedfeld V, Qiang L, et al. Hemodynamic, biochemical, and morphological characteristics during preservation of normal porcine livers by hypothermic machine perfusion. *Transplant Proc.* 2007;39(8):2652–2658. PMID: 17954200 https://doi.org/10.1016/j.transproceed.2007.08.009

31. Zhang J, Wang X, Vikash V, Ye Q, Wu D, liu Y, et al. ROS and ROS-Media-ted cellular signaling. *Oxid Med Cell Longev.* 2016;2016:4350965. PMID: 26998193 https://doi.org/10.1155/2016/4350965

32. Dirkes MC, Post IJH, Heger M, van Gulik TM. A novel oxygenated machine perfusion system for preservation of the liver. *Artif Organs.* 2013;37(8):719–724. PMID: 23614839 https://doi.org/10.1111/aor.12071

33. da Silvacosta Fl, Teixeira RKC, Yamaki VN, Valente Al, Silva AMF, Brito MVH, et al. Remote ischemic conditioning temporarily improves antioxidant defense. *J Surg Res.* 2015;200(1):105–109. PMID: 26316445 https://doi.org/10.1016/j.jss.2015.07.031

34. Zhang Q, Raoof M, Chen Y, Sumi Y, Sursal T, Junger W, et al. Circulating mitochondrial DAMPs cause inflammatory responses to injury. *Nature.* 2010;464:104–107. PMID: 20203610 https://doi.org/10.1038/nature08780

35. Hausenloy DJD, Yellon DDM. The therapeutic potential of ischemic conditioning: an update. *Nat Rev.* 2011;8(11):619–629. PMID: 21691310 https://doi.org/10.1038/nrcardio.2011.85

36. Hausenloy DJ, Iliodromitis EK, Andreadou I, Papalois A, Gritsopoulos G, Anastasiou-Nana M, et al. Investigating the signal transduction pathways underlying remote ischemic conditioning in the porcine heart. *Cardiovasc Drugs Ther.* 2012;26(2):87–93. PMID: 22207395 https://doi.org/10.1007/s10557-011-6364-y

37. Jamieson RW, Zilvetti M, Roy D, Hughes D, Morovat A, Coussios CC, et al. Hepatic steatosis and normothermic perfusion-preliminary experiments in a porcine model. *Transplantation.* 2011;92(3):289–295. PMID: 21681143 https://doi.org/10.1097/TP.0b013e318223d817

38. Oniscu GC, Randle LV, Muiesan P, Butler AJ, Currie IS, Perera MTPR, et al. In situ normothermic regional perfusion for controlled donation after circulatory death – the United Kingdom experience. *Am J Transplant.* 2014;14(12):2846–2854. PMID: 25283987 https://doi.org/10.1111/ajt.12927

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