Organ preservation solutions: The past, the present and the future

Aikaterini Stylianaki[1*], Christos Iordanou[2], Georgios C. Zografos[3], Apostolos Papalois[4], Dimitrios Dimitroulis[5]

Transplantation is the therapy of choice in end-stage organ failure. The increasing need for transplants, combined with the decreasing number of donors, creates the necessity of broadening the donor inclusion criteria and optimizing the organ preservation procedure to avoid early and late graft dysfunction. This review aims to provide a summarized overview of the available preservation solutions and their development, the pathophysiology of ischemia/reperfusion injury, and underline the necessity and the future directions in the field of organ preservation.

Key Words: *Organ transplantation, Organ preservation, Ischemia/reperfusion injury, Preservation solutions, Graft dysfunction*

INTRODUCTION

Medical research and progress have been advancing rapidly over the last three decades. Historically, organ transplantation is considered one of the milestones in medical practice together with the introduction of antibiotics, massive vaccinations, practices that can be regarded as the most significant medical achievements of the twentieth century [1]. Organ transplantation was and remains the therapy of choice in irreversible and end-stage organ failure [2]. The procurement and use of organs of high quality and efficacy have always been of great importance in organ transplantation research. In order to achieve that, it is crucial to develop a preservation mechanism that helps us "buy time" and bridge the distance between donor and recipient sites. Organ preservation has been described as the "supply line" for organ transplantation [3].

The goal of the preservation science is to "freeze time" and slow down the metabolic needs of the organs by imitating the physiological tissue environment ex vivo in order to avoid tissue damage caused by ischemia stress and minimize the ischemia/ reperfusion injury (IRI).

The more profound understanding of organ physiology and the ischemia pathophysiology led us to the development of multiple techniques aiming to enhance and support organ preservation and minimize the complications at the recipient site and the risk of organ rejection. This review aims to present the history, the present and possible future applications of preservation solutions in static cold storage in organ transplantation.

HISTORY

The idea of treating diseased or damaged body parts by replacing them has been around for millennia. There are many historical references to the vision of using complex transplants as therapeutic options, such as the successful transplantation of an entire leg during the 3rd century by physicians Cosmos and Damien, which is depicted in several famous paintings [4,5]. The first descriptions of autogenous local skin flaps as the workhorse for plastic surgery procedures for the reconstruction and replacement of missing noses goes back to 600 BC. In the 16th century, many pioneering plastic surgeons were successfully practicing those techniques [4]. The obvious extension of these methods was to use regional or "free" flaps/grafts of autogenous or allogenic tissues.

Interestingly, it was not until the 20th century that the first graft failures were reported. It was only in the last half of the 20th century that there has there been a consensus regarding the difference in the success outcomes between homographs and autografts [4].

Georg Schöne may deserve recognition as the first transplantation immunologist; he and Ehrlich started working together, but his observations were the ones, which three decades later, set the basis for the discovery of the "second set response." The next milestone in transplantation history was in the late 1920s when scientists at the Rockefeller Institute firmly described the complex immunological cascades of transplantation underlying the central role of the lymphocyte [6].

Alexis Carrel is considered to be the pioneer of modern transplantation medicine. He was awarded the Nobel Prize in 1912 for the development of the vascular anastomosis technique and its use in organ transplantation. Apart from the progress made in transplantation surgery alone, there was simultaneously an increasing interest regarding the organ preservation methods after procuration and prior transplantation. As early as 1905, Carrel's colleague Charles Guthrie had advocated cooling to protect donor organs before transplantation [4].

Later, Starzl used total body hypothermia to protect donor organs, and he switched his cooling method into infusing cold solution into the portal vein to protect liver grafts [7]. Calne et al. studied and compared the effectiveness of simple kidney surface cooling to organ cooling via the vascular bed with perfusion of the renal artery with cool heparinized blood. This study concluded that vascular flush perfusion was the more efficient method of the two compared above in cooling the organ mass [8]. The use of blood and blood derivatives during organ procurement and preservation still created many problems at transplantation practice like vascular stasis after graft replantation, underlining the necessity of developing acellular solutions to be used in organ preservation.

Collins et al. described in 1963 and acellular preservation solution mimicking in a primary, simple fashion the intracellular electrolyte environment and balance of mammalian cells. This attempt triggered the interest in the progress of preservation solution research, having as orientation the physiology of organ cooling. In that way, the pre-transplant infusion of cold solution into the renal artery of the donor's kidneys became standard [9].

Collins solutions permitted successful renal preservation for 24 to 36 hours, which was long enough to allow the process of tissue matching and sharing of organs between transplant centers. These approaches were parallel to the continuous research in the field of cool preservation and low-pressure perfusion [10,11]. Due to the limited reliability of perfusion equipment at that time, static flush cooling of the organs followed by ice storage became the Golden standard in organ preservation in the second half of the 20th century [2].

Following the expansion of transplantation as clinical therapy after the 1980s, the development of surgical methods for multiple organ procurement and preservation was needed in order to retrieve kidneys, liver, pancreas, heart, and lungs or various combinations of these organs without jeopardizing any of the individual organs [12].

[1]Department of Plastic, Aesthetic and Hand Surgery Brunswick General Hospital, Brunswick, Germany;[2]Department of General Surgery, Metropolitan Hospital Piraeus, Attica, Greece;[3]Department of the First Propaedeutic Surgical Clinic, Hippocration Hospital, Athens, Greece;[4]Department of Biomedical Research and Education, Aristotle University of Thessaloniki, Athens, Greece;[5]Department of the Second Propaedeutic Surgical Clinic, Laikon Hospital, Athens, Greece

Correspondence: *Aikaterini Stylianaki, Department of Plastic, Aesthetic and Hand Surgery Brunswick General Hospital, Brunswick, Germany, E-mail: stylkat@icloud.com*

Received: *December 22, 2020,* **Accepted**: *January 5, 2021,* **Published**: *January 12, 2021*

In cases of multiple organ procurement, in situ cooling by infusion of cold solution to the aorta was used. The introduction and use of the University of Wisconsin (UW) solution started a new era in the preservation solution domain [13].

The problems of the continuing shortage of donor organs and the change in transplant donor demographics have maintained and even enhanced the pressure to achieve the optimal and efficacious approach to organ preservation which is the driving force of the research into organ preservation.

PRESERVATION SOLUTIONS

Principles of development of preservation solutions

Traditionally, the development of effective OPS was based on understanding the underlying pathophysiology and consequently minimizing ischemia/reperfusion (I/R)-induced cellular injury. Preservations methods and the choice of solutions themselves impact organs on a molecular basis so that they can modify the ischemia-reperfusion tissue response. The molecular microenvironment alterations tend to affect both the intracellular and the extracellular space, changing the cell and tissue behaviour in ischemic conditions.

The experiments studying the effect of I/R demonstrated that the severity of the injury after reperfusion is directly correlated to the duration of ischemia. It is believed that the cellular reactions upon I/R are based on a sterile inflammation phenomenon [14] involving reactive oxygen species (ROS), endothelial leukocyte and platelet sequestration, transmigration of neutrophils, and the release of endogenous inflammatory mediators [15].

It is a micro vascular wall dysfunction that triggers the immune cell response cascade in I/R-Induced sterile Inflammation that creates the pattern of I/R injury (IRI) and forms the basis for elaborating the underlying mechanisms of this pathological process.

It has been shown that even a short duration of 20 minutes of warm ischemia in the liver results in decreasing the sinusoidal diameter, which is associated with plugging of leukocytes upon reperfusion as well as sinusoidal obstruction caused by endothelial cell swelling. [16] On the contrary, cold ischemia protects from hepatic microcirculatory perfusion failure after 90 minutes of lobar ischemia [17]. However, a prolonged hypothermia time of 24 hours significantly reduced ischemia/reperfusion complication rates [18].

The microcirculatory basis of ischemia and reperfusion injury was attributed to a series of interrelated events observed being in common in different organs. Among those is interstitial edema being caused due to increased capillary permeability, driven by increased pressure of the interstitial tissue, which mechanically compresses the capillaries [19], and microvascular spasm caused by vasoactive substances [20]. In that fashion, the composition of some preservation solutions impacts the microcirculatory properties of the procured organs. For example, flushing the organ with a low potassium medium prior to preservation may protect microvessels from the adverse effects of cold storage and improve reperfusion after transplantation in situations where vasoconstriction could be caused by high potassium content in the OPS [21]. Another essential factor and phenomenon that has to be reported is the "no-reflow" phenomenon in IR, which is attributed to the leukocyte plugging of the capillary lumen. Leukocytes are large and stiff cells that adhere to the vascular endothelium and are more likely to become captured in capillaries obstructing the luminal flow. This adherence obstructs the capillaries and the flow as well as leukocytic adhesion to the vascular wall itself, which can cause further impairment of endothelial cells [22].

The mechanisms mentioned above underline the fact that the choice of the most suitable OPS and the science underpinning OPSs development are crucial to organ preservation in both cases of hypothermic metabolic perfusion or static cold storage (SCS) [23]. Ischemia comes with a massive cost to all cells, resulting in cellular injury via multiple and complex molecular cascades leading to cell death. Hypothermia initially suppresses the metabolic rate, but prolonged cold ischemia leads to depletion of cellular adenosine triphosphate (ATP) and accelerated glycolysis, which leads to lactic acid production. The accumulation of adenine breakdown products, such as hypoxanthine, stimulates the production of oxygen free radicals. Lactic acid production causes cellular acidosis, which changes the pH- and energy-dependent cellular processes, including transmembrane ion pumps (Na^+/ K^+ and Ca^{2+}) that influx ions (Na^+ and Cl^-) and water, causing loss of membrane potential and progressive cell swelling. Additionally, cell membrane injury occurs due to lysosomal enzyme release in response to intracellular acidosis and direct oxidative damage from ROS [21].

This cascade is also characterized by the activation of proteases and phospholipases caused by increased intracellular Ca^{2+}, as mentioned above they causing injury of the mitochondrial membrane, increased mitochondrial permeability the release of cytochrome C, which activates an apoptosis signaling pathway in the cell. The combination of all intracellular events mentioned above contributes to a prooxidant environment triggering ROS production and oxidative stress at the early stages of reperfusion. It is the basic understanding of the pathophysiology of cell injury during cold preservation that is crucial for the development of preservation solutions that aim to target and suspend programmed cell death [21].

As a consequence of the above, OPSs include colloids to control water and electrolyte movement across the cell membrane and prevent cell edema; buffers to control pH changes; antioxidants as free radical scavengers and nutrient precursors for ATP production and energy supply.

Below we provide an overview of the available preservation solutions that are widely used and their biochemical properties (Table 1)

TABLE 1

Overview of the properties of preservation solution

	UW	Celsior	HTK	IGL⁻ 1	Euro-Collins
Osmolarity	320	320	310	320	375
pH	7.4	7.3	7.2	7.4	7.1
Viscosity (cp)	5.7	1.15	1.8	1.28	N/a
Na⁺ (mmol/l)	25-30	100	15	120	10
K⁺ (mmol/l)	125-130	15	10	30	115
Mg²⁺(mmol/l)	5	13	4	5	-
Ca²⁺(mmol/l)	-	0.25	0.015	-	-
Cl⁻(mmol/l)	-	41.5	50	20	15
PO₃(mmol/l)	25	-	-	25	47.5
SO₄(mmol/l)	5	-	-	5	30

COLLINS SOLUTION

Collins solution was historically the first solution created for organ preservation. It was based on a combination of high potassium iron content and osmotic barriers supported by glucose [24]. The Europe transplant foundation modified the original column solution in 1976, eliminating magnesium, which was a simple and cheap intracellular-like preservation solution. This solution contains an intracellular electrolyte composition with low sodium and high potassium aiming to prevent trans membranous fluid and electrolyte shifts. The high concentration of glucose in the solution provides an osmotic balance between the intracellular and extracellular space and suppresses hypothermia-induced cell edema. Collins used at his prototype solution a phosphate buffer to prevent intracellular acidosis that is mainly caused by the anaerobic glycolysis during cold ischemia. Collins solution was further modified in Europe by creating the so-known Euro Collins solution (EC), which had an increased glucose concentration. The Euro-Collins solution's osmotic potency was increased by the higher glucose concentration(195 mmol/L versus 140 mmol/L). Furthermore,magnesium sulphate was excluded because the presence of magnesium and phosphate resulted in the formation of magnesium phosphate precipitates [25]. Both types of Collins solutions are effective for cold storage preservation of kidneys for 24 to 30 hours. Other modifications of the Euro Collins solution by substitution of glucose for mannitol [26] sucrose provided excellent protection during cold ischemia. The Euro-Collins solution has been used by many transplant centers throughout the world for many years.

Since the introduction of the University of Wisconsin Cold Storage Solution (UW-CSS), most centers have been using this solution for the preservation of intraabdominal organs.

UNIVERSITY OF WISCONSIN SOLUTION (UW)

This solution became the clinical practice standard of organ preservation throughout the world with excellent results. It has been accepted as the gold standard for liver transplantation since 1989 and is usually referred to as the

"clinical solution." The detailed study of Na^+ and K^+ redistribution using microdialysis techniques suggests that Na^+/K^+ diffusion into interstitial spaces may not follow the stoichiometric rule of 3:2 $Na^+:K^+$ exchange [27-29]. In a prospective, randomized trial of 695 cadaveric renal transplants comparing kidneys preserved in UW and EC, the incidence of delayed graft function was significantly less in transplant recipients receiving UW-preserved kidneys than those receiving EC-preserved kidneys (23% versus 33%, respectively; P=0.003) [30]. Another study by Todo et al. demonstrated UW to safely increase preservation time for livers to more than 15 hours (maximum of 37 hours) compared with EC [31]. The solution has an approximately calculated osmolarity of 320 mOsm, a sodium concentration of 29 m Eq/l, a potassium concentration of 125 m Eq/l, and a pH of about 7.4 at room temperature. The introduction of metabolically inert substrates such as lactobionate and raffinose made UW solution universal for multiple organ preservation. Additionally to the facts mentioned above, combining two osmotically active components enables a successful transplantation outcome and beneficial physiological function combined with less histological damage of the kidney compared to the Euro Collins solution [32].

The preservation strategy achieved with the UW can be summarized as follows: prevention of cell edema (raffinose, lactobionate), supplementation with precursors of ATP (adenosine), and antioxidant defense (allopurinol, reduced glutathione) [2]. UW is used for the preservation of multiple different organs such as the liver, heart, lung, and kidney.

CITRATE SOLUTIONS (MARSHALL/ROSS)

Marshall citrate solution and its modifications were developed as an alternative to Collins solution for kidney preservation. The electrolytic composition of that solution is characterized by high potassium, sodium, and magnesium content. Citrate was added to its content in order to replace phosphate and as a buffer agent to maintain the intracellular pH. The citrate can be replaced with hydroxyethylpiperazine-ethane sulphonic acid (HEPES) [33] to provide appropriate buffer capacity. The citrate mechanism is presumably linked to the chelation of magnesium that produces a semi-permeable molecule, which may support membrane integrity [34]. However, the mechanism of action is still uncertain. Citrate calcium-binding capacity helps to prevent cytosolic detrimental cation accumulation. Replacement of glucose by mannitol provided better osmotic properties and lower viscosity. The safe preservation period for the kidney with this solution is 24–30 h [35].

BRETSCHNEIDER'S (CUSTODIOL) SOLUTION

Histidine-tryptophane-ketoglutarate (HTK) solution was first described by H.J. Bretschneider. It was initially a preservation solution developed for cardiac surgery. Still, it was shown effective in both liver and kidney preservation to an extend that was found competing with UW for its effectiveness in intraabdominal organ preservation [36,37].

The solution consists of histidine, mannitol, tryptophan, and a-ketoglutarate acid. These components function as a buffer with membrane-stabilizing properties and substrate for anaerobic metabolism.

Electrolyte composition is characterized by a low concentration of Na^+, K^+, Mg^{2+}, which allow a safe solution release into the recipient's blood circulation. The low viscosity of Bretschneider solution provides an effective organ flushing and cooling during organ procurement [2].

Most recently, a modified less toxic histidine-tryptophan-ketoglutarate (HTK; Custodiol®) the so-called histidine-tryptophan-ketoglutarate-N (HTK-N) for both better cardioplegia and organ preservation for transplantation has been developed. It is characterized as an electrolyte balanced, iron chelator supplemented, and amino acid-fortified organ preservation solution with replaced buffer ameliorating resistance to tissue injury during the cold static preservation with subsequent IRI. Numerous in vitro and in vivo experiments have shown the superiority of the HTK-N in ROS generation, microcirculation, and subsequent inflammatory response compared with HTK [38].

CELSIOR SOLUTION

Celsior is an extracellular type Solution with a high Na^+ concentration that combined the osmotic principles of UW solution (lactobionate and mannitol) with the buffer properties of HTK solution. This solution has a

low concentration in glutathione, which functions as an antioxidant agent.

Celsior Solution is an excellent preservation Solution for heart and lung transplantation [39] and has also shown promising potentials in preservation of intraabdominal organs such as the liver [40], pancreas [41] and kidney [42]. This preservation solution showed excellent properties in tissue cooling, cell swelling, scavenging of ROS and energy depletion.

KYOTO UNIVERSITY PRESERVATION SOLUTION

The Kyoto University research team used and evaluated the importance of polysaccharides and electrolytes in lung preservation in order to develop their original preservation Solutions also known as Kyoto solution. They considered and compared multiple agents regarding the protection of vasculature, and eventually, they primarily created the so-called ET (extracellular type) Kyoto solution. In hypothermic organ preservation, the K/Na ATPase function decreases, causing an increase in sodium and chlorium flow with water from the extracellular space into the cell according to the ion gradient resulting in intracellular edema. The use of saccharides was considered a treatment for this cellular edema, which is why trehalose was used in this solution. In the primary research, the glucose of EC solution was replaced by trehalose [43]. After a comparative study among the effects of monosaccharides, disaccharides, and trisaccharides in lung preservation, the University of Kyoto research group drew the conclusion that trehalose was shown to be superior to the other saccharides [44].

IGL-1 SOLUTION

This solution was developed at the George Lopez Institute in France and is a relatively new preservation solution with lower potassium concentration and lower viscosity than the University Wisconsin solution (UW). These characteristics have been shown to improve liver preservation were evaluated by multiple randomized controlled comparative studies with UW. IGL-solution is characterized by the inversion of K^+ and Na^+ concentrations of the UW solution combined with polyethylene glycol 35 (PEG 35) substitution for hydroxyl-ethyl-starch (HES), resulting in lower viscosity of IGL-1 compared to UW solution [45,46]. The protective actions of PEG are not fully elucidated yet. Still, PEGs are considered to stabilize the lipid monolayer in cell membranes, and the polymer has different effects on monolayers under diverse (low or high) surface pressure. In cases of low surface pressure, PEG stabilizes the membrane. Biochemically, the denser packing of lipids causes decreased membrane fluidity through dehydration caused by PEG [47].

PERFADEX SOLUTION

Perfadex, a low-potassium dextran (LPD) solution, provides excellent lung preservation for up to 24 hours and limits the extent of ischemia/reperfusion injury due to its low potassium and high sodium concentration. High potassium concentrations induce significant pulmonary vasospasm, which was one of the main observations leading to the development of extracellular type solutions [48,49].

Perfadex has a high concentration in dextran 40 to counteract the cell swelling induced by cold ischemic storage. The principle behind it is that protein molecules are the only dissolved substances in plasma that do not penetrate the pores of the capillary membrane. Therefore, the plasma and interstitial fluids' dissolved proteins are responsible for the osmotic pressure at the capillary membrane [50]. Considering that albumin (molecular weight of around 69,000 daltons) is responsible for about 70% of the oncotic pressure of plasma, the average concentration of albumin in plasma is about 4 g/100 mL, i.e., 4%. Perfadex contains 5% dextran with an average molecular weight of 40,000 daltons, which means that there are more than twice as many dextran molecules in Perfadex as albumin molecules in an equivalent volume of plasma. Dextran 40, like albumin, does not readily penetrate cell membranes; therefore, Perfadex has an oncotic pressure about twice as high as that of plasma [50].

FUTURE PERSPECTIVES

Despite the long and very intensive research made in the field of organ preservation so far and the optimization of the preexisting/already available organ preservation solutions, there are still many unanswered questions and multiple aspects regarding OPSs that need to be improved. There are several studies aiming to modify the different preservation solutions through

pharmacological maneuvers and modifications. Other strategies combine organ perfusion strategies with preservation solutions. The concept of long-term organ preservation at deep subzero temperatures continues to be current, although it was considered to be out of date some years ago [51-53]. There have been many scientific efforts in combining machine perfusion techniques (normothermic, subnormothermic, hyponormothermic) with preservation solutions in order to optimize organ preservation and minimize ischemia/reperfusion injury. The progress made in the field of genetics and biotechnology helps us develop other promising strategies in organ preservation, such as organ regeneration, organ immunomodulation, and organ repair.

There are already some studies showing what effect tissue and organ engineering may have on organ preservation. Ott et al . were the first in our knowledge to use ex vivo machine perfusion as a platform and decellularized rat hearts through coronary perfusion with detergents in a Langendorff apparatus. Then they reseeded these constructs by perfusion with cardiac or endothelial cells in a bioreactor that simulated cardiac physiology for 28 days [54]. Ott et al. continued their research on the field with bioengineering lung tissue for transplantation and started a new era in the field of transplantation research [55].

CONCLUSION

Since the very first speculation regarding organ preservation made by Cesar Julien Jean Le Gallois over two centuries ago, there has been a tremendous progress in that field of research. In the very early days, organs were perfused with blood at physiological temperatures, the progress of science led to the use of static cold storage (SCS), which was a revolution in the field of organ preservation. This fact was combined with the development of different preservation solutions that had properties which were minimizing ischemia reperfusion injury in the grafts. Every solution has a dynamic and functions with mimicking the intra- and extracellular environment of the precured organs in order to protect from the aseptic Inflammation and endothelial cascade caused after reperfusion. There is a great scientific interest in developing these solutions either by adding pharmacological agents or by bioengineering. The optimization of preservation solutions together with prolonged ex vivo machine perfusion creates a new horizon in organ repair and reprogramming, warranting further research in the optimization of organ preservation prior to transplantation.

REFERENCES

1. Grinyo JM Why is organ transplantation clinically important? Cold Spring Harb Perspect Med. 2013;3(6).

2. Guibert EE, Petrenko AY, Balaban CL,et.al. Organ Preservation: Current Concepts and New Strategies for the Next Decade. Transfus Med Hemother. 2011;38(2):125-42.

3. Southard JH, Belzer FO Organ preservation. Annu Rev Med. 1995; 46:235-47.

4. Barker CF, Markmann JF Historical overview of transplantation. Cold Spring Harb Perspect Med. 2013; 3(4):a014977.

5. KW Z One leg in the grave revisited: The miracle of transplantation of the black leg by Saint Cosmos and Damian. Maarsen, The Netherlands: Elsevier; 1998 1998.

6. Silverstein AM The lymphocyte in immunology: from James B. Murphy to James L. Gowans. Nat Immunol. 2001; 2(7):569-71.

7. Marchioro TL, Huntley RT, Waddell WR, et.al. Extracorporeal Perfusion for Obtaining Postmortem Homografts. Surgery. 1963;54:900-11.

8. Calne RY, Pegg DE, Pryse-Davies J, et.al. Renal Preservation by Ice-Cooling: An Experimental Study Relating to Kidney Transplantation from Cadavers. Br Med J. 1963; 2(5358):651-5.

9. Collins GM, Bravo-Shugarman M, Terasaki PI Kidney preservation for transportation. Initial perfusion and 30 hours' ice storage. Lancet. 1969; 2(7632):1219-22.

10. Humphries AL, Russell R, Stoddard LD, et.al. Successful five-day kidney preservation. Perfusion with hypothermic, diluted plasma. Invest Urol. 1968; 5(6):609-18.

11. Humphries AL, Moretz WH, Peirce EC Twenty-Four Hour Kidney Storage with Report of a Successful Canine Autotransplant after Total Nephrectomy. Surgery. 1964; 55:524-30.

12. Starzl TE, Hakala TR, Shaw BW, et al. A flexible procedure for multiple cadaveric organ procurement. Surg Gynecol Obstet. 1984; 158(3):223-30.

13. Belzer FO, D'Alessandro AM, Hoffmann RM, et al. The use of UW solution in clinical transplantation. A 4-year experience. Ann Surg. 1992; 215(6):579-83.

14. van Golen RF, Reiniers MJ, Olthof PB, et.al. Sterile inflammation in hepatic ischemia/reperfusion injury: present concepts and potential therapeutics. J Gastroenterol Hepatol. 2013;28(3):394-400.

15. Olanders K, Sun Z, Borjesson A, et al. The effect of intestinal ischemia and reperfusion injury on ICAM-1 expression, endothelial barrier function, neutrophil tissue influx, and protease inhibitor levels in rats. 2002;18(1):86-92.

16. Vollmar B, Glasz J, Post S, et.al. Role of microcirculatory derangements in manifestation of portal triad cross-clamping-induced hepatic reperfusion injury. J Surg Res. 1996; 60(1):49-54.

17. Biberthaler P, Luchting B, Massberg S, et al. Ischemia at 4 degrees C: a novel mouse model to investigate the effect of hypothermia on postischemic hepatic microcirculatory injury. Res Exp Med (Berl). 2001; 200(2):93-105.

18. Schauer RJ, Bilzer M, Kalmuk S, et al. Microcirculatory failure after rat liver transplantation is related to Kupffer cell-derived oxidant stress but not involved in early graft dysfunction. Transplantation. 2001; 72(10):1692-9.

19. Durand MJ, Gutterman DD. Diversity in mechanisms of endothelium-dependent vasodilation in health and disease. Microcirculation. 2013; 20(3):239-47.

20. Nanobashvili J, Neumayer C, Fuegl A, et al. Development of 'no-reflow' phenomenon in ischemia/reperfusion injury: failure of active vasomotility and not simply passive vasoconstriction. Eur Surg Res. 2003; 35(5):417-24.

21. Petrenko A, Carnevale M, Somov A, et al. Organ Preservation into the 2020s: The Era of Dynamic Intervention. Transfus Med Hemother. 2019; 46(3):151-72.

22. Ballermann BJ, Dardik A, Eng E, et.al. Shear stress and the endothelium. Kidney Int Suppl. 1998; 67:S100-8.

23. Fuller B, Froghi F, Davidson B Organ preservation solutions: linking pharmacology to survival for the donor organ pathway. Curr Opin Organ Transplant. 2018; 23(3):361-8.

24. Collins GM, Hartley LC, Clunie GJ Kidney preservation for transportation. Experimental analysis of optimal perfusate composition. Br J Surg. 1972; 59(3):187-9.

25. Heinrich B Temperature Regulation in the Bumblebee Bombus vagans: A Field Study. Science. 1972; 175(4018):185-7.

26. Andrews PM, Bates SB Improving Euro-Collins flushing solution's ability to protect kidneys from normothermic ischemia. Miner Electrolyte Metab. 1985; 11(5):309-13.

27. Kozlova I, Khalid Y, Roomans GM Preservation of mouse liver tissue during cold storage in experimental solutions assessed by x-ray microanalysis. Liver Transpl. 2003; 9(3):268-78.

28. Lopukhin SY, Southard JH, Belzer FO University of Wisconsin solution containing 2, 3-butanedione-monoxime extends myocardium preservation time. Transplant Proc. 1993; 25(6):3017-8.

29. Belzer FO, Southard JH Principles of solid-organ preservation by cold storage. Transplantation. 1988; 45(4):673-6.

30. Ploeg RJ, van Bockel JH, Langendijk PT, et al. Effect of preservation solution on results of cadaveric kidney transplantation. The European Multicentre Study Group. Lancet. 1992; 340(8812):129-37.

31. Todo S, Nery J, Yanaga K,et.al. Extended preservation of human liver grafts with UW solution. JAMA. 1989; 261(5):711-4.

32. Ueda Y, Todo S, Imventarza O, et al. The UW solution for canine kidney preservation. Its specific effect on renal hemodynamics and

microvasculature. Transplantation. 1989; 48(6):913-8.

33. Jablonski P, Howden B, Marshall V, et.al. Evaluation of citrate flushing solution using the isolated perfused rat kidney. Transplantation. 1980; 30(4):239-43.

34. Marshall MR, Ma TM, Eggleton K, et.al. Regional citrate anticoagulation during simulated treatments of sustained low efficiency diafiltration. Nephrology (Carlton). 2003; 8(6):302-10.

35. Howden B, Jablonski P, Rigol G, et al. Studies in renal preservation using a rat kidney transplant model: II. The effect of reflushing with citrate. Transplantation. 1984; 37(1):52-4.

36. Kalayoglu M, Sollinger HW, Stratta RJ, et al. Extended preservation of the liver for clinical transplantation. Lancet. 1988; 1(8586):617-9.

37. Den Butter G, Saunder A, Marsh DC, et.al. Comparison of solutions for preservation of the rabbit liver as tested by isolated perfusion. Transpl Int. 1995; 8(6):466-71.

38. Kahn J, Schemmer P Comprehensive Review on Custodiol-N (HTK-N) and its Molecular Side of Action for Organ Preservation. Curr Pharm Biotechnol. 2017;18(15):1237-48.

39. Wittwer T, Wahlers T, Cornelius JF, et.al. Celsior solution for improvement of currently used clinical standards of lung preservation in an ex vivo rat model. Eur J Cardiothorac Surg. 1999; 15(5):667-71.

40. Matias JE, Morais FA, Kato DM, et al. [Prevention of normothermic hepatic ischemia during in situ liver perfusion with three different preservation solutions: experimental analysis by realtime infrared radiation thermography]. Rev Col Bras Cir. 2010; 37(3):211-7.

41. Hackl F, Stiegler P, Stadlbauer V, et al. Preoxygenation of different preservation solutions for porcine pancreas preservation. Transplant Proc. 2010; 42(5):1621-3.

42. Nunes P, Mota A, Figueiredo A, et al. Efficacy of renal preservation: comparative study of Celsior and University of Wisconsin solutions. Transplant Proc. 2007; 39(8):2478-9.

43. Chen F, Nakamura T, Wada H Development of new organ preservation solutions in Kyoto University. Yonsei Med J. 2004; 45(6):1107-14.

44. Fukuse T, Hirata T, Nakamura T, et al. Role of saccharides on lung preservation. Transplantation. 1999; 68(1):110-7.

45. Codas R, Petruzzo P, Morelon E, et al. IGL-1 solution in kidney transplantation: first multi-center study. Clin Transplant. 2009; 23(3):337-42.

46. Wiederkehr JC, Igreja MR, Nogara MS, et al. Use of IGL-1 preservation solution in liver transplantation. Transplant Proc. 2014; 46(6):1809-11.

47. Ohno H, Sakai T, Tsuchida E, et.al. Interaction of human erythrocyte ghosts or liposomes with polyethylene glycol detected by fluorescence polarization. Biochem Biophys Res Commun. 1981; 102(1):426-31.

48. Latchana N, Peck JR, Whitson B, et.al. Preservation solutions for cardiac and pulmonary donor grafts: a review of the current literature. J Thorac Dis. 2014; 6(8):1143-9.

49. Jing L, Yao L, Zhao M, et.al. Organ preservation: from the past to the future. Acta Pharmacol Sin. 2018; 39(5):845-57.

50. Steen S, Kimblad PO, Sjoberg T, et.al. Safe lung preservation for twenty-four hours with Perfadex. Ann Thorac Surg. 1994; 57(2):450-7.

51. Bruinsma BG, Berendsen TA, Izamis ML, et.al. Supercooling preservation and transplantation of the rat liver. Nat Protoc. 2015; 10(3):484-94.

52. Mandolino C, Pizarro MD, Quintana AB, et.al. Hypothermic preservation of rat liver microorgans (LMOs) in bes-gluconate solution. Protective effects of polyethyleneglycol (PEG) on total water content and functional viability. Ann Hepatol. 2011; 10(2):196-206.

53. Carnevale ME, Balaban CL, Guibert EE, et.al. Hypothermic machine perfusion versus cold storage in the rescuing of livers from non-heart-beating donor rats. Artif Organs. 2013; 37(11):985-91.

54. Ott HC, Matthiesen TS, Goh SK, et al. Perfusion-decellularized matrix: using nature's platform to engineer a bioartificial heart. Nat Med. 2008; 14(2):213-21.

55. Ott HC, Clippinger B, Conrad C, et al. Regeneration and orthotopic transplantation of a bioartificial lung. Nat Med. 2010; 16(8):927-33.