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Preservation of Renal Allografts for Transplantation

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1. Introduction

Kidney transplantation requires the availability of allografts obtained from diverse types of donors. Once the kidney is outside of the donor's body, it must be preserved in a state in which, after being transplanted, its normal operation can be quickly restored. Proper preservation of the renal graft is crucial, because it extends the viability of the organ, thus providing time for the complex preparation steps that are required for the transplantation procedure. These preparatory steps include the selection of the recipient, histocompatibility testing, transportation of the organ over long distances, and preparation of the recipient in the operating room.

The first documented case of perfusion and preservation of an isolated organ was performed by Loebel in 1849. Other pioneers have subsequently contributed to this area: Langendorf in 1845 used a siphoning tube connected to the organ, while Martin created a method to perfuse the coronary artery *in vitro* in the early 1900's. In 1905 Carrel published "Anastomosis and Transplant of Blood Vessels". Around 1930, Heinz Rosenberg built a perfusion machine, and in 1935 Lindbergh built a pulsatory perfusion machine.

In the early 1960's, the only known preservation method was simple organ cooling. Lapchinsky in the former Soviet Union started transplanting extremities and kidneys that were preserved at +2°C and +4°C, preserving them for up to 28 hours. In 1963 Calne and Pegg demonstrated that perfusion of cold blood to an ischemic kidney could prolong its preservation up to 12 hours. In 1967, Belzer preserved kidneys for up to 72 hours, using a method of continuous perfusion "*ex situ*". In 1969 Collins described the use of a preservation solution that resembled the composition of the intracellular fluid, and was used for perfusion/rinsing of the organ in cold temperature "*in situ*", and also for its further hypothermic storage, achieving kidney preservation for up to 30 hours. In the 1980's Belzer,

Southard and many other investigators started to lay the foundations for understanding the metabolic changes that occur in the extracted organs after explantation.

In this chapter the techniques for kidney allograft preservation will be briefly reviewed, and the pathophysiological changes that occur during preservation and reperfusion of the allograft will be discussed. Finally, the currently used preservation solutions will be described.

2. Techniques for preservation of the renal allograft

2.1 Hypothermic perfusion techniques

The combination of continuous perfusion and hypothermic storage used by Belzer *et al.* in 1967 represented a new paradigm in regards to organ preservation, achieving successful canine kidney preservation for 72 hours. In this technique, after the initial washes performed during perfusion in the operating room, the organ is introduced in a device that keeps a controlled flow (continuous or pulsatory) with cold preservation solution (0-4°C). This flow allows complete perfusion of the organ and clearing of any micro thrombi in the blood stream, while facilitating the elimination of final metabolic products. Its beneficial effects include a lower incidence of delay in the initial functioning of the graft, the possibility to assess its viability in real time, and the possibility of providing metabolic (oxygen or substrates) or pharmacologic support during the perfusion. The hypothermic perfusion machine (HPM) with continuous flow has not shown advantages with respect to the pulsatory flow machine. Figures; 1 and 2, shows some of the perfusion machines currently being used.

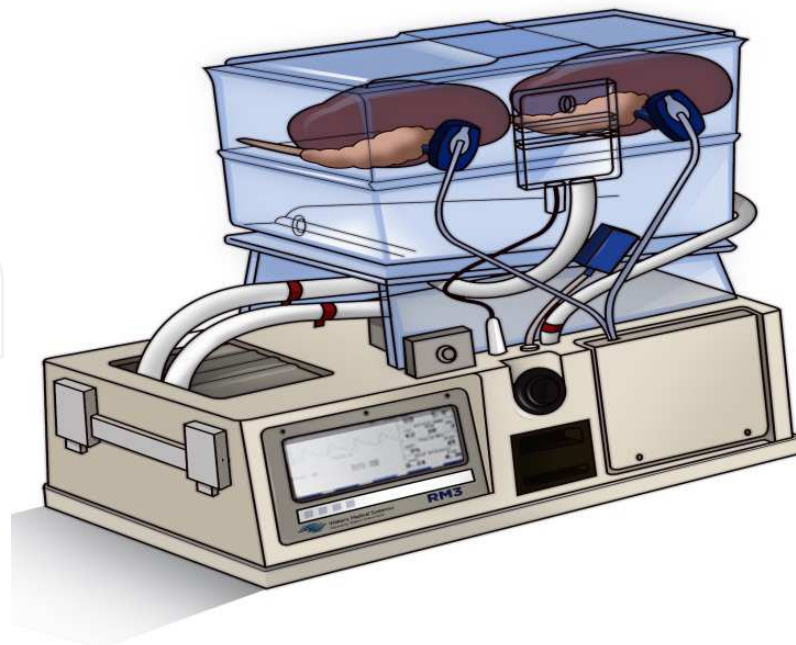


Fig. 1. Hypothermic perfusion machine: Waters RM3® Renal Preservation System from Waters Medical System®.

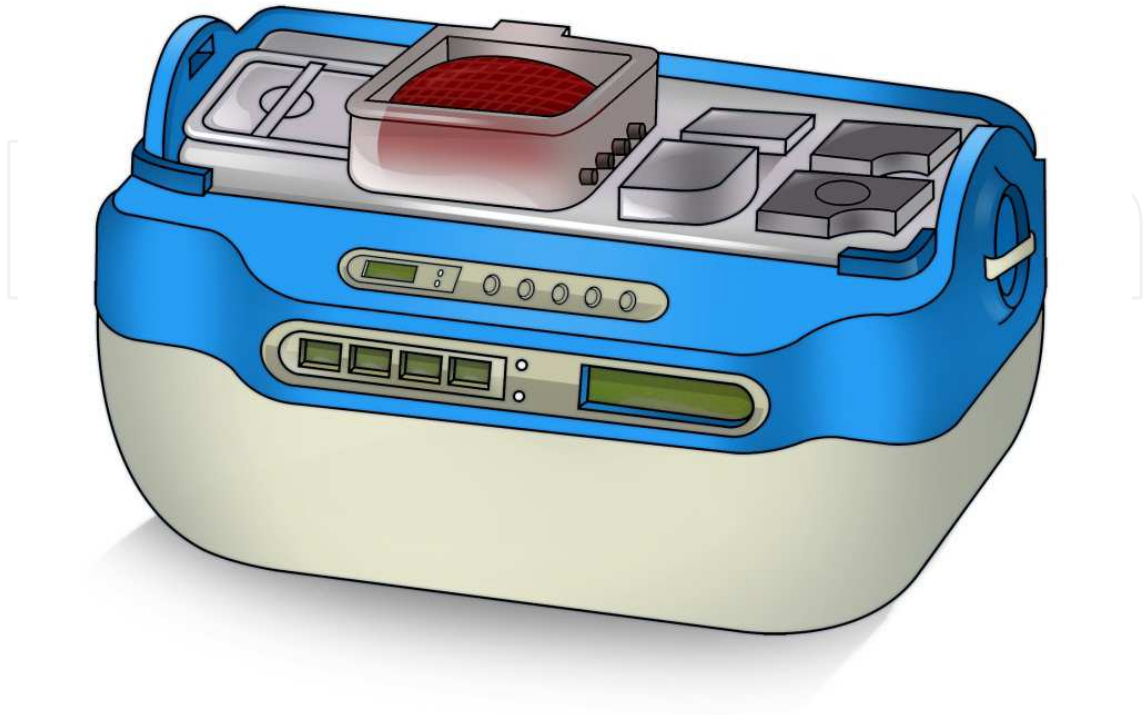


Fig. 2. Hypothermic perfusion machine: Life Port Kidney Transporter® from Organ Recovery Systems®.

To date, hypothermic perfusion is the approach that provides the longest possible preservation time for renal allografts. However, due to its complexity, high cost, and the need for abundant equipment, these techniques are only suitable for use in facilities highly specialized in renal preservation. Additionally, they require well prepared personnel with vast experience in the field of allograft preservation.

The use of HPM has the following advantages and disadvantages:

Advantages:

1. Less incidence of delay in the re-initiation of kidney allograft function.
2. Better preservation for longer periods of time (especially greater than 24 hours)
3. Ability to control flow and pressure, therefore ability to monitor intrarenal resistance during perfusion.
4. Decreased renal vasospasm.
5. Ability to provide metabolic support during perfusion.
6. Potential for pharmacological manipulation during perfusion.

Disadvantages:

1. Increased cost.
2. Endothelial injury.
3. Possibility of mechanical failure.

2.2 Normothermic preservation techniques

Just recently, interest has been arising on the beneficial effects of continuous normothermic or subnormothermic perfusion (25-37 °C) in the preservation process, especially of kidneys from non-beating heart donors. The potential benefits of normothermia during perfusion are the decrease of vascular resistance and the increase in oxygen release.

2.3 Oxygen insufflation technique

This technique was first described by Isselhard *et al.* in 1972, in which oxygen is insufflated through the kidney vessels and then escapes through small perforations on the organ's surface. This technique was attempted for the first time in canine kidneys, and has been the subject of a pilot clinical study.

2.4 Preservation by cold storage

This technique consists in substituting the vascular contents for a cold preservation solution, replacing the intracellular fluid for that of the solution. It is a very simple technique, but it only partially achieves its objective, because, in contrast to the continuous perfusion techniques, it does not maintain cellular metabolism in hypothermia. This is the technique that the majority of renal explantation teams utilize. The following is required for its application:

1. Preservation solution.
2. The temperature of the preservation solution should be 4°C.
3. The perfusion fluid should be infused at a pressure greater than 60 torr, ensuring the complete elimination of the graft's vascular contents. In practice, this is achieved by placing the perfusion fluids at 100-150 cm above the organs to be perfused.
4. The amount of solution necessary to preserve the kidney is 1 liter, but it is standard practice to stop perfusion only after the effluent fluid from the graft does not contain any blood.

3. Pathophysiology and basis for the preservation of a renal allograft

The extraction, storage, and transplantation of a renal allograft from a donor significantly alter the kidney's internal homeostasis. The extent of these changes influences the extent to which kidney function will be recovered after transplantation. Kidney injury mainly occurs as a result of ischemia, and the different preservation techniques serve to minimize this injury and improve the allograft's function and survival.

3.1 Basis for the preservation of the renal allograft

Any kidney that has been extracted from the body suffers a process known as ischemia. The graft does not receive oxygen or nutritional support, and at the same time, products of its own metabolism accumulate, resulting in injury. The injury to the tissue is initially reversible, but after a certain interval it becomes irreversible. This phenomenon is known as "hot ischemia", and under these conditions the time limit for organ viability is between 30 and 60 minutes.

The deterioration caused by ischemia is mediated by chemical reactions that happen more or less rapidly depending on the temperature. During hypothermia, reversible ischemic injury also appears early on ("cold ischemia"), but differs from hot ischemia in several ways.

The fundamental cause of ischemic injury resides in the molecular changes suffered by cellular membranes. Initially, the cells swell and become turgid due to the alterations in the functionality of the cell membrane. After 60 minutes of hot ischemia, rupture of renal cell membranes is observed, followed by cellular necrosis.

Another phenomenon also observed in hot ischemia is called "absence of reflux", which comprises the lack of blood flow when circulation is restored to the organ. This occurs when erythrocytes accumulate in the vessels. Therefore, completely eliminating erythrocytes in the vessels through rinsing during the ischemic period is essential.

3.2 Effects of hypothermia (cold ischemia)

The key to successful organ preservation is hypothermia. Cooling reduces the rate at which intracellular enzymes degrade the components that are essential for cellular viability. Hypothermia does not completely stop cellular metabolism, it only slows it down for a limited time, after which function ceases completely and viability is lost (cellular death). The length of this period is organ-specific.

The majority of enzymes in normothermic animal cells show a decrease in their activity from 1.5- 2 times for each 10°C decrease in temperature, following the Van Hoff rule:

$$Q_{10} = (K_2/K_1)^{10/(t_2-t_1)}$$

Where Q_{10} is the coefficient for a change of 10°C in temperature, and K_1 and K_2 are the rates of the enzymatic reactions at temperatures t_1 and t_2 , respectively. In a renal cell with a Q_{10} of 2, a change in temperature from 37°C to 0°C decreases the rate of the metabolic reactions by a factor of 12 to 13.

The majority of organs tolerate between 30 to 60 minutes of hot ischemia, without completely losing their function. Thus, the simple cooling of a kidney increases its preservation time up to 12 to 13 hours, as shown by Calne and Pegg in 1963. After 13 hours, ultrastructural changes can be observed in the proximal tubules and, to a lesser extent, in the distal tubules.

The only methods that could in theory maintain a kidney viable for months or years are freezing of the organ, or its continuous aerobic perfusion. Temperatures below 0°C have been used to successfully preserve isolated cells and some simple tissues, but not kidneys. Cryopreservation is still an exciting and complex field of research. The method of continuous aerobic perfusion is complex, expensive and requires trained personnel with vast experience in organ preservation, and thus this technique is not routinely used in clinical practice.

The ideal preservation temperature for kidney allografts is between 0°C and 5°C (4°C seems to be the ideal temperature). Higher temperatures would accelerate cellular metabolism, making it necessary to provide nutrients to support its metabolic requirements through continuous perfusion during the preservation period.

As previously mentioned, in cold ischemia, besides hypothermia, perfusion fluids are also needed. Therefore, the renal allograft is subjected to ischemia in anaerobic hypothermia, which is accompanied by the events described below.

3.2.1 Cellular edema induced by ischemia and hypothermia

Under normal conditions, the cells are in an extracellular environment rich in sodium and low in potassium, while the intracellular environment is poor in sodium and rich in potassium. This equilibrium against a gradient between both sides of the plasma membrane is maintained by the Na^+/K^+ pump which requires energy (ATP) obtained from oxidative phosphorylation. The pump keeps this balance by avoiding the entrance of sodium into the cell and counteracting the colloidal osmotic pressure derived from proteins and other intracellular anions. Under normal conditions, the intracellular osmotic force is 110-140 mOsm/Kg.

Anaerobic hypothermia (such as in the kidney stored in the cold) decreases the activity of the Na^+/K^+ pump and reduces the plasma membrane potential. Sodium and chloride enter the cell following a concentration gradient, dragging with them water, which causes the cell to swell, causing cellular edema (Fig 3). This edema could be counteracted by adding to the preservation solution 110-140 mmol/l of substances that are impermeable to the cell (i.e. they cannot pass the plasma membrane due to their elevated molecular weight). We will refer to these substances as “waterproofing agents”.

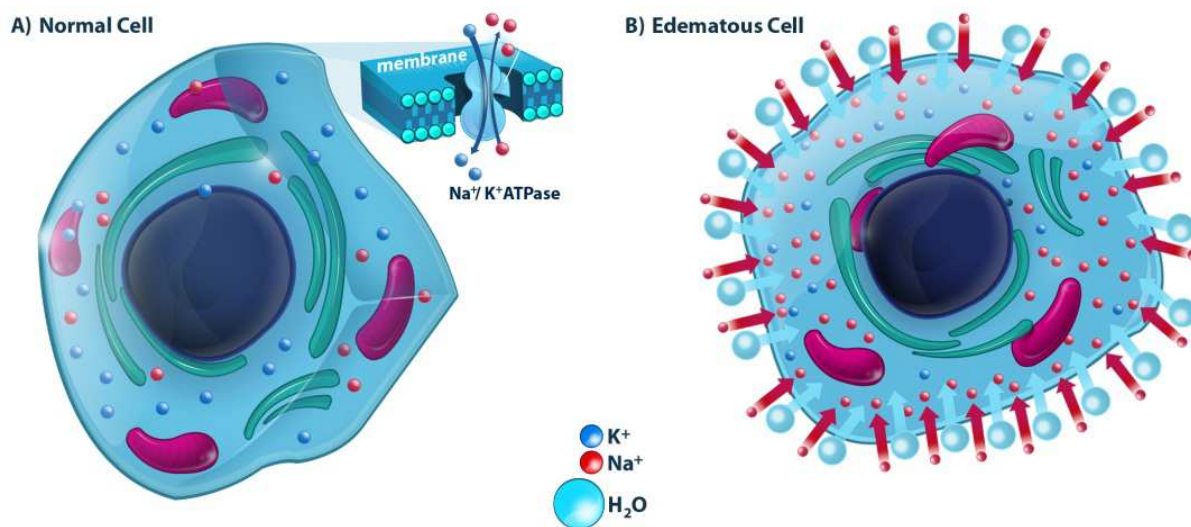


Fig. 3. Cellular edema.

The problem posed by waterproofing agents is that, even though they diffuse poorly across the membrane, they will eventually enter the cell over time. Therefore, when implanting the kidney in its new environment, the cells will suddenly be exposed to a relatively hypotonic extracellular osmolarity. Because the Na^+/K^+ pump is unable to start functioning quickly enough, potassium cannot be easily expelled to counteract this effect. One example of such agents is mannitol, which can be used as a waterproofing agent in preservation solutions.

Mannitol accumulates intracellularly, cannot be metabolized, and is only slowly eliminated from the cytosol, leading to cellular edema not directly related to hypothermia. Edema in endothelial cells can interfere with the reestablishment of normal blood flow, which by itself results in hot ischemia. Edema of parenchymal cells will also involve the mitochondria, with subsequent structural and functional deterioration of the tissue. The majority of preservation solutions contain waterproofing agents at a concentration close to 110 mmol/l. It seems that obtaining an adequate concentration of waterproofing agents in these solutions is essential to achieve adequate preservation by storage in cold.

3.2.2 Cellular acidosis

The cells of the organs stored in cold are under anaerobic conditions. To maintain their energy needs (ATP), they use anaerobic glycolysis which increases the concentration of lactate and hydrogen ions intracellularly. This causes acidosis that leads to lysosomal instability, activates lysosomal enzymes, and alters mitochondrial properties, which causes cell injury and death. (Fig 4).

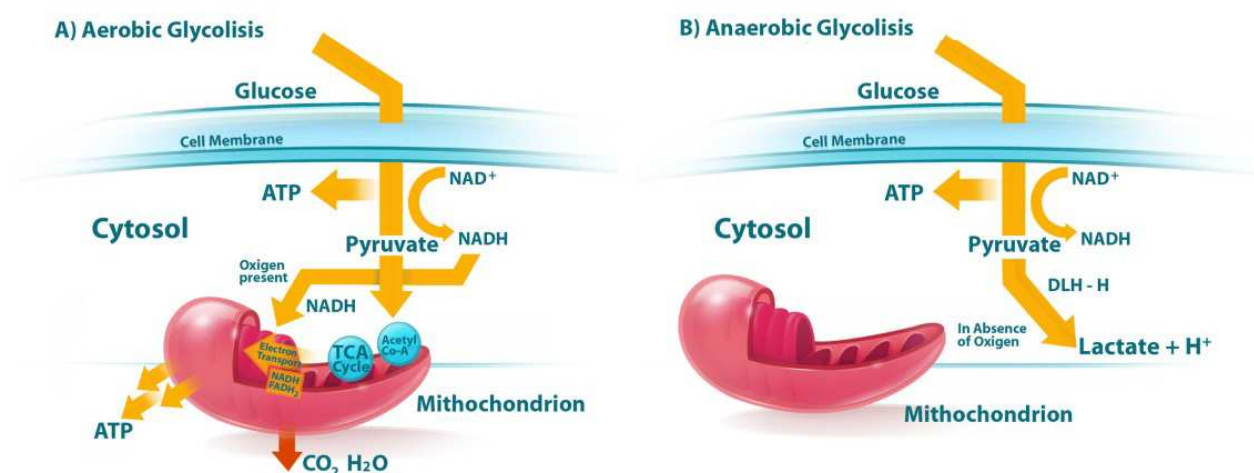


Fig. 4. Glycolysis.

To prevent intracellular acidosis, preservation solutions that contain substances that counteract acidosis (buffers) are used. Substances such as phosphate or histidine are used for this purpose. On the other hand, it seems advisable to have a slightly alkaline pH (7.6 - 8.0 at 37°C) in the solution destined for cold rinsing.

3.2.3 Expansion of the interstitial space

When an organ is perfused, and also later during its storage, there is an expansion of the interstitial space. This compresses the capillary system, causing the inadequate distribution of the preservation fluid across the tissue. Solutions that do not contain oncotic substances (such as albumin and other colloids) quickly diffuse to the interstitial space and cause edema when perfused. The preservation solution needs to contain substances that will create enough osmotic colloidal pressure to allow the free exchange of essential substances with the preserving solution, without expanding the interstitial space (Fig 5).

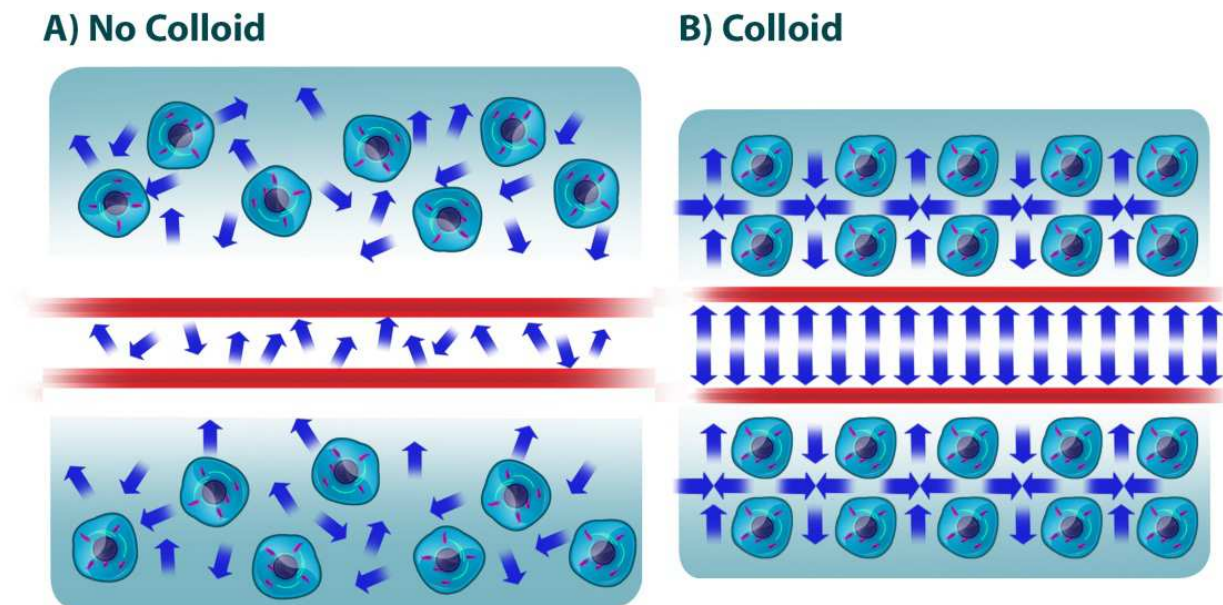


Fig. 5. Osmotic colloidal pressure.

3.2.4 Decrease of cellular energy output

Hypothermia blocks the production of energy at various levels, with cold-resistant enzymatic reactions remaining active, and with a limited supply of glycolytic intermediates and energetic reserves necessary for the maintenance of cellular integrity. These reactions stimulate synthesis of triglycerides from glucose.

The main source of energy in the renal cortex during hypothermia is the metabolism of free fatty acids. The octanoic acids (especially caprylic acid) are degraded to acetyl-coenzyme A and enter the Krebs cycle. In contrast, long-chain free fatty acids, such as palmitic and miristic acids, cannot be degraded in energy-producing cycles but are incorporated to tissue triglycerides through an energy-consuming process. Furthermore, phosphorylation is suppressed during hypothermia due to the inability of adenosine diphosphate to penetrate the mitochondrial inner membrane after hypothermic inactivation of adenosine diphosphate translocase. The adenosine diphosphate stays in the cytosol and degrades to adenosine monophosphate, and finally to hypoxanthine, which easily diffuses outside of the cell. Recovery of the depleted adenosine diphosphate occurs through *de novo* synthesis, and could require several hours after reestablishment of normal temperatures and appropriate oxygen levels. Thus, the preservation solution needs to contain substances that will maintain or replenish ATP (for example adenosine and glutamate).

3.2.5 Intracellular accumulation of calcium

The calcium-calmodulin complex plays a central role in the regulation of multiple enzymes responsible for mitochondrial respiration, adenosine triphosphate transport and regulation of the ion transport and membrane potentials. These effects increase the chances that the control of cytosolic calcium could help restore or preserve the enzymatic

reactions necessary to maintain the integrity of cells subjected to hypothermic ischemia. Some calcium-mediated cellular reactions require maintenance of low levels of cytosolic calcium, together with an ability to rapidly fluctuate these levels along large ranges of concentration, in such a way that specific intracellular targets can be alternatively activated and deactivated.

During hypothermic ischemia, the enzymatic systems primarily responsible for calcium efflux are deactivated at the plasma membrane (calcium-specific adenosine triphosphatase and calcium-sodium exchange system). The rapid depletion of the energy reserves during hypothermic ischemia results in deactivation of calcium-specific adenosine-triphosphatase, which causes a massive influx of sodium into the cytosol; as a consequence, there is failure of the calcium-sodium exchange system. There is also a massive influx of calcium, which adversely affects numerous cellular enzymes, producing deterioration of cellular function and eventually cellular death.

The changes in the calcium-calmodulin complex can also generate mitochondrial and membrane dysfunction, damaging the phospholipid nature of these structures by activating the phospholipase pathway with subsequent production of prostaglandin derivatives. This damage primarily affects endothelial cells, and is observed prior to the damage to the parenchymal cells. Endothelial separation, due to cytoskeletal damage, could result in collagen exposure, which in turn produces platelet aggregation and intravascular coagulation. Although an organ in which the parenchymal cells have been damaged can be recovered, this is not feasible when the damage affects the endothelial cells.

4. Pathophysiology of renal allograft reperfusion upon implantation

Much of the injury to transplanted kidneys does not occur during ischemia, but instead during reperfusion at the time of implantation. This damage is a consequence of the following events:

4.1 Release of accumulated toxic metabolites

Re-establishment of blood flow allows the recovery of the oxygen supply and the elimination of accumulated toxic metabolites. Although reperfusion is necessary to recover the organ after the ischemic injury, the systemic release of these toxic metabolites into circulation could have metabolic consequences in distant sites, as well as produce local tissue damage. Additionally, some of these events can trigger inflammatory processes which are a direct stimulus to the immune system, significantly contributing to the risk of acute graft rejection.

4.2 Reactive oxygen species

Damage due to free radicals is less significant in the kidneys than other organs. The greatest source of oxygen radicals comes from the activation of the enzyme xanthine oxidase, although leukocyte and macrophage activation can also be involved. The end products of the degradation of ATP are frequently metabolized to urea by the action of xanthine dehydrogenase. However, in an acidic environment, xanthine dehydrogenase becomes xanthine oxidase. When oxygen is supplied to the cellular environment during reperfusion,

xanthine oxidase converts accumulated extracellular waste into xanthine and superoxide anion (a reactive oxygen species). This anion rapidly reacts with itself to form hydrogen peroxide, a potent oxidizing agent capable of injuring the cell by oxidizing lipid membranes and cellular proteins. Hydrogen peroxide also triggers the production of other potent reactive oxygen species, including hydroxyl radical and singlet oxygen. Finally, these events lead to alteration of mitochondrial respiration and to lipid peroxidation with subsequent cellular destruction. The production of reactive oxygen species also initiates production of prostaglandins (by direct activation of phospholipase), including Leukotriene B4 and Platelet Activating Factor. These substances increase leukocyte adhesion to the vascular endothelium. Neutrophils could contribute to local injury by blocking microcirculation and by degranulation, which results in proteolytic damage to the kidney. It is therefore advisable to add substances to the preservation solution that protect against the formation of reactive oxygen species (for example, allopurinol), or “radical cleansers” (superoxide dismutase, iron chelating agents, mannitol, dimethylnitrosamine). However, it should be noted that the potential benefits of these components are the subject of debate.

4.3 Release of cytokines

Ischemia-reperfusion is associated with strong release of Tumor Necrosis Factor alpha, Interferon gamma, Interleukin 1 and Interleukin 8. These cytokines cause an up-regulation of adhesive molecules which produce leukocyte adherence and platelet plugs after revascularization, resulting in graft failure and kidney rejection.

The vascular endothelium modulates smooth muscle tone in the vessel by releasing various local hormones or autacoids. The production of one of them, nitric oxide, which is induced by inflammatory cytokines, correlates with acute rejection.

5. Available preservation solutions

For kidney preservation by cold storage, the Euro-Collins (EC) solution, University of Wisconsin (UW) solution, Histidine-Tryptophan-Ketoglutarate (HTK) solution, or Celsior solution can be used. The components are described in table 1.

The UW solution seems to be associated with better results when compared to the EC solution, showing better initial graft function and a 10% reduction in the need for dialysis after transplantation (the mean need for dialysis with preservation by storage in cold is between 20 and 50%). Both solutions guarantee preservation of up to 30 hours, so the kidney implantation surgery is completely elective (programmed).

Continuous hypothermic perfusion reduces the incidence of initial graft failure (need for postransplant dialysis) to 10%.

5.1 Euro-Collins solution

This solution is nowadays used as a preservation solution in isolated renal explantation, yielding preservation times of up to 30 hours with less cost than UW solution. However, multicentric studies show a better initial graft function with less need for dialysis in grafts preserved in UW solution.

COMPONENT	EC (mmol/l)	UW (mmol/l)	HTK (mmol/l)	Celsior (mmol/l)	Function
Sodium	10	30	15	100	Electrolyte
Potassium	115	120	10	15	Electrolyte
Magnesium	-	5	4	13	Electrolyte y cytoprotector
Chloride	15	-	50	-	Electrolyte
Calcium	-	-	0,015	0,25	Electrolyte
Phosphate	50	25	-	-	Buffer
Sulphate	-	5	-	-	Buffer
Bicarbonate	10	-	-	-	Buffer
Histidine	-	-	180	30	Buffer and waterproofing
Histidine ClH	-	-	18	-	Buffer
Glucose	195	-	-	-	Waterproofing
Mannitol	-	-	30	60	Waterproofing
Raffinose	-	30	-	-	Waterproofing
Lactobionate	-	100	-	80	Waterproofing and chelating Fe and Ca
Adenosine	-	5	-	-	Energy
Ketoglutarate	-	-	1	-	Energy
Glutamate	-	-	-	20	Energy
Glutathione	-	3	-	3, reduction	Anti-free radicals
Allopurinol	-	1	-	-	Anti-free radicals (inhibits xhantine-oxidase)
Tryptophan	-	-	2	-	Membrane stabilizer
Dexamethasone	-	8	-	-	Membrane stabilizer
Insulin	-	100 U/l	-	-	Membrane stabilizer
HES (Hydrox-Ethyl-Starch), a synthetic starch	-	50 g/l	-	-	Synthetic colloid
pH	7	7,4	7,2	7,3	
Osmolarity	355	320	310	340	
Viscosity	Low	High	Low	Low	

Table 1. Preservation solutions and their components. EC=Euro-Collins, UW=Universtiy of Wisconsin, HTK= Histidine-Tryptophan-Ketoglutarate.

5.2 Belzer or University of Wisconsin solution

Currently, this is the solution used for preservation of all abdominal organs, including the kidneys. Basically, it is composed of lactobionate and raffinose as waterproofing agents, hydroxyl-ethyl-starch (colloid), phosphate (buffer), adenosine (precursor of ATP synthesis),

and glutathione and allopurinol (to counteract oxygen radicals). It does not contain glucose and it is an “intracellular” solution (rich in potassium and low in sodium), similar to the EC solution.

The disadvantages of UW are the following:

1. High cost
2. It has to be kept refrigerated until its use.
3. Supplements need to be added immediately before its use (insulin, penicillin and dexamethasone), although this can be excluded without adverse effects.
4. The glutathione loses efficacy with time (unstable).
5. The solution can precipitate, requiring filtering during kidney perfusion and rinsing.

5.3 HTK-bretschneider (Custodiol)

It is named HTK because of its components (Histidine-Tryptophan-Ketoglutarate) It is an “extracellular solution” (low in potassium) and its components include histidine (buffer and osmotic effect), mannitol (waterproofing agent, osmotic effect and anti-reactive oxygen species), tryptophan (membrane stabilizer) and ketoglutarate (substrate for cellular metabolism). Its osmolarity is similar to that of the UW solution (310 *vs.* 320) and has a lower osmotic pressure (15-25 mmHg *vs.* 0 mmHg). It has lower viscosity, which is why a smaller volume of solution is used during perfusion.

Regarding cost, HKT is comparable to the UW solution, when the specific requirements for the use of either solution are taken into account. HKT remains stable at room temperature, so it does not need to be refrigerated (unlike UW, although cooling to 4°C should be performed at least 2 to 3 hours before its use). HKT also does not precipitate and does not require filtering during perfusion. Being a low potassium solution, HKT also has the (theoretical) advantage of minimizing vascular injury.

5.4 Celsior

This is an “extracellular solution” (low in potassium). Its composition includes waterproofing agents like lactobionate and mannitol, antioxidants like reduced glutathione, metabolic substrates like glutamate, and a buffer (histidine). The solution is stable, it does not need refrigeration or filtering during perfusion. The volume needed to perfuse and its cost are similar to those of the UW solution.

6. Conclusions

Despite evidence that preservation techniques with perfusion machines provide better graft quality and longer periods of preservation, perfusion and subsequent storage at 4°C (for the shortest period possible) is still the standard procedure for preservation of renal grafts. A valid argument in favor of this practice is that it provides acceptable results with a simpler and cheaper method than the use of perfusion machines, which requires expensive and cumbersome equipment, as well as additional personnel. An important limitation of the preservation of organs by storage in cold is the impossibility of assessing whether the organ will adequately function after implantation. In this sense, machine perfusion offers a series of added advantages with respect to the preservation by simple cooling: a) it reduces the

vascular resistance induced by ischemia and facilitates the elimination of erythrocyte remnants from the microcirculation, which allows better reperfusion after implantation, and b) it allows testing of the viability or quality of the organ before implantation, by monitoring the flow and pressure, or by determination of biochemical markers related to organ viability released into the preservation solution (alpha glutathione-S-transferase, pi-glutathione-S-transferase, alanineaminopeptidase, among others).

Preservation with HPM is routinely used in only few centers around the world. In Europe its use is not extensive, but in the United States it is used in about 20% of kidney transplant centers.

The most frequently used preservation fluids are Euro-Collins, University of Wisconsin and HTK-Custodiol, which yield preservation times between 18 and 36 hours.

7. Acknowledgment

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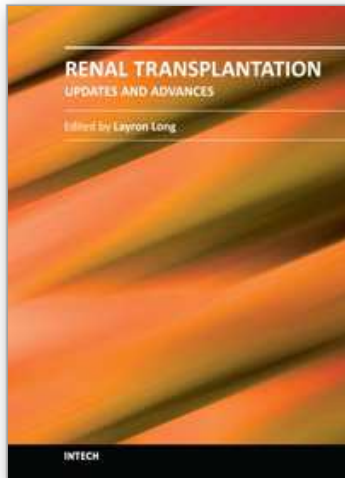
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This book presents a nice international compilation of scholarly papers and chapters which address the latest advances in renal transplant surgery. These works cover a variety of topics; the last advance and success of renal transplant science: biochemistry, immunology, molecular genetics, pharmacology - pharmacogenetics, pediatric transplant and a few rare uropathies that warrant organ replacement.

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