



# Renal Procurement: Techniques for Optimizing the Quality of the Graft in the Cadaveric Setting

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## Abstract

**Purpose of Review** Kidney transplantation is the best treatment for end-stage renal disease. However, due to organ shortage, suboptimal grafts are increasingly being used.

**Recent Findings** We carried out a review on the methods and techniques of organ optimization in the cadaveric setting.

**Summary** Donor care is the first link in a chain of care. Right after brain death, there is a set of changes, of which hormonal and hemodynamic changes are the most relevant. Several studies have been conducted to determine which drugs to administer, although in most cases, the results are not definitive. The main goal seems rather achieve a set of biochemical and hemodynamic objectives. The ischemia–reperfusion injury is a critical factor for kidney damage in transplantation. One of the ways found to deal with this type of injury is preconditioning. Local and remote ischemic preconditioning has been studied for various organs, but studies on the kidney are scarce. A new promising area is pharmacological preconditioning, which is taking its first steps. Main surgical techniques were established in the late twentieth century. Some minor new features have been introduced to deal with anatomical variations or the emergence of donation after circulatory death. Finally, after harvesting, it is necessary to ensure the best conditions for the kidneys until the time of transplantation. Much has evolved since static cold preservation, but the best preservation conditions are yet to be determined. Conservation in the cold has come to be questioned, and great results have appeared at temperatures closer to physiological.

**Keywords** Kidney transplantation · Organ preservation · Tissue and organ procurement · Ischemic preconditioning

## Introduction

Kidney transplant is the best treatment for end-stage renal disease [1]. However, due to organ shortage, the majority of patients do not get a transplant. To increase organ pool available, we resort to new forms of donation, like expanded criteria donors (ECD) or donation after circulatory death

(DCD) [2]. These new donors are suboptimal comparing with living donors or standard donors after brain dead (DBD) [3].

To get the best results from these organs and to harvest the maximum number of organs from each donor, a keychain of medical and technical care is established since death (DBD or DCD) is declared, until the organ is implanted on the recipient.

We performed a review of current and possible future care in renal procurement on the cadaveric setting, making a summary of the evidence on the various stages of renal procurement: donor care, preconditioning, and surgical.

## Donor Optimization Prior Harvest

One of the critical points for graft quality optimization is donor care [4]. Immediately after brain death, changes start to occur in different organ systems (cardiac, pulmonary, endocrine, hematological, and musculoskeletal), which must be optimized before harvest surgery to increase the number of organs transplanted per donor (OTPD) and to improve graft function [5, 6]. Some transplant coordinating entities have established hemodynamic and biochemical goals for the brain-dead donor maintenance until

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harvest surgery [7]. However, the way to achieve these goals and donor pharmacological management is still a subject of study.

One of the most prominent areas is catecholamine usage. Animal studies [8–10] show that among catecholamines, dopamine has the highest therapeutic potential. It reduces kidney graft inflammation by decreasing the expression of major histocompatibility class (MHC) II, P-selectin and tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), and by inducing antioxidant defenses. These effects resulted in less leukocyte infiltration and reduced endothelial injury associated with reperfusion–ischemia and cold storage. However, clinical studies show different results. Two retrospective studies [11, 12] have shown an advantage in donor treatment with dopamine or norepinephrine, by reducing acute rejection and improving long-term graft survival. However, two randomized control trials (RCTs) showed opposite results, as one failed to achieve kidney graft survival improvement [13] and the other one succeeded on that goal [14]. Hence, there is no definite evidence to support systematic catecholamine use in donor management to improve kidney transplant results.

Fluid management is another relevant factor. Various authors raised questions about how to manage donor fluid replenishment and which fluids to use. When addressing fluid resuscitation, retrospective studies [15] showed that an aggressive approach increased the number of OTPD. This observation led to an RCT [16] that aimed to establish a fluid therapy protocol in organ donors, but this showed no advantage over a standard and clinically guided management.

Regarding which fluids to use, different approaches have been studied. A retrospective series [17] that compared crystalloids with colloid resuscitation demonstrated that when only crystalloids were used, there was more delayed graft function (DGF) compared to an approach with crystalloids and colloids. Also, the type of colloid to use is a matter of debate. Hydroxyethyl starch has been the focus of several studies [18–20], showing an increased risk of DGF when this colloid was used in donor resuscitation.

As mentioned before, one of the physiological changes that happen on the donor immediately after brain death is serum hormonal level variations [21]. Among these, one of the most relevant pertains to thyroid hormones, as T3 and T4 decrease to a half hour after brain death and become undetectable between 9 and 16 h, while TSH remains stable [21, 22]. Retrospective studies and non-randomized studies [15, 23, 24] showed an advantage in donor thyroid hormone treatment, by facilitating their hemodynamic stability, reducing catecholamines use, and by improving the number of OTPD, especially the kidneys. However, RCT and literature reviews fail to show this advantage [22, 25, 26].

Other hormones whose replacement has been studied are insulin and antidiuretic hormone (ADH). After brain death, insulin decreases to 20% at 13 h, and ADH becomes undetectable at 6 h [21]. Administration of desmopressin to the brain-dead donor showed an advantage in both renal graft

survival and the number of kidneys harvested by donor in two retrospective studies [23, 27], but one RCT failed to show any advantage [28]. Regarding insulin administration, it seems that more important than its administration to the donor, which in itself is not beneficial [23], the focus should be on keeping blood glucose below 180 mg/dL, which allows to improve graft function and increase the number OTPD [29].

The other crucial hormonal group studied are the corticosteroids. The rationale for their application lies in the observation that most brain-dead donors have adrenal insufficiency [30] and the presumption that using them would reverse the systemic inflammation affecting the donor [31]. However, retrospective studies [23] and RCT [32, 33] showed no advantage in terms of the number of kidneys harvested by donor, DGF, or graft survival. Furthermore, two systematic reviews [34, 35] showed no beneficial effect.

Controlled hypothermia is a promising donor management care option. An RCT [14] showed that spontaneous donor hypothermia 4–20 h before the harvest was associated with lower kidney DGF. The authors associated this improvement with less systemic inflammation, which resulted in less kidney damage. Another RCT [36] showed the same benefit, which was more significant in expanded criteria donors (ECDs). However, this may not be beneficial for all types of donors, namely for heart transplant donors, since hypothermia has been shown to lead to worse heart graft function [37].

Maintaining different hemodynamic and biochemical objectives until the time of harvest seems to be more critical than focusing on a single one drug or parameter [7]. The so-called donor management goals (DMGs), set by the US Department of Health and Human Services and the Health Resources and Services Administration, is a set of nine donor hemodynamic and biochemical parameters proposed to be achieved in brain-dead donor care. Different studies have shown that meeting at least seven of these nine goals increases the number of OTPD and decreases the rate of DGF in kidney transplant recipients [7, 38–40].

The use of other drugs such as statins [41, 42], cyclosporin [43], *N*-acetylcysteine [44], or therapeutics such as blood transfusions [45] is under investigation.

## Preconditioning and Ischemia–Reperfusion Injury Modulation

Optimizing organ preservation starting even before harvest until implantation is another critical aspect to achieve a quality graft for transplantation. One of the main, if not the primary, mechanisms of organ damage until transplantation is the so-called ischemia and reperfusion injury (IRI) [46, 47]. After the circulation stops, the organ becomes anaerobic, leading to a depletion in cellular stored ATP and to dysfunction of ATP synthetase. There is an intracellular accumulation of anaerobic products, causing acidosis and hyperosmolarity. An ionic movement from

extracellular to intracellular space aggravates this state of hyperosmolarity [46–48]. Finally, dysfunction of endoplasmic reticulum protein production and mitochondrial damage activate apoptotic pathways [47, 49, 50]. There are several mechanisms and cellular pathways involved in IRI, including the mitogen-activated protein kinase (MAPK) family pathways [51, 52], antioxidant defenses, reactive oxygen species [53], and IL-8 [54]. To prevent graft IRI, one line of study has focused on modulating the mechanisms of IRI by organ preconditioning [55, 56].

The preconditioning concept was first described by Murry in 1986 when he presented the first studies in myocardial preconditioning [57]. Since his work, the preconditioning study extended to different organs, including the kidney. In its purest form, ischemic preconditioning (IP) consists of exposing an organ to a short period of ischemia, followed by reperfusion and subsequent new ischemia. This was the principle first applied in the field of kidney transplantation by Torras [58], when he presented the first animal studies, concluding that the best IP time scheme consisted of 15 min of warm ischemia followed by 10 min of reperfusion since these were the intervals with the best histological and functional protection of renal function. Torras also demonstrated that NO was involved in the IP process [58]. As the works progressed, it was possible to realize that IP is a two-phase process, with an early and late window [59]. The initial phase is rapid, occurring within minutes and without protein synthesis. The late phase requires hours to begin and involves protein synthesis. Between them, there is a period in which there is no protection for ischemia [59]. More recently, new forms of preconditioning have emerged, such as remote IP [60] (in which organ preconditioning is achieved through limb ischemia) and pharmacological preconditioning.

IP was initially tested in animal models [61, 62] without advantage, like reducing renal dysfunction or morphological injury. It was later retested on rodent kidney transplant models [63–66], and at this time with success, showing biological improvement. These studies have shown that pathways involved in protection against IRI by IP are related to endothelial NO production, induced NO synthetase, and activation of cellular pathways such as NF- $\kappa$ B or hypoxia-induced factor (HIF) 1 $\alpha$ /HIF-2. Another mechanism related to IP is heme oxygenase (HO), a key enzyme in redox homeostasis processes [67]. Overall, IP studies on renal transplantation have shown beneficial effects in inflammation inhibition, coagulation inhibition, oxidative attenuation, induction of antiapoptotic state, and modulation of HIF pathways [55]. However, despite the absence of clinical studies in renal transplantation, a meta-analysis of animal studies showed a reduction in serum creatinine, blood urea nitrogen, and histological damage in IP kidneys, and the beneficial effect was attained both with local and remote IP [68].

The field that has concentrated most of the research is pharmacological preconditioning. One extensively studied drug is erythropoietin [53, 69–73]. Its administration before ischemia has shown beneficial effects in animal models. It increases

creatinine clearance and sodium excretion fraction, and reduces visible tubulointerstitial lesions on biopsy [53, 73] and lipid peroxidation of renal tissue [71]. Another study that aimed to evaluate IRI by urinary excretion of neutrophil gelatinase-associated lipocalin (NGAL) concluded that administration of erythropoietin significantly reduced urinary NGAL [73]. An additional beneficial effect of erythropoietin administration is the reduction of proinflammatory cytokines such as IL-6 [72], IL-2, and TNF- $\alpha$  [71]. The positive impact of erythropoietin appears to result from activation of tyrosine kinases, named Janus kinase 2 (JAK2) [70, 71], mediated by heat shock protein-70 (HSP70) [70], and also increased expression of the anti-apoptotic gene Bcl-2 [70].

Other composites tested showed varying results. One is carbon monoxide (CO) [74–76]. CO is produced at low doses by mammalian cells through HO catalysis and helps to maintain cellular protection, vascular tone, and neuromessenger [76]. Experimental studies in animal models have shown advantages in CO application on preservation fluid, namely better functional outcomes [75], better histology by reducing fibrosis, inflammatory infiltrate, and lipid peroxidation [75]. One of the mechanisms involved in CO action is cytochrome P450 levels maintenance [74].

Several other compounds are in the early stages of study such as cardiotropin-1 [77], which have been shown to reduce oxidative stress markers, inflammation, and vascular injury. Another example is melgatran, a thrombin inhibitor, which when applied to the kidney storage fluid has been shown to reduce the immune cells' proinflammatory state after transplantation, improving graft function, reducing inflammation and kidney damage. Hydrogen sulfide (H<sub>2</sub>S) is an endogenously produced gas with anti-inflammatory, antioxidant, and antiapoptotic functions [78]. Applying H<sub>2</sub>S to the kidney preservation fluid improved early graft function and survival, decreasing necrosis and apoptosis [78]. The manipulation of IRI-related pathways may also be beneficial. For example, in a study with a HIF hydroxylase inhibitor administration, it reduced the effects of IRI [66]. Other compounds also studied with beneficial effects were cyclosporine [51], 1–25 dihydroxy vitamin D3 [79], tin-protoporphyrin IX (an HO inhibitor) [80], bosentan [81], ozone [82], or sildenafil [83].

## Optimization of Surgical Harvesting Technique

Establishment of organ harvest main surgical techniques was done at the end of twentieth century [84–86]. Despite having similar surgical procedures, DBD and DCD surgical techniques are different.

In DBD, there are two different approaches. The oldest is the “warm dissection technique” [87] in which the anatomical structures are dissected before perfusing the corpse. This technique is associated with more vasospasm and vascular and parenchymal lesions [88], requiring a 30- to 60-min recovery period before ischemia to reverse some of the damages. However, this technique facilitates anatomical dissection.

The most commonly used method is “dissection in the cold” [88, 89]. With this technique, there is minimal dissection until ischemia and perfusion are established. Dissection and organ separation only takes place after exsanguination and when the organs are cold. Studies indicate that functional results are similar between these two techniques [90].

With DCD, we have two main techniques: “super-rapid” and “premortem cannulation.” With “super-rapid” method, the main principle is to perform the laparotomy and cannulate the distal aorta in less than 4 min [91]. Following cannulation, the supraceliac aorta should be cross-clamped and the intrapericardial inferior vena cava should be incised. With “premortem cannulation,” the cannulas are inserted on the femoral vessels (artery and vein) before withdrawal of support on the donor. Immediately after death is declared, perfusion is started, and the explantation surgery starts. This approach decreases warm ischemia time [89].

The main surgical procedure for kidney harvest is the same in DBD and DCD and was already described by our group [92]. It starts with a midline incision from the xiphoid process to the symphysis pubis. In high BMI donors, a cruciform prolongation or chest incision might be needed [93]. The round and the falciform hepatic ligaments are sectioned up to the diaphragm. To get access to the retroperitoneum, we have to perform a Cattell Braasch maneuver. For that, an incision is made in the white line of Toldt, starting in the right iliac artery, laterally to the ascending colon, up to the hepatoduodenal ligament. An incision is performed on the peritoneum at the right side of the duodenum, as well as in the inferior border of the foramen ovale. The head of the pancreas and the duodenum are mobilized. An incision is performed on the mesenteric root to free the duodenum. The left white line of Toldt is cut, and the freed bowel is covered with gauze and is held outside of the upper part of the abdomen.

After this exposition, the aorta and the inferior vena cava (IVC) are dissected immediately above the bifurcation. It is essential to identify an accessory lower pole renal artery originating from the iliac artery, which happens in 1–3% of individuals. In that case, cannulating the ipsilateral iliac has to be considered, instead of the aorta. The inferior mesenteric artery is ligated and cut, and a thick silk thread is passed behind the aorta (two threads) and the IVC (one thread).

If only the kidneys are being harvested, the superior mesenteric artery (SMA) must be ligated and cut, and the aorta above the superior mesenteric artery is encircled. Another thread is passed behind the IVC above the renal veins. If an abdominal multiorgan harvest is performed, the supraceliac aorta must be controlled instead. To access this aortic segment, the left liver lobe must be freed. After that, the lesser omentum is inspected to check the presence of a left accessory hepatic artery (occurs in approximately 15% of individuals) and is cut next to gastric

smaller curve. The diaphragm crus is exposed and should be divided, and the supraceliac aorta is encircled.

In order to get the best results, it is of paramount importance to administer 25,000–30,000 U (or 300–500 U/kg) of non-fractionated heparin at least 3 min before cannulation. To cannulate, the two inferior threads (on the aorta and IVC) are tied, the perfusion cannula is placed on the aorta, and the second inferior aortic thread is tied to fix it in place. If the portal perfusion is considered necessary, another cannula can be placed on the inferior mesenteric vein.

To start perfusion on a kidney-only harvest, all the threads are tied, and an incision on the IVC next to the inferior ligature is made. In an abdominal multiorgan harvest, the diaphragm and the pericardium are opened, and the intrathoracic IVC is identified, the thread above the supraceliac aorta is tied, and the intrathoracic IVC is cut. Quickly after starting perfusion, the abdomen is filled with ice. Perfusion is most frequently made with Celsior (40–60 mL/kg) or UW (75–100 mL/kg).

After perfusion, to remove the kidneys, the inferior ligatures are cut. The left renal vein is sectioned at its entrance on the IVC. On the right side, the IVC must be divided above and below the right renal vein to perform elongation plasty on the bench. The anterior wall of the aorta is opened longitudinally until the SMA origin. After inspection of the aorta and identification of the renal arteries' origin, the Carrel patch is cut. Each kidney is mobilized with perirenal and pararenal fat, and the ureter is sectioned near the bladder. In the end, the organs are inspected and perfused on the bench.

## Organ Preservation Methods Optimization

After surgical harvest, a crucial stage starts in transplantation: the organ preservation. The first and still most used strategy used for organ preservation is cold storage (CS) after perfusion with preservative liquid. Different perfusion solutions available were designed to maintain cellular integrity during CS [94]. The most commonly used solution is the University of Wisconsin (UW) because it is compatible with different organs preservation, has buffers to keep the pH close to neutrality, and presents a high concentration of impermeable molecules that prevent cellular edema [94]. Alongside the UW, the other commonly used solutions are histidine–tryptophan–ketoglutarate (HTK), Eurocollins, and Celsior. Two retrospective studies comparing UW and HTK showed that HTK increases the risk of primary non-functioning (PNF) kidneys [95] and decreases graft survival after the first 12 months [96]. Regarding DGF, one of the previous retrospective studies [96] and a meta-analysis [97] (citing two RCTs) showed no difference between these two fluids. However, another retrospective study comparing UW and HTK showed a higher DGF in deceased donors' kidneys preserved with HTK, but, on the other hand, the DGF risk

was higher with UW-treated grafts in living donor kidneys [98]. Comparing UW with the Eurocollins solution, the same meta-analysis [97] cites two RCTs where the Eurocollins solution had a higher risk of DGF. Comparing UW with Celsior, there are two retrospective studies [99, 100] and one review [101] showing similar results in transplanted kidneys preserved with either solution. However, small details such as a UW higher fluid viscosity have been pointed out as an essential property to attend to at the time of choosing the preservation solution to use, as organ perfusion time increases [102].

Hypothermic machine perfusion (HMP) was the next step in organ conservation. These machines improve the condition of the organs, particularly the kidneys, by various mechanisms. A study in an animal model [103] showed that one of the physiological mechanisms that the HMP helps to preserve is endothelial nitric oxide (NO) production. This improvement translates into better and earlier reperfusion of the kidney. Other physiological mechanisms proposed are ATP production preservation and organ immunogenicity modulation [104].

Regarding the experience of using the pulsed machine, the initial study by Moers [105] showed lower DGF and more prolonged graft survival by the end of the first and the third years, particularly in ECD [106], although other early studies have not seen this advantage [107]. Experimental animal studies [103, 108], clinical human studies in donation after cardiac death (DCD) [109], ECD [110], and meta-analysis [111–113] were unanimous in showing lower DGF and less PNF kidneys with HMP preservation, although long-term results of its usage are still unknown [114].

More recently, there have been advances in the composition of the preservation fluids and organ preservation temperature. Conservation in hypothermia has increasingly been questioned, as hypothermia can aggravate IRI [115, 116]. There are several proposed and proved mechanisms for hypothermic preservation-induced organ damage. One of those mechanisms is protein conformational alteration, as hypothermia reduces protein hydrogen bond length, leading to altered conformation and function [115]. Another proven mechanism in an animal model is endothelial injury that leads to the expression of several adhesion molecules, which will lead to increased inflammation within the graft [117]. Reduced ATP production, redox imbalance, and increased intracellular calcium levels were other proven mechanisms in experimental models [118]. Hypoxia has also been questioned as it has harmful effects on cell function, namely in protein folding and in cytoskeleton elements [119, 120]. Different studies are underway in the field of organ preservation based on the physiological mechanisms associated with animal hibernation [121]. During hibernation, the metabolic rate and oxygen consumption drop more than body temperature, hinting that

the use of these pathways may in the future offer hope in organ preservation optimization.

Regarding oxygenated preservation techniques of the kidney, there are different methods to achieve oxygenation: retrograde persufflation, hyperbaric oxygenation, hypothermic perfusion, artificial oxygen carriers, and oxygenation at normothermic temperatures [122]. Initial studies in animal models have shown different results [123, 124]. The various human clinical studies carried out to date have not yet led to conclusions about the usefulness of these techniques [125].

Experimental studies in animal models comparing kidneys preserved only in an HMP with preservation in an HMP followed by controlled heating with oxygenated liquid showed better mitochondrial recovery, with less activation of apoptotic pathways and better graft function after transplantation [126]. In other studies, this controlled heating has also been shown to lead to less parenchymal, tubular, and endothelial damage, better mitochondrial function in renal cells, and better kidney graft function [116, 127], and may even promote graft regeneration [128]. Early human studies have shown that preservation with normothermic machine perfusion (NMP) reduces DGF, albeit not improving graft survival at 12 months [129]. More recently, human clinical studies have shown that the use of the NMP has allowed the use of kidney grafts that would otherwise be considered not viable through better evaluation of previously discarded kidney for transplantation [130, 131].

## Conclusion

This review summarized the evidence available on organ optimization in the cadaveric setting. Organ shortage and the subsequent increased use of suboptimal organs call upon the need for better strategies in donor management and organ preservation. As previously stated, optimal donor care and meeting DMG increase the OTPD. To do that, it is essential to correct imbalances, mainly endocrine and hemodynamic. Preconditioning is a promising area but is currently making its first steps in the clinical setting. Surgical techniques were established in the late twentieth century, and more innovations are needed. Finally, preservation has evolved since CS, but the best conditions to do so are still to be determined.

## Compliance with Ethical Standards

**Conflict of Interest** Edgar Tavares da Silva and Amaldo Figueiredo each declare no potential conflicts of interest.

**Human and Animal Rights and Informed Consent** This article does not contain any studies with human or animal subjects performed by any of the authors.

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