# Hypothermic Preservation of Transplanted Kidneys

Subjects: Others

Contributor: Katarzyna Kotfis

Kidney replacement therapy is a general term used to describe medical procedures that help to treat end-stage renal disease (ESRD). It is possible to obtain this goal, with certain limitations, by dialysis; however, the only method for obtaining a healthy organ is kidney transplantation (KTx). A growing number of patients on the transplant waiting lists and an insufficient donor pool remain a significant concern in all countries. There are strategies focused on increasing the number of donations, including the promotion of living donations. Despite donation after brainstem death (DBD), which is the primary source of organs for transplantation, there are an increasing number of extended criteria donor (ECD) and donation after circulatory death (DCD) cases. Improvement of transplantation procedures allowed to overcome past restrictions and possible contraindications. KTx outcomes are improving, and there are many factors involved, including gender.

Keywords: kidney transplantation ; oxidative stress ; ischemia-reperfusion injury ; enzymes ; antioxidants ; malondialdehyde ; hypothermic machine perfusion ; static cold storage ; LifePort ; outcome

## 1. Overview

Ischemia-reperfusion injury (IRI) after renal transplantation is a complex biochemical process. The first component is an ischemic phase during kidney storage. The second is reperfusion, the main source of oxidative stress. This study aimed to analyze the activity of enzymes and concentrations of non-enzymatic compounds involved in the antioxidant defense mechanisms: glutathione (GSH), glutathione peroxidase (GPX), catalase (CAT), superoxide dismutase (SOD), glutathione reductase (GR), glutathione transferase (GST), thiobarbituric acid reactive substances (TBARS), malondialdehyde (MDA), measured in preservation fluid before transplantation of human kidneys (KTx) grafted from brain dead donors. The study group ($N$ = 66) was divided according to the method of kidney storage: Group 1—hypothermic machine perfusion (HMP) in LifePort perfusion pump, $n1$ = 26, and Group 2—static cold storage (SCS), $n2$ = 40. The measurements of kidney function parameters, blood count, and adverse events were performed at constant time points during 7-day hospitalization and 3-month follow-up. Kidney perfusate in Group 2 was characterized by significantly more acidic pH ($p < 0.0001$), higher activity of GPX [U/mgHb] ($p < 0.05$) and higher concentration of MDA [µmol/L] ($p < 0.05$). There was a statistically significant improvement of kidney function and specific blood count alterations concerning storage method in repeated measures. There were aggregations of significant correlations ($p < 0.05$) between kidney function parameters after KTx and oxidative stress markers: diuresis & CAT, $Na^+$ & CAT, $K^+$ & GPX, urea & GR. There were aggregations of significant correlations ($p < 0.05$) between recipient blood count and oxidative stress markers: CAT & MON, SOD & WBC, SOD & MON. Study groups demonstrated differences concerning the method of kidney storage. A significant role of recipient's gender, gender matching, preservation solution, and perfusate pH was not confirmed, however, basing on analyzed data, the well-established long-term beneficial impact of HMP on the outcome of transplanted kidneys might partially depend on the intensity of IRI ischemic phase and oxidative stress, reflected by the examined biomarkers.

## 2. Kidney Replacement Therapy

Kidney replacement therapy is a general term used to describe medical procedures that help to treat end-stage renal disease (ESRD). It is possible to obtain this goal, with certain limitations, by dialysis; however, the only method for obtaining a healthy organ is kidney transplantation (KTx). A growing number of patients on the transplant waiting lists and an insufficient donor pool remain a significant concern in all countries. There are strategies focused on increasing the number of donations, including the promotion of living donations. Despite donation after brainstem death (DBD), which is the primary source of organs for transplantation, there are an increasing number of extended criteria donor (ECD) and donation after circulatory death (DCD) cases. Improvement of transplantation procedures allowed to overcome past restrictions and possible contraindications. KTx outcomes are improving, and there are many factors involved, including gender [1]. The organs with extended criteria are known to be more susceptible to ischemia-reperfusion injury (IRI), which is a major determinant of delayed graft function (DGF) and related complications, including acute rejection (AR) [2][3][4]. AR

and IRI are major causes of graft loss and dysfunction in clinical transplantation [3][5]. Advances in IRI studies regarding its molecular mechanisms are associated with different strategies used to reduce IRI's detrimental effects. Numerous pathways open the field for therapies against certain points of interest—impairment of endothelium relaxation, scavenging of free radicals, or the blockade of neutrophil activation and adhesion [2]. IRI consists of two phases—ischemia when the blood flow is interrupted for preservation time and reperfusion when the blood flow is restored, the leading cause of oxidative stress. Ischemia results in cell energy depletion and oxidative stress with microcirculatory impairment, inflammation, and apoptosis [6][7][8]. Those two phases involve different organ responses, but the total damage is additive. One of the modifiers of the ischemic phase is the usage of hypothermic machine perfusion (HMP). It is a well-established approach for decreasing the incidence of DGF and improving late outcomes, especially for DCD and ECD, with the advantage of preventing mitochondrial and tissue damage [9][10]. However, perfusion pumps are also widely used for standard criteria donors (SCD). Expected cold ischemic time (CIT) is unpredictable at the moment of procurement due to allocation procedures, and SCD kidney transplantations are known to gain similar advantages from this method of preservation in reducing DGF [11] or AR [12]. On the other hand, in static cold storage (SCS), a massive accumulation of metabolites derived from anaerobic respiration during the ischemic phase increases the hazard caused by oxidative stress in reperfusion [13][14].

Oxidative stress and reactive oxygen species (ROS) generation in the kidney disrupts the excretory function of each section of the nephron. As a result, it makes it impossible for the kidney to compensate for water-electrolyte and acid-base disturbances. In addition, renal regulatory mechanisms are affected: tubular glomerular feedback, myogenic reflex in the supplying arteriole, and the renin-angiotensin-aldosterone system [15]. Oxidative stress is also a broadly emphasized factor in the etiology of many diseases [16][17][18][19] and numerous antioxidative therapies, including the latest COVID-19 related pathologies [20][21].

## 3. Conclusions

Kidneys preserved in static cold storage (SCS) suffered significantly more intense acidosis measured in extracellular fluid. Increased acidosis significantly correlated with higher donor BMI and lower donor age. In the SCS group, there was a considerably higher mean concentration of MDA and higher mean activity of GPX, suggesting more intense oxidative stress. There were statistically significant correlations between oxidative stress markers and perfusate pH; however, they did not confirm that oxidative stress is directly related to the observed acidosis. There was a statistically significant improvement of kidney function in repeated measurements, suggesting that hypothermic perfusion pump (HMP) storage might have some advantages concerning the outcome. Study groups were characterized by the statistically significant difference in the dynamics of urea concentrations alteration in the postoperative period.

There were statistically significant correlations between oxidative stress markers and kidney function; however, they could not confirm that kidney function after transplantation is related to oxidative stress markers measured in preservation time. There were certain alterations of blood count observed in repeated measures after KTx; however, they seemed to relate to other factors than oxidative stress or acidosis. Despite few statistically significant relations, the influence of recipient gender, gender matching, preservation solution, and perfusate pH was not confirmed.

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