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OBM Transplantation

Case Report

Dual Kidney Transplantation after Hypothermic Oxygenated Perfusion from Marginal Donor after Circulatory Death with Acute Kidney Injury: A Case Report

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Academic Editor: Yasuhiko Sugawara

OBM Transplantation
2020, volume 4, issue 1
doi:10.21926/obm.transplant.2001096

Received: November 22, 2019
Accepted: January 14, 2020
Published: February 03, 2020

Abstract

Donation after circulatory death (DCD) is an increasingly used resource to alleviate chronic renal graft shortages. Organs from donors with progressively increased creatinine levels due to acute kidney injury are used, but the effects of this condition on kidney transplantation are still unclear. Ex-situ machine perfusion is emerging as a potential tool to preserve and resuscitate vulnerable grafts. We report a case of DCD kidneys discarded due to severe acute kidney injury with favorable histological Karpinski score and transplanted after in-situ normothermic regional perfusion (NRP) and ex-vivo hypothermic oxygenated perfusion (HOPE). Kidneys from a 57-years-old man with circulatory death were discarded by other Italian transplant centers due to high serum creatinine level (3.66 mg/dL) at the beginning of

NRP and for high values during perfusion. The histological Karpinski score was 2 for both kidneys. We performed in-situ NRP for six hours and subsequently HOPE (240 min for the right kidney and 315 min for the left one). Both kidneys showed good median renal flow and low perfusate's lactate levels and led us to use them for dual kidney transplantation. The transplant was performed without any complication. The recipient was discharged with serum creatinine 1.44 mg/dL. At two years of follow-up, no complications were registered and serum creatinine level was 0.8 mg/dL.

Keywords
Machine perfusion; marginal donors; graft resuscitation

1. Background

The shortage of suitable organs for transplantation has led to an increase in the use of "higher risk grafts" defined as marginal or extended criteria donors (ECD) and donors after circulatory death (DCD). In several countries, these grafts represent an increasing source of kidneys suitable for transplantation [1].

In Italy, the use of donors in asystole has developed only recently, mainly because of legislative reasons related to the requirement of more time for the assessment of cardiac death. In fact, 20 min cardiac arrest demonstrated by continuous electrocardiography recording is the time interval necessary in Italy for diagnosis of death based on cardiopulmonary criteria [2, 3]. This "no-touch" period is longer in comparison to worldwide legislation and may have serious implications for early and late graft function after transplantation due to the inevitable period of warm ischemia sustained after circulatory arrest [4]. However, data indicate up to 40-min warm ischemia time to preserve organ viability, and this encouraged Pavia's group to establish the first program of DCD organ transplants in 2007 [2]. Long-term outcomes of transplants from DCD donors appear comparable with those of transplants from donors with beating hearts[5], moreover, for patients waiting for kidney transplantation, standard criteria DCD kidney transplantation is associated with a survival advantage compared with conventional therapy [6]. Recently, kidneys from DCD donors with progressively increased serum creatinine levels (sCr) were used with encouraging outcomes [7-12].

Marginal grafts need histological analyses to quantify viable renal mass and predict the outcome of kidney transplantation. The transplant of two marginal kidneys destined to be differently discarded offers an improved filtration power, is safe and well-tolerated as a single transplant. Accordingly, DKT (dual kidney transplantation) and SKT (single kidney transplantation) show comparable data on renal function retrieval and graft survival [13].

In recent years, an increase in the number of marginal donors has led to a rethinking of the organ preservation method. High-risk donation requires an appropriate evaluation of eligibility and alternative storage methods to prevent injury during preservation, restore graft viability, and improve post-transplant function [14]. In DCD, ischemic injury after transplantation can be potentially minimized by restoring circulation with oxygenated blood to the abdominal organs in-situ, through extracorporeal membrane oxygenation (ECMO), or normothermic regional perfusion

(NRP) [15]. Ex-situ machine perfusion is an emerging potential tool to preserve and resuscitate vulnerable grafts, and reduce the discard of organs [16]. Further, hypothermic machine perfusion (HMP) has been shown to improve graft survival and reduce delayed graft function [17-21]. Oxygen delivery during hypothermic preservation (HOPE), also called hypothermic oxygenated perfusion prevents hypoxic injury [22] by increasing adenosine triphosphate content [23]. Although results obtained from preclinical studies are promising [24-26], only a few clinical trials have evaluated oxygenation during HMP in kidney transplantation [27-29] and some trials are ongoing [30]. The development of modern organ preservation techniques have enabled to overcome the restrictions imposed by law related to the prolonged warm ischemia time; the Italian practice for DCD involves starting the regional normothermic perfusion immediately after death declaration, followed by ex-vivo machine perfusion (hypothermic or normothermic) [2, 3, 31]. In the last three years, there has been a significant expansion in the use of this type of donor [32].

Herein, we used HOPE to recover two DCD kidneys that were declined for use due to donor high sCr level and sCr rise after NRP. We used these kidneys for DKT with a good outcome.

2. Case Presentation

2.1 Donor and Recipient Data

The DCD donor was a 57-years-old man who developed anoxic encephalopathy after a cardiogenic shock. Risk factors were obesity and dyslipidemia. The donor developed oligo-anuric acute renal injury and the serum creatinine before the cardiac arrest was 3.66 mg/dL (Table 1).

Table 1 Donor features.

DONOR	
Sex	Male
Age	57y
Cause of death	Anoxic encephalopathy
sCr (mg/dL)	3,66
eGFR (mL/min/1.73m2)	31,5
Karpinski score	Left Right
Glomerulosclerosis	0 0
Interstitial fibrosis	0 0
Tubular atrophy	1 1
Arterial/Arteriolar narrowing	1 1
Total	2 2
Tubular necrosis	<15 %

We performed NRP to allow a period of organ assessment and biochemical evaluation of the organ function. The total warm ischemia was 54 min, after which, the NRP was started and performed for six hours. During NRP the laboratory values showed an increase in serum creatinine (from 3.66 mg/dL to 4.35 mg/dL) and the hemogas–analysis showed a decrease in lactate value (from 17mEq/lt to 9 mEq/lt) and an increase in pH (from 6.78 to 7.48). A biopsy was performed

and the histological analysis reported a Karpinski score of 2 for both kidneys (37, Table 1). Other transplant centers declined the kidneys due to the acute injury as well as increased sCr level during NRP. We decided to recover the grafts and preserve them by means of HOPE.

The recipient selected for the DKT was a 75-years-old male patient with chronic renal insufficiency due to autosomal dominant polycystic kidney and liver disease in peritoneal dialysis. The sCr value before transplant was 12.9 mg/dLand the only comorbidity was hypertension (Table 2).

Table 2 Demographical and clinical data of the recipient.

RECIPIENT	
Age	75
Sex	Male
BMI	28.2
Blood group	0 -
IRC Cause	Autosomal dominant polycystic kidney and liver disease
sCr before transplant	12,9 mg/dL
eGFR (mL/min/1.73mC)	3.3 ml/min

Ethics approval was not sought as this report contains a single case report for which patient consent was obtained.

2.2 Ex-Vivo Hypothermic Oxygenated Perfusion

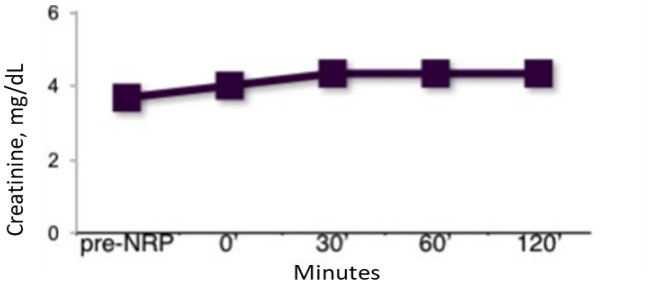
During the time of hospital transfer following surgical back-table preparation, kidneys were preserved in static cold storage in Belzer solution. Subsequently, organs were connected to the perfusion machine. HOPE was performed for 240 min for the right and 315 min for the left kidney, without any complication. For this, we used 1 L of Belzer solution at 4 °C. The renal artery pressure was 25 mmHg. We continuously monitored flow, pressure and temperature values. The median flow was 139 mL/min for the right kidney and 58 mL/min for the left kidney. Every 15 min, we performed a hemo-gas analysis of the effluent perfusate to monitor oxygen and carbonic dioxide partial pressure (pO2 and pCO_2), pH, and lactate production. The oxygen partial pressure was between 600- and 750-mmHg. Carbon dioxide production was not evaluated because it was removed by the oxygenator. Each kidney had perfusion lactate of 1.4 mmol/L at T1 (Table 3). Figure 1 presents data prior to and after the treatment.

Based on our previous organ perfusion experience, the low level of lactate following HOPE led us to deem both kidneys as transplantable for DKT [28, 33].

Table 3 Perfusion and metabolic parameters of the kidneys.

	Right K	Left K
Flow median (ml/min)	139	58
Pressure (mmHg)	25	25
Resistance Ru	0,17	0,41
Temperature (°C)	4	5
Time (min)	240	315
pH T0	7,32	7,32
pCO2 To (mmHg)	<6	<6
pO2 T0 (mmHg)	375	206
Lat T0 (mg/dL)	5,4	3,6
pH T1	7,17	7,2
pCO2 T1 (mmHg)	<6	<6
pO2 T1 (mmHg)	>760	>760
Lat T1 (mg/dL)	12,6	12,6

A)



B)

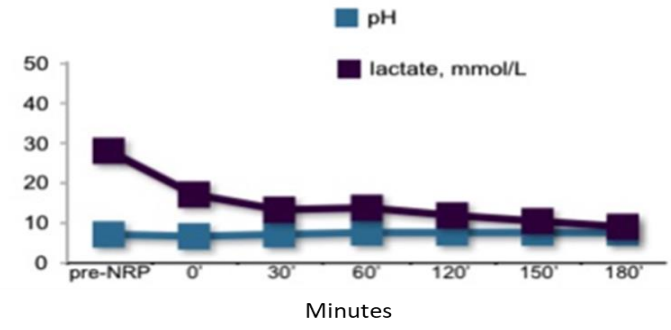


Figure 1 Serum values during NRP. A) Serum creatinine, B) serum lactate and pH.

2.3 Kidney Transplant and Patient Outcome

The DKT was performed without any complications. Kidneys were implanted in the right iliac fossa. The vein and artery anastomosis were performed on external iliac vessels. Cold ischemic time was 13h for the right kidney and 14 h for the left kidney. Ureter-to-bladder anastomosis was performed over a single stent. The post-operative immunosuppression therapy was based on thymoglobulin infusion, steroids, and tacrolimus, as per standard protocols [34].

The recipient was discharged in 14 days after surgery without any complication. The graft indicated a good function: 4.7 mg/dLsCr five days after surgery and 3200 mL/day of diuresis. Serum creatinine level was 1.44 mg/dL at the time of discharge, 0.83 mg/dL one month-after-transplant, and 0.72 mg/dL six month-after-transplant (Figure 2). At two years of follow-up, no complications were registered and serum creatinine level was 0.8 mg/dL.

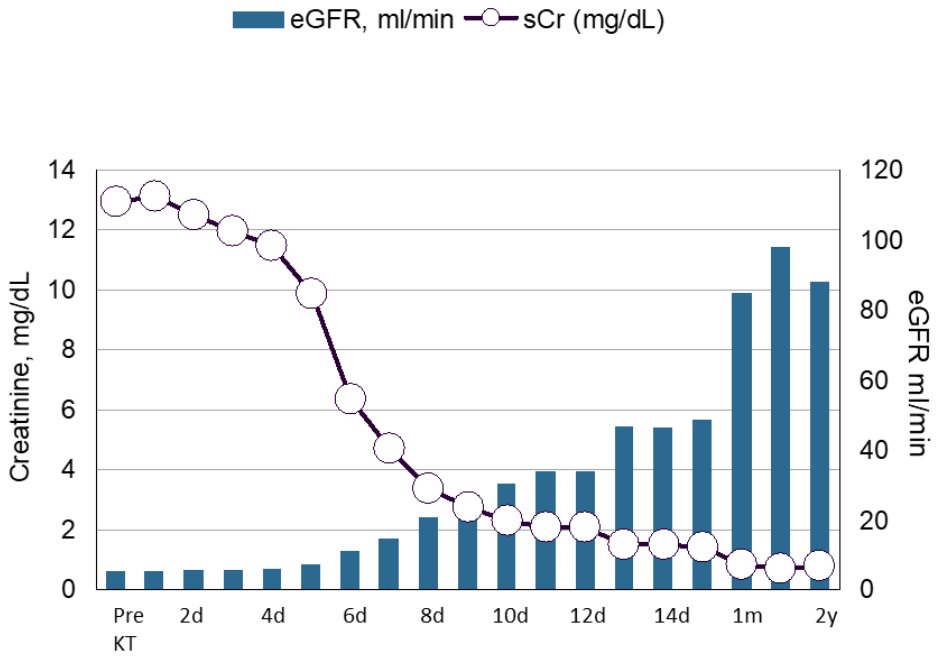


Figure 2 eGFR and serum creatinine levels of the recipient pre and after transplantation. KT= kidney transplant; d=days; m= months; y= years, eGFR estimated Glomerular Filtration Rate, calculated with Cockcroft- Gault equation.

3. Discussion and Conclusions

We report a case of dual kidney transplantation of DCD kidneys. The kidneys were declared untransplantable by other transplant centers because of high serum creatinine levels and increased value during NRP probably due to acute kidney injury during the cardio-circulatory arrest. The histological report showed a Karpinski score of 2 for both kidneys (37) and we decided to perform HOPE to improve the quality of the organs before transplantation. Following HOPE, the level of lactate was low; therefore, we used organs to perform a DKT allowing a greater filtration power, having two marginal organs because the donor was DCD with acute kidney injury (AKI).

The transplant was performed without complication. The renal function and the sCr were within limits one-month and after two years post-transplantation.

In recent years, because of the shortage of kidneys for transplantation, there has been greater interest in the use of DCD. Several studies have shown that although the use of DCD kidneys is associated with the high-risk incidence of delayed graft function, and transplant outcome, at least in the short term, these indicators are broadly comparable to that of kidneys from donation following brain death [35]. In Italy, there is an issue of the prolonged “no-touch“ period with the consequential damages related to the time of ischemia. In this setting, HOPE has a pivotal role in

reconditioning a marginal graft; moreover, the evaluation of perfusion parameters like flow and pressure is fundamental to defining the suitability of the organ for transplantation.

The prospect of transplanting both kidneys from a high-risk donor, DKT, is a successful approach for optimizing the donor kidney pool [36]. The selection of kidneys for transplantation (SKT or DKT) includes donor data like age, donor history, renal function, macroscopic aspect and histological findings in kidney biopsy [1, 13, 36-39].

Acute kidney injury (AKI) in a previously healthy person, AKI can usually be attributed to a rapid deterioration of the kidney function because of hypoxia, ischemia, or a nephrotoxic agent. Frequently, AKI patients recover spontaneously with the regeneration of damaged tubules [40]. In a recent Japanese study [41] renal grafts from DCD donors with high levels of terminal Cr showed good long-term graft survival, indicating that acute ischemic injury is reversible, even in transplanted kidneys.

The histology score is an important determinant of organ discard but not the only parameter to be considered for SKT or DKT assignment. Some authors added that, besides the histological score, the machine perfusion parameters are also important determinants in deciding to discard an organ [42]. Kayler et al. [43] found that despite a lack of stabilization of the sCr, kidneys with a urine output ≥30 cc/h, or with favorable machine perfusion characteristics (flows greater than 100 mL/min) and an absence of chronic changes observed through biopsy, performed just as well as kidneys from donors with stabilized creatinine in terms of primary non-function, exhibited delayed graft function and one-year renal allograft survival.

In this case, we used kidneys from a marginal donor with sCr values beyond that reported in the literature [7-12, 41, 43]. HOPE allowed us to use these marginal kidneys that showed good histological findings but were discarded due to the acute renal injury. In the reported case, the information gained during perfusion was useful in the selection process. The choice to use both organs to perform DKT was helpful in improving renal function and avoiding graft dysfunction.

We had a previous experience of normothermic perfusion and ex-vivo HOPE for DCD kidneys with good result [44], but to the best of our knowledge, this is the first case to be reported in Italy of AKI in DCD kidney with prolonged warm ischemic time due to 20 min‘no-touch’ period (as per the Italian law), and with a worse creatinine level during NRP, but which was successfully transplanted with after ex-vivo HOPE.

4. List of Abbreviations

ECD: Extended Criteria Donor;DCD: Donation after Circulatory Death Donor; sCr: Serum Creatinine; DKT: Dual Kidney Transplantation; SKT: Single Kidney Transplantation; ECMO: Extra-Corporeal Membrane Oxygenation; NRP:Normothermic Regional Perfusion; HMP: Hypothermic Machine Perfusion; HOPE: Hypothermic Oxygenated Perfusion; DGF: Delayed Graft Function; DBD: Donation after Brain Death; AKI: Acute Kidney Injury

Consent for Publication

Written informed consent was given by the patient to publish the information in this case report. Written informed consent was given by the next of kin of the deceased person to publish the information in this case report.

Availability of Data and Materials

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

Author Contributions

FO: study design, article drafting, VDP and GG: clinical activity and revision of the article, GF: surgical activity and revision of the article, GC: clinical activity and revision of the article, FV: histopathological diagnosis and revision of the article, GLM: clinical activity and revision of the article, MR: surgical activity and revision of the article. All authors reviewed and approved the final version of the manuscript.

Competing Interests

The authors have declared that no competing interests exist.

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