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PO_2 21% oxygenated hypothermic machine perfusion in kidney transplantation: Any clinical benefit?

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Abstract

Background: In deceased donor kidney transplantation (KT), the use of hypothermic machine perfusion (HMP) has been acquiring the status of best practice in the pre-transplant management of kidney grafts. Two types of HMP are currently available, oxygenated HMP and non-oxygenated HMP. However, data on the real clinical impact of oxygenation on KT outcome are still heterogeneous.

Methods: Retrospective study on a cohort of 103 patients transplanted with a single kidney graft that was managed either with end-ischemic oxygenated (O_2 group, Waves Machine, $n=51$, 49.5%) or non-oxygenated HMP (no-O_2 group, Life Port Kidney Transporter Machine, $n=52$, 50.5%), during the period January 2016–December 2020. Oxygenation was performed at pO_2 21%.

Results: The median cold ischemia time was 29 h:40 min [IQR 26 h:55 min–31 h:10 min] and the prevalence of grafts from extended criteria donors (ECD) was 46.7%, with a median kidney donor profile index (KDPI) of 72 [41–94]. The study groups were homogeneous in terms of recipient characteristics, ischemia times and donor characteristics. O_2 and no-O_2 groups showed comparable outcomes in terms of delayed graft function (O_2 vs no-O_2, 21.5% vs 25%, $p=0.58$), vascular (0.2% vs 0.2%, $p>0.99$) and urologic (13.7% vs 11.5%, $p=0.77$) complications, and episodes of graft rejection (11.7% vs 7.7%, $p=0.52$). At 1 year follow up, even creatinine serum levels were comparable between the groups (1.27 mg/dL [1.09 and 1.67] vs 1.4 mg/dL [1.9–1.78], $p=0.319$), with similar post-transplant trend ($p=0.870$). No significant benefit was either observed in ECD or KDPI > 60 subgroups, respectively.

Conclusions: Oxygenation at pO_2 21% during HMP seems not to significantly enhance the KT outcomes in terms of postoperative complications or graft function.

Keywords

Kidney transplantation, hypothermic oxygenated machine perfusion, delayed graft function, surgical morbidity

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Introduction

In deceased donor kidney transplantation (KT), the use of hypothermic machine perfusion (HMP) has been acquiring the status of best practice in the pre-transplant management of kidney grafts.[1–3] It improves graft hemodynamics by lowering vascular resistance, and preserves/reconditions the graft metabolic function, resulting in a decreased incidence of delayed graft function (DGF).[1–3] Oxygen does play a critical role in graft ischemia-reperfusion injury (IRI).[4–6] As a matter of fact, the pathogenesis of IRI

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comprise both oxygen deprivation during ischemia time, resulting in ATP and antioxidants depletion due to anaerobic metabolism, and production of reactive oxygen species (ROS) during reperfusion, with cytotoxic effect.[4–6] Two types of HMP are currently available, oxygenated HMP and non-oxygenated HMP. In animal model studies, graft oxygenation during HMP seems to exert a protective metabolic effect, but in clinical practice, data supporting a real benefit are limited and heterogeneous.[4–6] For example, while the COMPARE trial[7] found that oxygenated HMP enhanced KT outcomes when started immediately after procurement and used in grafts donated after circulatory death, the COPE trial[8] showed no significant benefit when HMP was used as end-ischemic reconditioning of grafts from brain deceased, expanded criteria donors (DBD-ECD). Moreover, the appropriate oxygenation pressure has not been identified yet and the majority of studies have investigated supraphysiologic levels.[5,6] However, any potential metabolic benefits of organ oxygenation should be tempered against the potentially deleterious effects of ROS injury, and it would seem rational that oxygen delivery should occur at the lowest therapeutic concentration possible to achieve such benefits. Therefore, the aim of the present study was to assess the clinical benefit associated with oxygenated HMP at pO_2 21% (air pressure), compared with standard non-oxygenated HMP, in deceased donor KT.

Methods

This is a retrospective study from a single-center cohort of 103 patients transplanted with a single kidney graft that was managed either with oxygenated HMP (O_2 group, Waves Machine, $n=51$, 49.5%) or non-oxygenated HMP (no-O_2 group, Life Port Kidney Transporter Machine, $n=52$, 50.5%). Both devices have been approved for hypothermic perfusion in KT with no different clinical indications, and they are currently used in clinical practice in a interchangeable way, according to availability. Therefore, graft allocation to either oxygenated or non-oxygenated HMP was a priori established as alternate HMP devices in alternate patients. All procedures were performed at the Liver-Kidney Transplant Unit of the Udine University Hospital, Italy, during the period January 2016–December 2020. All KT cases with grafts managed with HMP ($n=123$) were considered eligible for the study, and only double-graft KT ($n=10$) and combined KT cases ($n=10$) were excluded. Graft management with HMP was decided only on the base of logistic reasons and it was started after a preliminary period of static cold storage (SCS) following organ procurement, as previously reported.[9] Oxygenation was performed at pO_2 21% (corresponding to an oxygen pressure in the perfusate of 8–18 kPa), following the manufacturer's guidelines. KPS-1 was used as perfusion solution in both HMP devices. No grafts from donation after circulatory death were used. Extended criteria donors (ECD) were defined according standardized protocols, as follows: donor age >70 years; creatinine clearance <60 mL/min; presence of at least two of the following circumstances: severe hypertension in pharmacological treatment with two or more drugs, cardiovascular accident, diabetes mellitus in pharmacological therapy or presence of proteinuria >1 g/24 h. In such cases a Remuzzi score ⩽4 was required for single kidney graft allocation. Moreover, kidney graft quality was retrospectively assessed using the Kidney Donor profile Index (KDPI) and a conventional cutoff of KDPI > 60 was used for a high KDPI definition.[10] KT procedure and postoperative management have been described elsewhere.[9] Primary endpoints of the study were delayed graft function, defined as the need for dialysis within the first 7-days post-KT, and 1-year cumulative incidence of graft loss, defined as graft nephrectomy or return to dialysis;

Secondary endpoints were the followings:

- creatinine serum levels at post-operative month (POM) 1, 6, and 12;
- graft rejection: biopsy proven, within POM 12
- graft urologic complications: any case of urine leak or ureteric stricture due to any underlying cause, within POM 12
- graft vascular complications: any case of renal artery (thrombosis, stricture, mycotic arteritis, non mycotic pseudoaneurysm) or renal vein (thrombosis, stricture) complication, within POM 12.

Statistical analysis

Categorical variables were expressed by frequencies and percentage, while continuous variables were expressed by median and interquartile range (IQR). The comparison between O_2 group and no-O_2 group in terms of baseline characteristics and KT outcomes was performed using a chi-square test or Fisher's exact test for categorical variables, and a Mann-Whitney test for continuous variables. General Linear Model for measured repeats was used to compare the postoperative trend of serum creatinine levels at POM 1, 6, 12 between the study groups, after the assumptions had been verified. Statistical significance was accepted for $p<0.05$. Analyses were performed using Stata/SE 15.1 (Stata Corp LP, United States). The present study was approved by the local Institutional Review Board.

Results

Recipient and graft characteristics

The median recipient age at KT was 57 [50–65] years and the duration of dialysis was between 1 and 5 years in the majority

Table 1. Recipient and graft characteristics.

	Total ($n=103$)	O_2 group ($n=51$)	no-O_2 group ($n=52$)	p-Value
Recipient				
Age (years)	57 [50–65]	58 [50–65]	57 [47–66]	0.875
Male:female	70:33	34:17	36:16	0.780
BMI (kg/m²)	25 [23–28]	25 [22–27]	26 [23–29]	0.312
Pre-KT dialysis duration (%)				0.512
Pre-emptive	4 (3.8%)	3 (2.0%)	1 (2.0%)	
1–5 years	88 (84.6%)	45 (44.0%)	43 (44.0%)	
6–10 years	8 (7.7%)	3 (4.0%)	5 (4.0%)	
>11 years	4 (3.8%)	1 (2.0%)	3 (2.0%)	
Cardiopathy (%)	56 (53.3%)	29 (28.3%)	27 (27.7%)	0.774
Diabetes (%)	20 (19.1%)	13 (10.1%)	7 (9.9%)	0.149
Arterial Vasculopathy (%)	36 (34.3%)	21 (18.2%)	15 (17.8%)	0.245
Re-KT (%)	13 (12.4%)	6 (6.6%)	7 (6.4%)	0.739
Graft/donor				
Donor age (years)	60 [46–72]	62 [44–73]	60 [48–70]	0.743
Donor BMI (kg/m²)	26 [23–29]	26 [22–29]	26 [23–29]	0.396
Extended criteria donor (%)	49 (46.7%)	27 (24.7%)	22 (24.3%)	0.375
KDPI	72 [41–94]	86 [39–96]	68 [44–92]	0.464
CIT (min)	1780 [1615-1870]	1740 [1598-1860]	1787 [1655-1890]	0.438
SCS	517 [361–640]	486 [352–610]	541 [373–690]	0.428
HMP	1218 [1080-1340]	1217 [1086-1360]	1220 [1080-1335]	0.678
WIT (min)	45 [35–56]	50 [37–59]	44 [35–52]	0.197
Hemodynamic graft function at HMP start				
Arterial resistive index	0.34 [0.28–0.54]	0.40 [0.28–0.54]	0.33 [0.26–0.56]	>0.999
Arterial flow (ml/min)	70 [48–90]	65 [50–90]	72 [40–89]	0.689
Hemodynamic graft function at HMP end				
Arterial resistive index	0.23 [0.18–0.30]	0.28 [0.15–0.34]	0.22 [0.20–0.30]	0.702
Arterial flow (ml/min)	110 [77–137]	98 [66–165]	112 [82–134]	0.728

BMI: body mass index; CIT: cold ischemia time; HMP: hypothermic machine perfusion; SCS: static cold storage; KT: kidney transplantation; KDPI: kidney donor profile index; WIT: warm ischemia time.

of cases (84.6%). Kidney grafts from ECD were used in 46.7% of cases while the median KDPI was 72 [41–94]. The median CIT was 29 h:40 min [IQR 26 h:55 min–31 h:10 min], including a preliminary period of SCS (8 h:37 min [6 h:01 min-10 h:40 min]) and end-ischemic HMP (20 h:18 min [18–31 h:10 min]). The O_2 and no-O_2 groups were comparable for both recipients and donor/graft characteristics, as shown in Table 1. Moreover, the impact of oxygenation during HMP on graft hemodynamic function was not statistically significant. As a matter of fact, at the end of HMP period both arterial flow (O_2 vs noO_2 group, 98 mL/min [66–165] vs 112 mL/min [82–134], p 0.728) and resistive index (0.28 [0.15–0.34] vs 0.22 [0.20–0.30], p 0.702) were similar between the study groups.

KT outcomes

The overall prevalence of DGF was 22.9%, with no statistically significant difference between the study groups (O_2 vs no-O_2, 21.5% vs 25%, p 0.648). No cases of primary non function were recorded. At 1 year post-KT, the cumulative incidence of graft loss was 1.9% ($n=2$, both in the O_2 group, due to acute arterial thrombosis). Two patients died with functioning graft due to COVID. The post-transplant trend of creatinine serum level was similar in the study groups (Figure 1), with a median value at POM 12 of 1.27 mg/dL [1.09–1.67] vs 1.4 mg/dL [1.09–1.78] (O_2 vs no-O_2, $p=0.319$). Even in terms of graft rejection, urologic and vascular complications, the O_2 and no-O_2 groups showed comparable outcomes (Table 2). Neither subgroup analysis in KT cases with ECD grafts (O_2, $n=27$; no-O_2, $n=22$) or with high KDPI (O_2, $n=32$; no-O_2, $n=31$) showed any beneficial effect of ambient air oxygenation during HMP (Table 3).

Discussion

Considering the metabolic reactivity of oxygen, several factors should be considered when implementing oxygenation in HMP: graft quality and severity of accumulated ischemic injury, perfusate partial pressure of oxygen and duration of oxygenation.[4–6]

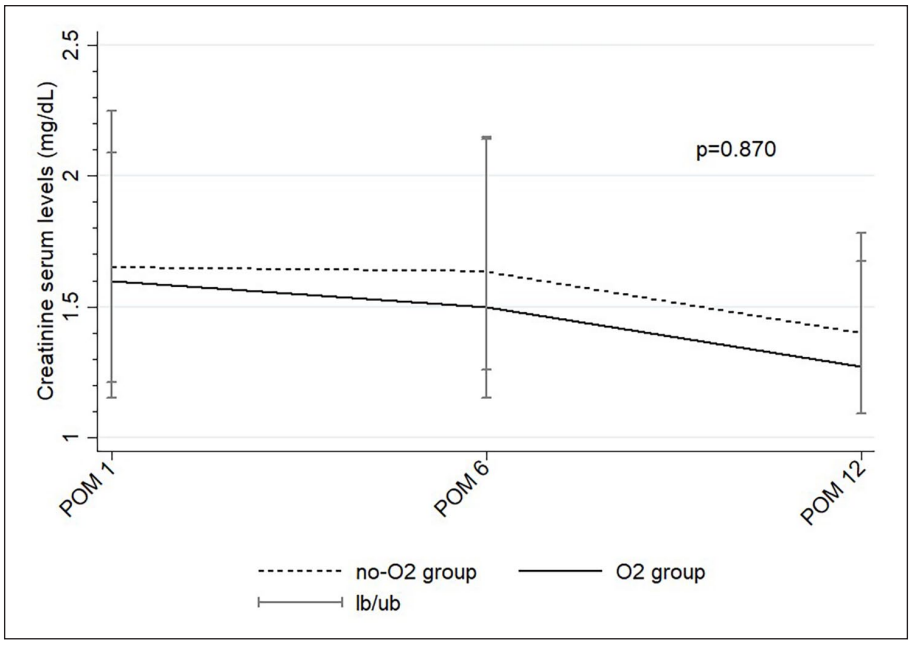

Figure 1. Postoperative trend of creatinine serum levels in the study groups.

Table 2. KT outcomes.

	Total ($n=103$)	O_2 group ($n=51$)	no-O_2 group ($n=52$)	p-Value
Delayed graft function (%)	24 (22.9%)	11 (21.5%)	13 (25%)	0.648
Vascular complications (%)	3 (2.9%)	2 (3.9%)	1 (1.9%)	>0.999
Urologic complications (%)	13 (12.4%)	7 (13.7%)	6 (11.5%)	>0.999
Clavien-Dindo score ⩾3 complications (%)	14 (13.3%)	8 (15.7%)	6 (11.5%)	0.775
Graft rejection (%)	10 (9.5%)	6 (11.7%)	4 (7.7%)	0.741
Serum creatinine level (mg/dL)				
POM 1	1.65 [1.20–2.20]	1.60 [1.15–2.09]	1.65 [1.21–2.25]	0.373
POM 6	1.62 [1.26–2.14]	1.50 [1.26–2.14]	1.63 [1.15–2.15]	0.887
POM 12	1.38 [1.09–1.75]	1.27 [1.09–1.67]	1.4 [1.09–1.78]	0.319
1-year post-KT cumulative graft loss (%)	2 (1.9%)	2 (3.9%)	0	0.495

POM: postoperative month.

In a porcine auto-transplantation model managed with a 20-h-long HMP, no benefit from oxygenating the perfusate at $pO_2 > 500$ mmHg has been observed, either in terms of post-KT graft function or graft histology.[11] Conversely, in DCD grafts porcine models, several studies have reported on the advantages of oxygenated HMP, comprising a reconditioned metabolic function, reduced inflammation and enhanced postoperative function.[5,6] Furthermore, the optimal oxygen partial pressure, timing and duration have been assessed. Initial HMP with no preliminary SCS period was identified as the best strategy.[6,12] Brief initial oxygenation (2 h of the total 22 h HMP) resulted in similar mitochondrial protection and initial graft function, as compared with prolonged continuous administration (22 h of the total 22 h HMP), while high perfusate oxygen concentrations, compared to low concentrations, were associated with faster early graft recovery but similar late outcomes.[12]

In clinical setting, the available data are limited and provide heterogeneous results, compared with basic science studies. The COMPARE study,[7] a randomized, double blind, paired trial investigated the impact of end-ischemic oxygenated HMP in DCD grafts from donors >50 years old ($n=106$ for each group). The control group comprised patients transplanted with the paired kidney from the same donor, being managed with non-oxygenated HMP. HMP was started immediately after procurement, and median HMP time and CIT were 6.85 and 11 h (in the intervention group), respectively. Supraphysiological 100% oxygen at 100 mL/min was delivered via a membrane oxygenator. It was shown that the renal function (estimated glomerular filtration rate) at 12 months post-transplantation as well as patient survival, DGF and primary non-function rates were similar in both groups. Nonetheless, fewer severe complications (Clavien–Dindo

Table 3. KT outcomes in ECD and high KDPI subgroups.

	ECD subgroup ($n=49$)			High KDPI subgroup ($n=63$)		
	O_2 group ($n=27$)	no-O_2 group ($n=22$)	p-Value	O_2 group ($n=32$)	no-O_2 group ($n=31$)	p-Value
Delayed graft function (%)	7 (25.9%)	7 (31.8%)	0.755	8 (25%)	7 (22.6%)	>0.999
Vascular complications (%)	2 (7.4%)	0	0.495	2 (6.2%)	1 (3.2%)	>0.999
Urologic complications (%)	5 (18.5%)	4 (18.2%)	>0.999	4 (12.5%)	4 (12.9%)	>0.999
Clavien-Dindo score ⩾3 complications (%)	7 (25.9%)	4 (18.2%)	0.775	7 (21.8%)	6 (19.3%)	>0.999
Graft rejection (%)	5 (18.5%)	2 (9%)	0.436	5 (15.7%)	3 (9.7%)	0.708
Serum creatinine level (mg/dL):						
POM 1	1.98 [1.68–2.88]	2.09 [1.54–2.56]	0.832	1.86 [1.32–2.69]	2.08 [1.5–2.71]	0.640
POM 6	2.10 [1.74–2.35]	1.87 [1.46–2.23]	0.251	2.05 [1.55–2.35]	1.84 [1.42–2.34]	0.320
POM 12	1.68 [1.56–1.95]	1.66 [1.23–2.03]	0.599	1.67 [1.24–1.81]	1.63 [1.21–1.96]	0.823
1-year post-KT cumulative graft loss (%)	2 (7.4%)	0	0.495	2 (6.3%)	0	0.492

ECD: extended criteria donor; POM: postoperative month; KDPI: kidney donor profile index.

grade IIIb or more), reduced acute rejection episodes and lower rates of graft failure at 12 months were recorded in the oxygenated HMP group.

The COPE trial[8] focused on the use of oxygenated HMP in grafts from ECD grafts, in a multicenter randomized control trial. The intervention group comprised 152 cases managed with pO_2 100% HMP for at least 2 h, after a preliminary period of SCS; the median CIT and perfusion time were 13.2 h and 4.7 h, respectively. The control group comprised grafts managed with only SCS and no significant differences between the groups were noted in terms of DGF, graft acute rejection episodes, 1-year graft function and survival. Similar results in the same clinical setting (ECD grafts) were also reported by Meister et al.[13] and Ravaioli et al.[14] The findings of our study are in line with these previous results; nonetheless, the specific peculiarities of the present investigation can provide some additional and complementary information: oxygenation was tested at lower partial pressure (ambient air); HMP was end-ischemic after a preliminary period of SCS and the median HMP time was significantly longer (20 h:18 min); the study population comprised also standard grafts. Thus, it was found that prolonged low oxygenation HMP did not have any detrimental effect but neither enhanced the KT outcomes, when compared with non-oxygenated HMP. Neither in ECD or high KDPI subgroups analysis, the KT outcome was significantly modified by oxygenation. Such data may possibly support further clinical investigations on prolonged, supraphysiological oxygenation during HMP and/or on the effect of oxygenated HMP in non-ECD KT. Conversely, they may also be interpreted as an additional evidence that the benefit of oxygenation, although metabolically evident at a molecular level,[6–10] may not currently result in a real clinical advantage. Under this perspective, studies on oxygen carries, preservation solutions with specific antioxidant and/or anti-inflammatory agents or normothermic MP may represent promising strategies to further improve KT outcomes.[15,16]

The present study has several limitations: the retrospective modality of study design; the small sample size of the study population; the use of different HMP devices (rather than the same device in oxygenated and non-oxygenated modality). Nonetheless, based on the present findings, 21% oxygenated HMP seems not to significantly enhance KT outcomes when it is used after SCS, in DBD grafts (either standard or ECD).

Author contributions

Conception and design of the study: RP, GLA, UB; acquisition of data: EM, VC, SB; analysis and interpretation of data: RP, GLA; writing the article and reviewing the literature: RP, GLA; supervision, study review and final approval: RP, GLA, UB, GT, AR.

Declaration of conflicting interests

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