Transplant International

LETTER TO THE EDITORS

Deceased-donor hyperoxia deteriorates kidney graft function

doi:10.1111/j.1432-2277.2010.01175.x

Deceased-donor kidney transplants offer an additional possibility for patients requiring renal replacement therapy [1]. Moreover, organ preservation has major impact on allograft renal function [2]. The incidence of delayed graft function (DGF), defined by the need for dialysis within the first week post-transplant, ranges from 13.3% to 52% and it may lead to a worse outcome [3]. Preharvest organ preservation has an impact on allograft renal function [2]. On the other hand, hyperbaric oxygen (HBO) therapy modulates both cellular and humoral immune response as well as lessens the severity of reperfusion injury [2]. Although oxygen is a vital substrate in the reduction of hypoxia, anoxia and ischemia, it also acts as a toxic metabolite because of reactive oxygen species production [1,2]. On the other hand, elevated oxygen tension during reperfusion may actually promote necrosis [4]. Regarding this controversy, we attempted to evaluate the effects of higher level of arterial partial pressure oxygen (PaO_2) in deceased donors on DGF.

A retrospective cross-sectional study was performed at three Iranian Kidney Transplant Centers from 2006 to 2007. A total of 180 adult patients with end-stage renal disease (ESRD) were enrolled. The participants received a kidney from deceased donor and were followed up at least for 12 months. The recipients older than 70 years, highly sensitized patients with panel-reactive antibody >40%, ABO incompatibility, recent or metastatic malignancy, severe irreversible extrarenal disease, drug abuser, noncompliance patients, recurrent active kidney disease, psychiatric illness and primary hyperoxalosis were excluded from our study. Moreover, we excluded deceased donor aged more than 70 years, with metastatic malignancy, severe hypertension, untreated bacterial sepsis, oliguric acute renal failure, hepatitis B or C and HIV infection and very prolonged warm ischemic time. The immunosuppressive protocol was triple therapy of cyclosporine, mycophenolate mofetil and prednisolone.

Deceased donors were exposed to 100% oxygen at least for 2 h and the patients were categorized according to their preoperative arterial PO_2 (PaO_2) into two groups; group 1, $PaO_2 < 200$ mmHg and group 2, $PaO_2 \geq 200$ mmHg.

There were no significant differences between the mean age of recipients and donors in both gender (46.6 ± 12.8 in male vs. 42.3 ± 14.5 in female recipients, $P = 0.1$ and 29 ± 14 in male vs. 30 ± 12.7 in female donors, $P = 0.7$).

Table 1. Comparison of donors' instability markers just before transplantation between groups.

Variable	$PO_2 \leq 200$ mmHg	$PO_2 > 200$ mmHg	*P*-value
Plasma Na (mean ± SD)	146.4 ± 10.5	146.4 ± 9.6	0.98*
Plasma K (mean ± SD)	3.9 ± 0.7	4.3 ± 0.7	0.01*
Plasma creatinine (mean ± SD)	1.1 ± 0.4	1.0 ± 0.2	0.23*
Blood sugar (mean ± SD)	262.0 ± 158.3	206.7 ± 83.1	0.15*
Hemoglobin (mean ± SD)	10.8 ± 3.9	12.9 ± 3.3	0.02*
24 h urinary output (mean ± SD)	4448.9 ± 4562.3	3568.3 ± 1246.2	0.12*
Plasma bicarbonate (mean ± SD)	17.8 ± 4.3	16.5 ± 3.3	0.21*
Blood PCO_2 (mean ± SD)	36.7 ± 12.0	30 ± 6.1	0.02*
Plasma pH (mean ± SD)	7.3 ± 0.08	7.3 ± 0.08	0.19*
ICU staying duration (mean ± SD)	5.2 ± 1.5	4.4 ± 1.3	0.02*
Vasoreactive requirement, *n* (%)	90 (94.7)	16 (100)	1*
More than one vasoreactive requirement, *n* (%)	46 (48.4)	7 (43.8)	0.7*
Prolong hypotension, *n* (%)	22 (23.2)	2 (12.5)	0.3†
Cardiac arrest, *n* (%)	28 (29.5)	2 (12.5)	0.2†

*Pearson.
†Fisher.

The most common cause of brain death in deceased donors was trauma (n = 64, 59.3%). Long operation time (more than 120 min) was seen in 61 (56.5%) recipients; however, it has no impact on DGF (P = 0.99).

The majority of our donors (n = 90, 83.3%) had PaO2 levels <200 mmHg. The direct parameters which describing the oxygen status of the donors such as arterial blood gas data and hemoglobin concentrations just before organ procurement shows no significant differences between two groups in the majority of instability markers (Table 1). A total of 18 patients have preoperative PaO2 ≥ 200 mmHg, four of them needed dialysis in the first week (i.e. DGF) and after 1 year five of them lost their graft while 13 had mild to moderate renal allograft failure (plasma Creatinine ≥ 1.8 mg/dl).

Table 2 summarizes the comparison of some donor and recipient variables with donors' preoperative PaO_2 level. In univariate analysis, there was no significant difference between all variables and preoperative PaO_2 level except for graft function; graft loss was significantly more frequent in recipients whose donor had higher preoperative PaO_2 (202.8 ± 74.7 vs. 138.4 ± 74.1 mmHg, P = 0.02). In addition, we found that DGF was higher in donors who had PaO_2 ≥ 200 mmHg, ICU staying more than 5 days and urinary output <3 l during 24 h before operation when compared with individuals with PaO2 < 200 mmHg (P = 0.02), ICU staying <5 days (P = 0.07) and urinary output more than 3 l during 24 h before operation (P = 0.0001). The other factors including donor's age, gender, cause of brain death, operation time, cold and warm ischemic times, vasoactive requirements, cardiac arrest, prolonged hypotension, arterial blood gas findings, blood urea nitrogen, serum creatinine, recipient's age and gender as well as cause of ESRD had no significant effect on DGF.

Table 2. Correlation between variables and PaO_2.

Variables	PaO_2 < 200 mmHg (%)	PaO_2 ≥ 200 mmHg (%)	*P*-value
Donor			
Gender			
Male	83.6	16.4	0.9*
Female	84.2	15.8	
Cause of brain death			
Trauma	87.3	12.7	0.2†
Toxicity	66.7	33.3	
Vascular event	83.3	16.7	
Tumor	66.7	33.3	
Cardiac arrest			
No	85.2	19.8	0.1†
Yes	93.3	6.2	
Prolonged hypotension			
No	83.9	16.1	1†
Yes	83.3	16.7	
Vasoactive agents requirement			
No	100	0	0.5†
Yes	83	17.1	
Operation time (min)			
<120	83.1	16.9	0.9*
≥120	83.3	16.7	
Recipient			
Gender			
Male	83.3	16.7	0.9*
Female	82.5	17.5	
Cause of ESRD			
Unknown	87.5	12.5	0.5†
Diabetes	80	20	
Hypertension	81.3	18.8	
GN	75	25	
ADPKD	66.7	33.3	

GN, glomerulonephritis; ADPKD, autosomal dominant polycystic kidney disease; ESRD, end-stage renal disease.
*Pearson; †Fisher.

In a multivariate logistic regression analysis, DGF was five times more prevalent in recipients whose donors had preoperative PaO_2 ≥ 200 mmHg than those who had preoperative PaO_2 < 200 mmHg (95% CI: 1.09–38.13, P = 0.04) (Fig. 1) and DGF was 30 times more prevalent in donors with urinary output <3 l during 24 h before operation (95% CI: 3.28–278.38, P = 0.003) (Table 1). Moreover, there was no significant relation between DGF and other predictors.

Despite reported beneficial effect of HBO, we found that deceased-donor hyperoxia (PaO_2 more than 200 mmHg), before recovery of kidney was associated with increased risk for DGF. This level of hyperoxia resulted in fivefold times of DGF compared with PaO_2 <200 mmHg in the studied population. On the other hand, DGF reduces renal allograft survival as well as prolongs length of hospital duration and enhances the costs of transplantation. However, in our

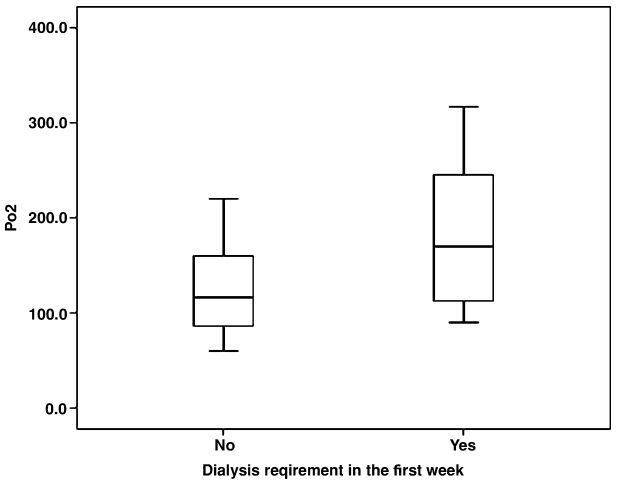

Figure 1 Correlation between delayed graft function and PaO_2.

study about 50% of DGF was seen in recipients who had donors with preoperative PaO2 ≥ 200 mmHg. Interestingly, our patients with a higher and better oxygenation value show worse organ function. The deteriorative effect of preoperative hyperoxia on DGF may be explained by toxic impact of oxygen-free radicals released during the reperfusion of the ischemic region [5].

Furthermore, some studies on other organ have also shown that 100% oxygen under normobaric for treatment of myocardial infarction and acute coronary syndromes during a short period of time had worst outcome because of the increased production of oxygen-free radicals [6,7].

In contrast to the reported literature, in our study some risk factors that contribute to DGF through several potential mechanisms such as donor female gender, increased donor age, prolong warm and cold ischemia times [8] in multivariate regression had no impact on DGF. Since our organ procurement is local, cold ischemic time would be short, consequently it is plausible that cold ischemic time has no considerable influence on DGF.

Behzad Einollahi,[1] Fatemeh Poor-Reza-Gholi,[2] Somaye Rezaeean,[2] Younes Jahani,[1] Mohsen Nafar,[2] Katayuon Najafizadeh[3] and Zohreh Rostami[1]

1 Nephrology and Urology Research Center, Baqyiatallah University of Medical Sciences, Tehran, Iran

2 Department of Nephrology, Shahid Beheshti University of Medical Sciences, Tehran, Iran

3 Department of Pulmonology, Shahid Beheshti University of Medical Sciences, Tehran, Iran

Funding sources

Baqyiatallah University of Medical sciences.

Acknowledgement

We would like to express our thanks to Dr Mohsen reza Heidari for his great assistance in editing the English language of this paper.

References

1. Israni AK, Li N, Cizman BB, *et al.* Association of donor inflammation- and apoptosis-related genotypes and delayed allograft function after kidney transplantation. *Am J Kidney Dis* 2008; **52**: 331.
2. Muralidharan V, Christophi C. Hyperbaric oxygen therapy and liver transplantation. *HPB (Oxford)* 2007; **9**: 174.
3. Malago M, Hertl M, Testa G, Rogiers X, Broelsch CE. Split-liver transplantation: future use of scarce donor organs. *World J Surg* 2002; **26**: 275.
4. Sterling DL, Thornton JD, Swafford A, *et al.* Hyperbaric oxygen limits infarct size in ischemic rabbit myocardium *in vivo*. *Circulation* 1993; **88**(4 Pt 1): 1931.
5. Novitzky D. Donor management: state of the art. *Transplant Proc* 1997; **29**: 3773.
6. Farquhar H, Weatherall M, Wijesinghe M, *et al.* Systematic review of studies of the effect of hyperoxia on coronary blood flow. *Am Heart J* 2009; **158**: 371.
7. Wijesinghe M, Perrin K, Ranchord A, Simmonds M, Weatherall M, Beasley R. Routine use of oxygen in the treatment of myocardial infarction: systematic review. *Heart* 2009; **95**: 198.
8. Ghods AJ, Savaj S, Abbasi M, Heidari H, Rokhsatyazdi H. The incidence and risk factors of delayed graft function in 689 consecutive living unrelated donor renal transplantation. *Transplant Proc* 2007; **39**: 846.