Beneficial Effect of Moderately Increasing Hypothermic Machine Perfusion Pressure on Donor after Cardiac Death Renal Transplantation

Chen-Guang Ding[1,2], Pu-Xun Tian[1,2], Xiao-Ming Ding[1,2], He-Li Xiang[1,2], Yang Li[1,2], Xiao-Hui Tian[1,2], Feng Han[1,2], Qian-Hui Tai[1,2], Qian-Long Liu[1,2], Jin Zheng[1,2], Wu-Jun Xue[1,2]

[1]Department of Renal Transplantation, Nephropathy Hospital, The First Affiliated Hospital of Xi'an Jiaotong University, Xi'an, Shaanxi 710061, China
[2]Institute of Organ Transplantation, Xi'an Jiaotong University, Xi'an, Shaanxi 710061, China

Abstract

Background: Vascular resistance and flow rate during hypothermic machine perfusion (HMP) of kidneys is correlated with graft function. We aimed to determine the effects of increasing HMP pressure versus maintaining the initial pressure on kidney transplantation outcomes.
Methods: We retrospectively reviewed the data of 76 primary transplantation patients who received HMP-preserved kidneys from 48 donors after cardiac death between September 1, 2013, and August 31, 2015. HMP pressure was increased from 30 to 40 mmHg (1 mmHg = 0.133 kPa) in kidneys with poor flow and/or vascular resistance (increased pressure [IP] group; 36 patients); otherwise, the initial pressure was maintained (constant pressure group; 40 patients). Finally, the clinical characteristics and transplantation outcomes in both groups were assessed.
Results: Delayed graft function (DGF) incidence, 1-year allograft, patient survival, kidney function recovery time, and serum creatinine level on day 30 were similar in both groups, with improved flow and resistance in the IP group. Among patients with DGF, kidney function recovery time and DGF duration were ameliorated in the IP group. Multivariate logistic regression analysis revealed that donor hypertension (odds ratio [*OR*]: 1.43, 95% confidence interval [*CI*]: 1.02–2.06, *P* = 0.035), donor terminal serum creatinine (*OR*: 1.27, 95% *CI*: 1.06–1.62, *P* = 0.023), warm ischemic time (*OR*: 3.45, 95% *CI*: 1.97–6.37, *P* = 0.002), and terminal resistance (*OR*: 3.12, 95% *CI*: 1.76–6.09, *P* = 0.012) were independent predictors of DGF. Cox proportional hazards analysis showed that terminal resistance (hazard ratio: 2.06, 95% *CI*: 1.32–5.16, *P* = 0.032) significantly affected graft survival.
Conclusion: Increased HMP pressure improves graft perfusion but does not affect DGF incidence or 1-year graft survival.

Key words: Delayed Graft Function; Donor after Cardiac Death; Hypothermic Machine Perfusion; Kidney Transplantation

INTRODUCTION

In recent years, donors after cardiac death (DCDs) have become the major source of organs for transplantation in China.[1,2] Nevertheless, studies in Europe, the USA,[3-5] and China[6,7] have shown that the transplantation of kidneys obtained from DCDs is associated with a high incidence of delayed graft function (DGF), as well as early graft dysfunction and failure. Indeed, DGF increases the risk of graft rejection and decreases graft survival.[8]

Static cold storage is considered the standard method of kidney preservation since the 1970s. Studies have suggested that compared with static cold storage, hypothermic machine perfusion (HMP) of kidneys obtained from DCDs is associated with improved early function and improved graft survival,[9-12] which remains controversial.[13,14] Comprehensive meta-analyses have confirmed a significant

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reduction in the risk of DGF when kidneys obtained from DCDs are preserved using HMP rather than static cold storage.[15,16] Furthermore, HMP enables the assessment of graft viability and quality prior to transplantation and might also enable the repair of potential grafts.[17-19] Therefore, various HMP parameters have been evaluated in order to optimize graft quality prior to transplantation; such parameters include the perfusate flow rate, vascular resistance, and perfusate pressure, as well as the changes in these parameters during persistent perfusion.[17,20,21] Elevated vascular resistance and reduced perfusate flow rate in potential kidney grafts may be corrected by increasing the perfusate pressure.[17,20,21] However, the ideal pressure required to perfuse donor kidneys has yet to be determined.

We therefore retrospectively analyzed the effects of two different HMP pressures on the outcomes of primary transplantation patients who received kidneys harvested from DCDs. We also studied whether the renal transplant recipients could benefit from increased perfusion pressure.

METHODS

Ethical approval
The local institutional review board of the First Affiliated Hospital of Xi'an Jiaotong University approved the study protocol, which was in compliance with the provisions of the current *Declaration of Helsinki* principles and good clinical practice guidelines. All patients provided written informed consent for participation in the study and to have their medical data used for research purposes.

Patient population
We retrospectively reviewed the effects of all consecutive Chinese patients aged between 18 and 65 years who underwent primary kidney transplantation with HMP-preserved DCD kidneys at The First Affiliated Hospital of Xi'an Jiaotong University between September 1, 2013 and August 31, 2015. Patients were excluded from the study if they (a) had undergone re-transplantation, received an organ other than a kidney, or showed loss of function of the transplanted kidney induced by surgical factors; (b) had a positive cross-match or panel-reactive antibody (over 30%); (c) had an active infection, hepatitis, or abnormal hepatic function; (d) had severe gastrointestinal disorders (such as diarrhea or active peptic ulcer disease) or uncontrolled diabetes mellitus before transplantation; (e) had leukopenia (leukocytes <3000/mm³), thrombocytopenia (platelets <100,000/mm³), or severe anemia (hemoglobin <60 g/L); (f) terminal flow rate <60 ml/min and/or terminal vascular resistance >0.6 mmHg·ml^{-1}·min^{-1}; or (g) initial (perfusion for 15 min) flow rate >60 ml/min and/or terminal vascular resistance <0.6 mmHg·ml^{-1}·min^{-1} (1 mmHg = 0.133 kPa).

Hypothermic machine perfusion and grouping
Seventy-six kidneys were classified into the following two groups based on whether the perfusate pressure was increased during pulsatile pump perfusion, for both the constant pressure (CP) group (40 patients) and increased pressure (IP)

group (36 patients). Patients were allocated kidney grafts by the attending physicians according to standard clinical practice guidelines, and 28 kidneys in both the CP and IP groups were from the same donors (left or right). The kidney grafts were provided by the Coordination Group of the Shaanxi Red Cross Organization and harvested from DCDs classified as controlled or uncontrolled DCDs according to the Maastricht classification. All kidneys were preserved in a Lifeport kidney transporter (Organ Recovery Systems, Chicago, IL, USA) and perfused with the kidney perfusion solution KPS-1. The initial pump pressure was set to 30 mmHg. Based on our previous observations, we found that perfusion parameters were unstable 15 min ago. After 15 min, the perfusion parameters began to change slowly. Therefore, the following perfusion parameters were measured 15 min after the beginning of perfusion: flow rate, vascular resistance, perfusion pressure, and trap temperature. In case of flow rate <60 ml/min and/or vascular resistance >0.6 mmHg·ml^{-1}·min^{-1} at 15 min, the perfusion pressure was increased to 40 mmHg (IP group). Otherwise, the perfusion pressure was maintained at 30 mmHg (CP group). This approach was used at our transplantation center during the study period, based on previous literature[17,20,21] and our clinical experience.

Immunosuppressive treatments
A triple immunosuppressive regimen was used in all patients, consisting of tacrolimus (0.06 mg·kg^{-1}·d^{-1}) or cyclosporine A (3.5 mg·kg^{-1}·d^{-1}) combined with mycophenolate mofetil (2 g/day) or mycophenolic acid (1440 mg/d) and prednisone (10 mg/d). In addition, all patients received thymoglobulin (Genzyme, Waterford, Ireland) at a dose of 1.25 mg·kg^{-1}·d^{-1} for 4 days, starting perioperatively.

Clinical assessments
Early graft function was assessed as follows: (a) DGF was defined as the requirement of dialysis during the 1st postoperative week; (b) the duration of DGF was the interval between the transplantation and last dialysis session; (c) slow graft function (SGF) was identified in patients who did not have DGF but whose serum creatinine (sCr) levels remained >2 mg/dl (177 mmol/L) by postoperative day 7; (d) immediate graft function (IGF) was identified in patients who did not have DGF or SGF and whose sCr levels were <2 mg/dl by postoperative day 7; and (e) kidney function recovery time was the interval from transplantation to recorded sCr levels <2 mg/dl.

Acute renal allograft rejection episodes were suspected with increased sCr levels in the presence of clinical findings such as reduced urine output, weight gain, increased blood pressure, and graft tenderness. A core biopsy was performed for suspected acute rejection. All biopsy specimens were assessed by local pathologists and graded according to the Banff 2013 classification.[22] The incidence, duration, and treatment of acute rejection were noted during the first 12 months after transplantation. Allograft biopsies were performed only for clinically indicated causes or every

7–10 days in recipients with DGF to exclude acute rejection. Biopsy-proven acute rejection episodes were treated with 500 mg methylprednisolone administered intravenously on 3 consecutive days, plus optimized calcineurin inhibitor and mycophenolic acid therapy. Thymoglobulin or rabbit antihuman thymocyte immunoglobulin was administered for 5–10 days in patients with steroid-resistant rejection or early high-grade rejection.[23,24] Rituxan® (200 mg) was administered for one or two times in patients with antibody-mediated rejection (AMR), plus plasmapheresis and intravenous immunoglobulin.

Statistical analysis

Quantitative variables are presented as frequency and percentage and qualitative variables as mean ± standard deviation (SD) or median. Demographic characteristics and the results of the baseline examination data were compared by Student's t-test or the Mann–Whitney U-test, depending on data normality. Dichotomous data were compared by the Pearson's Chi-square test or Fisher's exact test. A multivariate logistic regression model for DGF and a Cox regression model for graft failure were used. Patient and graft survivals were assessed by the Kaplan–Meier method and compared between groups by the log-rank test. All statistical analyses were performed on an intention-to-treat basis. A two-sided $P < 0.05$ was considered statistically significant. All calculations were performed using SPSS version 19.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

Demographic and clinical characteristics of donors and recipients

The 48 DCDs provided 96 kidneys. Twenty kidneys were excluded. Of these, 2 kidneys were abandoned due to renal abnormalities, 1 due to poor perfusion effect, and 3 due to a perfusion resistance index >0.6 before Lifeport transplantation. In the remaining 14 kidneys, the perfusion resistance index was unable to reach 0.6 within the required time. Therefore, 76 patients received 1 kidney each during the study period. Their demographic and clinical characteristics are shown in Table 1. Of the 76 patients, 40 and 36 were assigned to the CP and IP groups, respectively. There were no significant differences between these two groups with respect to donor and recipient age, duration of pretransplant dialysis, positivity for panel-reactive antibody, number of HLA mismatches, cold ischemic time, warm ischemic time (determined from the beginning of heartbeat to the start of perfusion), primary diseases in recipients, causes of death of donors, sCr levels, body mass index, and DCD Maastricht categories (all $P > 0.05$).

Hypothermic machine perfusion parameters

Initial (perfusion for 15 min) and terminal flow rates were 48.3 ± 10.6 ml/min and 76.3 ± 12.7 ml/min, respectively ($P < 0.001$), in the CP group and 47.4 ± 7.5 ml/min and 85.9 ± 14.6 ml/min, respectively ($P < 0.001$), in the IP group. The terminal flow rate was significantly lower in

the CP group than in the IP group ($P = 0.003$) [Table 2]. In both groups, initial vascular resistance (perfusion for 15 min) was significantly higher than the terminal resistance ($P < 0.001$) [Table 2]. In addition, terminal resistance was significantly higher in the CP group than in the IP group ($P = 0.023$). The trap temperature and HMP duration did not differ between the two groups.

Early graft function

The incidence of DGF did not differ between the CP (27.5%, 11/40 patients) and IP (25.0%, 9/36 patients, $P = 0.805$) groups; the rates of slow and immediate graft function also did not differ between the two groups ($P = 0.412$ and $P = 0.411$, respectively) [Table 3]. Multivariate logistic regression analysis revealed four significant risk factors for DGF, including donor hypertension history (odds ratio [OR]: 1.43, 95% confidence interval [CI]: 1.02–2.06, $P = 0.035$), donor terminal sCr (OR: 1.27, 95% CI: 1.06–1.62, $P = 0.023$), warm ischemic time (OR: 3.45, 95% CI: 1.97–6.37, $P = 0.002$), and terminal vascular resistance (OR: 3.12, 95% CI: 1.76–6.09, $P = 0.012$) [Table 4]. HMP pressure (CP vs. IP; OR: 0.51, 95% CI: 0.22–0.94, $P = 0.250$) and terminal flow (OR: 0.79, 95% CI: 0.47–0.96, $P = 0.053$) [Table 3] did not significantly influence the rate of DGF. Meanwhile, sCr levels at 30 days after transplantation did not differ between the CP (1.47 ± 0.31 mg/dl) and IP (1.39 ± 0.22 mg/dl; $P = 0.203$) [Table 3] groups.

Kidney function recovery time and delayed graft function duration

The overall kidney function recovery time did not differ between the CP (18.3 ± 9.1 days) and IP (16.7 ± 8.3 days, $P = 0.427$) groups; however, among patients who developed DGF, the kidney function recovery time was significantly longer in the CP group (25.4 ± 5.1 days) than in the IP group (20.2 ± 4.7 days, $P = 0.031$) [Table 3]. In addition, the duration of DGF was significantly higher in the CP group (15.6 ± 2.4 days) than in the IP group (13.2 ± 2.6 days, $P = 0.046$) [Table 3].

Acute rejection

Nine (22.5%) and 7 (19.4%) patients in the CP and IP groups, respectively, developed acute rejection within 1 year of transplantation ($P = 0.744$). Four of the 11 recipients with DGF in the CP group (36.4%) and 3 of the 9 in the IP group (33.3%) developed an acute rejection episode within 1 year of transplantation ($P = 0.742$) [Table 3].

Graft and patient survival rates

By the 1-year follow-up assessment, five patients (two cases of AMR did not recover, one case primary nonfunctioning, one case renal artery stenosis, and one case ureteral obstruction in transplanted kidney) in the CP group and four (two cases of AMR did not recover, one case rupture of transplanted kidney, and one case of renal allograft abscess) in the IP group had developed allograft failure. In the same time period, three patients each in the CP (one patient died from cardiovascular disease and two from pulmonary infection) and IP (one

Table 1: Demographic and clinical characteristics of recipients

Variables	CP group (n = 40)	IP group (n = 36)	t or χ^2	P
Recipients				
Age (years), mean ± SD	39.1 ± 6.6	40.2 ± 7.4	0.685*	0.495
Gender (male/female), n	24/16	20/16	3.840†	0.695
BMI (kg/m^2), mean ± SD	22.3 ± 4.7	22.6 ± 4.2	2.021*	0.768
Hemodialysis, n (%)	37 (92.5)	34 (94.4)	0.120†	0.733
Peritoneal dialysis, n (%)	3 (7.5)	2 (5.6)	0.120†	0.903
Dialysis duration (months), mean ± SD	26.4 ± 3.7	28.3 ± 5.3	1.793*	0.073
Primary disease				
Chronic GN, n (%)	33 (82.5)	30 (83.2)	1.390†	0.923
HN, n (%)	2 (5.0)	2 (5.6)	0.010†	0.685
Diabetic nephropathy, n (%)	1 (2.5)	1 (2.8)	0.010†	0.521
IgA nephropathy, n (%)	3 (7.5)	2 (5.6)	0.120†	0.903
Other, n (%)	1 (2.5)	1 (2.8)	0.010†	0.521
Primary transplantation, n (%)	40 (100)	36 (100)	–	–
HLA mismatches, mean ± SD	2.1 ± 1.3	2.2 ± 1.2	0.347*	0.729
Pretransplant PRA (%), mean ± SD	2.5 ± 1.2	2.3 ± 1.4	0.671*	0.505

*Student's t-test; †Chi-square test. –: Not applicable; CP: Constant HMP pressure; IP: Increased HMP pressure; BMI: Body mass index; GN: Glomerulonephritis; HN: Hypertensive nephrosclerosis; HLA: Human leukocyte antigen; PRA: Panel-reactive antibody; HMP: Hypothermic machine perfusion.

Table 2: Demographic and clinical characteristics of donors

Variables	CP group (n=40)	IP group (n=36)	t or χ^2	P
Age (years), mean ± SD	45.7 ± 10.4	44.9 ± 11.3	0.321*	0.749
BMI (kg/m^2), mean ± SD	23.2 ± 4.5	23.9 ± 3.7	0.736*	0.464
Cause of death, n (%)				
Craniocerebral trauma	18 (45.0)	17 (47.3)	0.040†	0.846
Cerebrovascular diseases	15 (37.5)	12 (33.3)	0.140†	0.705
Anoxic encephalopathy	4 (10.0)	4 (11.1)	0.020†	0.828
Other	3 (7.5)	3 (8.3)	0.020†	0.771
Hypertension history, n (%)	15 (37.5)	13 (36.1)	0.020†	0.900
sCr (mg/dl), mean ± SD	1.42 ± 0.25	1.38 ± 0.19	0.779*	0.439
CIT (h), mean ± SD	9.2 ± 2.4	9.3 ± 2.1	0.192*	0.848
WIT (min), mean ± SD	11.4 ± 2.6	11.6 ± 2.2	0.360*	0.720
DCD, n (%)				
Controlled	28 (70.0)	29 (80.6)	1.130†	0.120
Uncontrolled	12 (30.0)	7 (19.4)	1.130†	0.120

WIT was calculated from circulatory arrest until the start of cold perfusion. *Student's t-test; †Chi-square test. CP: Constant HMP pressure; IP: Increased HMP pressure; BMI: Body mass index; sCr: Serum creatinine; CIT: Cold ischemic time; WIT: Warm ischemic time; DCD: Donor after cardiac death; HMP: Hypothermic machine perfusion.

patient died from cardiovascular disease, one from a traffic accident, and one from pulmonary infection) groups had died. Both the allograft survival (87.5% vs. 88.9%, P = 0.845) and patient survival (92.5% vs. 91.7%, P = 0.880) rates at 1-year follow-up were similar between the two study groups [Table 3 and Figure 1]. Cox regression analysis was performed for 1-year graft failure. Owing to the low number of graft losses, we selected the following variables of interest: CP versus IP, terminal vascular resistance, donor terminal sCr levels, and warm ischemic time, which were the strongest independent risk factors for graft failure in the current study [Table 5]. In the Cox proportional hazards model, only terminal vascular resistance significantly affected the graft survival rate (hazard ratio: 2.06, 95% CI: 1.32–5.16, P = 0.032) [Table 6].

DISCUSSION

HMP of kidneys has been deemed superior to static cold storage due to improved perfusion of the microvasculature, decreased aggregation of blood components, mitigated endothelial activation, and reduced inflammatory upregulation.[14,18,25,26] Kidney graft viability and quality cannot be assessed when kidneys are stored on melting ice. In contrast, HMP enables the assessment of graft viability and quality prior to transplantation, as well as the evaluation of perfusion characteristics such as resistance and flow rate. Retrospective evidence suggests that resistance and flow rates during HMP correlate with kidney graft function.[15-17] Resistance at the end of HMP is considered an independent risk factor for the development of DGF.[15-17] Increased flow rate may be partly responsible for improved transplantation results. Furthermore, kidneys with higher resistance and lower flow rates have significantly higher discard rates. These two findings substantiate the case for increasing pressure during HMP to improve flow through the kidney. Nevertheless, this method of addressing reduced compliance in the hypothermic setting must be weighed against the risk of injury to endothelial cells secondary to shear stress that accompanies higher pressures. Of note, the vascular resistance of a kidney is a fixed factor that will only change slowly over time. Therefore, the aim of increasing pressure is not to improve the kidney's hemodynamics prior to its transplantation, but to ensure that enough fluid will overcome resistance and allow for proper perfusion of the kidney.

Table 3: Hypothermic machine perfusion of kidneys

Variables	CP group (n = 40)	IP group (n = 36)	t	P
Initial flow (ml/min)	48.3 ± 10.6	47.4 ± 7.5	0.423	0.667
Terminal flow (ml/min)	76.3 ± 12.7	85.9 ± 14.6	3.066	0.003
Initial resistance (mmHg·ml^{-1}·min^{-1})	0.66 ± 0.13	0.65 ± 0.16	0.303	0.765
Terminal resistance (mmHg·ml^{-1}·min^{-1})	0.43 ± 0.14	0.36 ± 0.12	2.327	0.023
Trap temperature (°C)	4.4 ± 0.9	4.2 ± 0.7	1.073	0.287
HMP duration (h)	9.2 ± 1.2	9.6 ± 1.9	1.109	0.279

Data were presented as mean ± SD. CP: Constant HMP pressure; IP: Increased HMP pressure; HMP: Hypothermic machine perfusion.

Table 4: Results of clinical assessments in the constant pressure and increased pressure groups

Variables	CP group (n = 40)	IP group (n = 36)	t or χ²	P
DGF, n (%)	11 (27.5)	9 (25.0)	0.060	0.805
IGF, n (%)	12 (30.0)	15 (41.7)	1.130	0.412
SGF, n (%)	17 (42.5)	12 (33.3)	0.670	0.411
sCr on day 30 (mg/dl), mean ± SD	1.47 ± 0.31	1.39 ± 0.22	1.284	0.203
Acute rejection within 1 year, n (%)	9 (22.5)	7 (19.4)	0.110	0.744
Acute rejection within 1 year among recipients with DGF, n (%)	4/11 (36.4)	3/9 (33.3)	0.020	0.742
Kidney function recovery time (days), mean ± SD	18.3 ± 9.1	16.7 ± 8.3	0.798	0.427
Kidney function recovery time among recipients with DGF (days), mean ± SD	25.4 ± 5.1	20.2 ± 4.7	2.105	0.031
DGF duration (days), mean ± SD	15.6 ± 2.4	13.2 ± 2.6	1.906	0.046
Graft survival rate at 1 year, n (%)	35 (87.5)	32 (88.9)	0.040	0.845
Patient survival rate at 1 year, n (%)	37 (92.5)	33 (91.7)	0.020	0.880

CP: Constant HMP pressure; IP: Increased HMP pressure; DGF: Delayed graft function; IGF: Immediate graft function; SGF: Slow graft function; sCr: Serum creatinine; HMP: Hypothermic machine perfusion.

Table 5: Risk factors considered in multivariable analysis of delayed graft function

Risk factors	OR	95% CI	P
Donor factors			
Age	1.21	0.71–2.19	0.370
Hypertension history	1.43	1.02–2.06	0.035
Diabetes mellitus	1.63	0.68–2.96	0.458
Hyperlipidemia	2.13	0.74–3.86	0.526
Cerebrovascular disease	1.36	1.09–1.64	0.022
Congestive heart failure	1.49	1.12–1.90	0.041
Primary COD	1.26	0.90–1.62	0.212
Terminal sCr	1.27	1.06–1.62	0.023
Perioperative factors			
WIT	3.45	1.97–6.37	0.002
IP versus CP	0.88	0.62–1.14	0.256
Terminal flow	0.79	0.52–1.06	0.059
Terminal resistance	3.12	1.76–6.09	0.012
Recipients factors			
Age	1.57	0.89–2.25	0.242
BMI	2.78	0.67–7.03	0.193
Time on dialysis	1.05	0.91–1.24	0.873
Pretransplant PRA	3.07	0.92–9.97	0.125
HLA mismatches	1.26	0.86–1.85	0.212

No donors had gout, and there were few donors with coronary artery disease. OR: Odds ratio; CI: Confidence interval; COD: Cause of death; sCr: Serum creatinine; WIT: Warm ischemic time; CP: Constant HMP pressure; IP: Increased HMP pressure; BMI: Body mass index; PRA: Panel-reactive antibody; HLA: Human leukocyte antigen; HMP: Hypothermic machine perfusion.

The present study was undertaken to determine the effects of HMP during which the initial perfusion pressure was maintained versus HMP during which pressure was increased on posttransplant outcomes of DCD kidneys in primary transplant recipients. Postoperative kidney function was judged by assessing the incidence of DGF, sCr levels at day 30, and the 1-year graft survival rate. Kidneys with IP HMP showed improved resistance and flow. Our data showed that the incidence of DGF, IGF, SGF, acute rejection, and the 1-year allograft and patient survival rates were similar between the two groups, despite the improved flow rates and resistance observed in the IP group. Overall, the kidney function recovery time and sCr levels on day 30 did not differ between the two study groups. Nevertheless, among recipients who developed DGF, the kidney function recovery time and DGF duration were improved in the IP group compared with the CP group. Multivariate analysis of DGF incidence identified the following four significant risk factors: donor hypertension history, donor terminal sCr level, warm ischemic time, and terminal vascular resistance. HMP pressure and terminal flow did not significantly influence the rate of DGF, indicating that high pressure may not actually contribute to posttransplant renal dysfunction. Thus, increased pump perfusion pressure accompanied by improved flow rate and resistance yielded acceptable graft survival and kidney function outcomes. The exact mechanisms underlying these observations need to be more precisely determined, but improved tissue perfusion may play a role in this process. Therefore, IP may allow greater utilization of marginal kidneys that show poor initial flow and perfusion
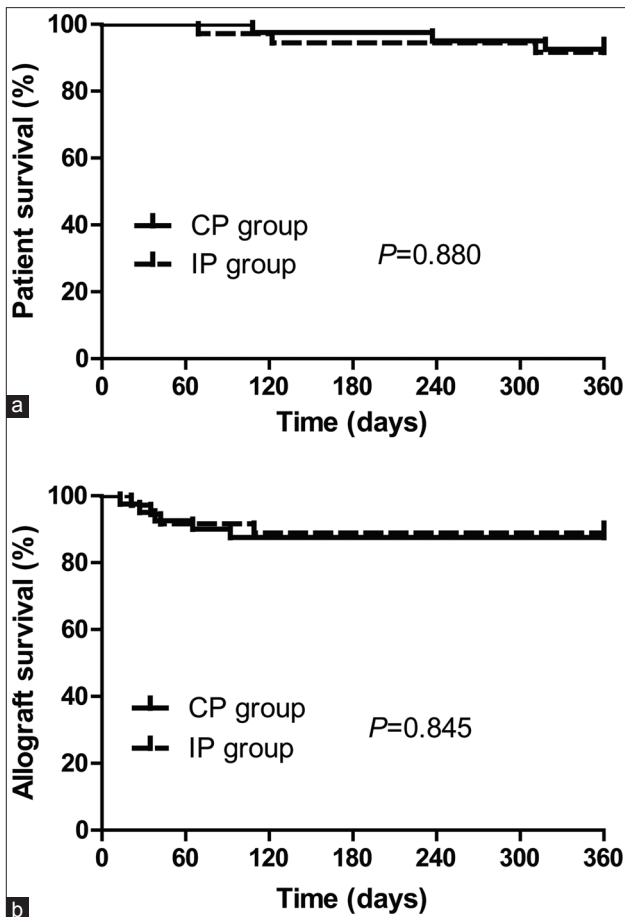
Figure 1: Allograft survival and patient survival in the constant pressure group and increased pressure group. (a) Patient survival rates at 1 year after kidney transplantation in the two groups. (b) Allograft survival rates at 1 year after kidney transplantation in the two groups. CP: Constant hypothermic machine perfusion pressure; IP: Increased hypothermic machine perfusion pressure.

Table 6: Cox regression analysis of graft failure			
Risk factors	*HR*	*95% CI*	*P*
Donor terminal sCr	1.07	0.66–1.61	0.105
WIT*	1.65	1.07–2.48	0.037
CP versus IP	0.58	0.36–1.14	0.670
Terminal resistance	2.06	1.32–5.16	0.032

*WIT was grouped into 10-min intervals, and a WIT below 10 min was used as the baseline. *HR*: Hazard ratio; *CI*: Confidence interval; sCr: Serum creatinine; WIT: Warm ischemic time; CP: Constant HMP pressure; IP: Increased HMP pressure; HMP: Hypothermic machine perfusion.

dynamics.[18,25,27] Conversely, Maathuis *et al*.[28] suggested that a pressure of 30/20 mmHg might be safer than that of 60/40 mmHg. Similarly, another study reported that during HMP, a pressure of 25 mmHg was found to be better than 30 mmHg.[29] Nevertheless, these studies were performed in a porcine kidney transplant model, and the results have not been confirmed in humans. A previous study demonstrated that pressure-mediated injury could occur in the human kidney when not optimally pumped, possibly due to suboptimal perfusion that leads to hypoxia, cell waste accumulation, and oxidative stress.[30] These mechanisms remain to be elucidated. Our data indicate that a perfusion pressure of 40 mmHg during HMP may be better in the IP group, considering the kidney function recovery time and sCr levels on day 30 among the DGF patients. Nevertheless, the HMP pressure did not affect 1-year graft survival.

The main limitation of this study is the small number of patients included. In addition, its retrospective nature limited the amount of data that could be collected from the patients' medical charts and prevented proper stratification of the kidneys. Furthermore, this was a single-center study. Importantly, the accuracy of single perfusion parameters in predicting transplant outcomes is limited, and those parameters should be used with caution.[17,21,31] Moreover, in light of the retrospective nature of the study, the quality of anastomosis could not be directly evaluated, and preoperative biopsies were not necessarily available. In addition, a possible bias existed in that the kidneys for which the perfusion pressure had to be increased were actually those with predicted poor outcomes because their vasculature already showed perfusion defects and could not be easily altered. Although this is merely a supposition, it might indicate that IP is somewhat advantageous since it enables the use of unsuitable organs for transplantation. However, this difference between the two groups may impair proper comparison, and additional studies are necessary to address this issue. Nevertheless, the need to increase perfusion pressure could be used as a prognostic factor after transplantation. Finally, there were some patients with uncontrolled DCD, which may affect transplantation outcomes,[32] but there were no significant differences between the two groups, although the proportion of uncontrolled DCD was higher in the CP group. Further studies involving a larger number of patients and longer follow-up are required to evaluate the effects of increased HMP pressure on DGF and long-term graft survival in patients receiving DCD kidneys. IP settings on expanded criteria donor kidneys should be used with caution. Biopsies and each donor's clinical data must be critically considered when a kidney displays high resistance.

In conclusion, this study showed that the flow rate through a kidney during HMP may be improved by increasing the perfusion pressure to overcome elevated vascular resistance. Therefore, for DCD organs not performing optimally under *ex vivo* hypothermic perfusion after 15 min of pumping, increasing perfusion pressure may yield similar early outcomes as those obtained with organs showing optimal perfusion parameters.

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Conflicts of interest

There are no conflicts of interest.

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适度提高低温机械灌注压力对心脏死亡器官捐献肾移植受益的临床研究

摘要

背景： 心脏死亡后捐献肾脏低温机械灌注（hypothermic machine perfusion， HMP）时的血管阻力和灌注流量与移植肾功能相关。研究报道提高灌注压力可以改善血管阻力和灌注流量，因此本研究的目的是观察适度提高HMP压力对心脏死亡器官捐献肾移植是否临床受益。

方法： 我们回顾性的分析了从2013年9月1日到2015年8月31日期间76例首次接受肾脏移植的受者的资料，这76例肾脏来自于48例心脏死亡后器官捐献的供体，并均接受了HMP保存。根据是否将HMP压力从最初的30 mmHg (1 mmHg = 0.133 kPa)提高至40 mmHg分为两组，提高灌注压力组（IP组，36例）和维持灌注压力组（CP组，40例），并采用多元logistic、Cox回归分析评估是否提高HMP压力与移植肾功能延迟恢复（delayed graft function，DGF）及移植肾功能衰竭的相关性。

结果： 1年移植物/患者存活率、DGF发生率、肾功能恢复时间和第30天血清肌酐水平两组相似，IP组HMP流量和血管阻力均有改善。在两组DGF患者中，IP组肾功能恢复时间（P=0.031）和DGF持续时间（P=0.046）均较CP组有改善。多元logistic回归分析提示供体高血压病史(*OR*: 1.43, 95% *CI*: 1.02–2.06, P=0.035)、供体获取前血肌酐水平(*OR*: 1.27, 95% *CI*: 1.06–1.62, P=0.023)、热缺血时间 (*OR*: 3.45, 95% *CI*: 1.97–6.37, P=0.002)及HMP终末阻力指数 (*OR*: 3.12, 95% *CI*: 1.76–6.09, P=0.012)均为DGF的独立危险因素. Cox回归分析提示HMP终末阻力指数(*HR*: 2.06, 95% *CI*: 1.32–5.16, P=0.032) 与移植物存活率相关.

结论： 适度增加HMP压力提高移植物灌注并不影响DGF发病率和1年移植物存活率,但能缩短DGF患者肾功能恢复时间和减少DGF持续时间。