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ORIGINAL ARTICLE

Retrospective Cohort Study

Perioperative risk factors associated with delayed graft function following deceased donor kidney transplantation: A retrospective, single center study

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Abstract

BACKGROUND

There is an abundant need to increase the availability of deceased donor kidney transplantation (DDKT) to address the high incidence of kidney failure. Challenges exist in the utilization of higher risk donor organs into what appears to be increasingly complex recipients; thus the identification of modifiable risk factors associated with poor outcomes is paramount.

AIM

To identify risk factors associated with delayed graft function (DGF).

METHODS

Consecutive adults undergoing DDKT between January 2016 and July 2017 were identified with a study population of 294 patients. The primary outcome was the occurrence of DGF.

RESULTS

The incidence of DGF was 27%. Under logistic regression, eight independent risk factors for DGF were identified including recipient body mass index ≥ 30 kg/m^2,

baseline mean arterial pressure < 110 mmHg, intraoperative phenylephrine administration, cold storage time ≥ 16 h, donation after cardiac death, donor history of coronary artery disease, donor terminal creatinine ≥ 1.9 mg/dL, and a hypothermic machine perfusion (HMP) pump resistance ≥ 0.23 mmHg/mL/min.

CONCLUSION

We delineate the association between DGF and recipient characteristics of pre-induction mean arterial pressure below 110 mmHg, metabolic syndrome, donor-specific risk factors, HMP pump parameters, and intraoperative use of phenylephrine.

Key Words: Delayed graft function; Outcome; Kidney transplant; Risk factors; Phenylephrine; Mean arterial pressure

Core Tip: There is an abundant need to increase the availability of deceased donor kidney transplantation to address the high incidence of kidney failure. Challenges exist in the utilization of higher risk donor organs into what appears to be increasingly complex recipients; thus the identification of modifiable risk factors associated with poor outcomes is paramount. We delineate the association between delayed graft function and recipient characteristics of pre-induction mean arterial pressure below 110 mmHg, metabolic syndrome, donor-specific risk factors, hypothermic machine perfusion pump parameters, and intraoperative use of phenylephrine.

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INTRODUCTION

Chronic kidney disease and end stage renal disease are leading contributors to patient morbidity, mortality, and economic burden[1,2]. Kidney transplantation is the therapy of choice, with superior survival and improved quality of life over dialysis[3,4]. Regrettably, in the United States alone nearly 5000 patients perish each year while on the wait-list due to organ shortage[5]. A common strategy to minimize the ever-increasing gap between organ supply and demand is *via* expansion of criteria for acceptable donors[6,7]. These higher-risk kidney allografts, however, frequently exhibit delayed graft function (DGF), which in turn is associated with acute rejection, chronic allograft nephropathy, shorter allograft survival, and increased costs[8-10]. A clear need exists for the identification and optimization of modifiable perioperative risk factors associated with DGF[11]. Prior studies have pointed to an association between recipients' blood pressure and DGF, but conflicted on the clinical setting in which it contributes to DGF[12-15].

The aim of this analysis is to identify risk factors associated with DGF, with a particular focus on perioperative hemodynamic factors, since these can be more readily optimized to improve graft and patient outcomes.

MATERIALS AND METHODS

After approval by the institutional review board, all consecutive adult (age ≥ 18 years) patients who underwent a deceased donor kidney transplant (DDKT) at our center between January 2016 and July 2017 were identified. Recipients of multi-organ

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allografts were excluded, and the medical records of the remaining 313 patients were retrospectively reviewed. Recipients of *en-bloc* two kidney allografts (2 cases), or for whom hypothermic machine perfusion (HMP) pump data was not available (17 cases) were subsequently excluded, resulting in a final study population of 294 patients. The requirement for informed consent was waived by the institutional review board.

All recipients' demographic, comorbidities, preoperative medications, and echocardiographic data within one year prior to transplant, as well as laboratory evaluation upon admission and intraoperative data were recorded. Donor data and kidney donor profile index (KDPI) were extracted from the United Network for Organ Sharing DonorNet® database. All donor kidneys were biopsied at our transplant center and placed on hypothermic machine perfusion (HMP) pumps using a DCM-100 Cassette (RM3 Renal Preservation Machine, Waters Instruments, Rochester, MN), and perfused with Belzer-MPS Machine Perfusion Solution (Trans-Med Corporation, Elk River, MN) at 4 °C, as previously described[16]. A HMP pump resistance upper limit index of 0.3 mmHg/mL/min is used at our center and as such no allografts transplanted in this study had a terminal resistance value above this cutoff.

Study variables definition

Cold storage time: Time from donor cross-clamp until the allograft was placed on the HMP pump[17]. Total cold ischemia time: Time from donor cross-clamp until the allograft was taken out of ice and placed on the surgical field, inclusive of time spent on the HMP pump. Total warm ischemia time: Time from when the kidney was taken out of ice until reperfusion. HMP pump parameters are reported as terminal values at the time the kidney was removed from pump. Blood pressures measured at baseline (i.e before induction of general anesthesia), 5 min and 30 min post-reperfusion, and immediately upon arrival to either the post-anesthesia care unit (PACU) or the intensive care unit were extracted from the anesthesia record. Hypotension was defined as a decrease in mean arterial pressure (MAP) of ≥ 30 mmHg from baseline[18]. Diagnosis of postoperative pulmonary edema was based on radiographic evidence of pulmonary edema as determined by a board-certified radiologist coupled with clinical symptomatology requiring supplemental oxygen or mechanical ventilation. A postoperative adverse cardiac event was defined as the occurrence of myocardial infarction, new-onset atrial or ventricular arrhythmia, or cardiac arrest within the first postoperative month. Perioperative surgical complications were evaluated using the Clavien-Dindo classification grading system[19]. Occurrence of DGF, the primary study outcome, was defined as the need for dialysis within seven days after transplantation as determined by the attending transplant nephrologist[20,21]. Graft function was evaluated at one week and six months post-transplant using the estimated glomerular filtration rate (eGFR) by the Chronic Kidney Disease Epidemiology Collaboration equation[22]. Graft failure was defined as either a permanent need for dialysis or death with a functioning graft and was evaluated from the time of transplant until one year after transplantation[16].

Intraoperative protocol

All patients underwent ABO-compatible DDKTs under general endotracheal anesthesia with radial arterial line for hemodynamic monitoring placed after induction of general anesthesia. Our local protocol targeted a MAP ≥ 100 mmHg starting at the time of reperfusion of allograft until arrival to the postoperative unit. This hemodynamic goal was primarily achieved with crystalloid and/or colloid, reserving ephedrine or phenylephrine bolus administration for severe or refractory hypotension (MAP ≤ 65 mmHg and/or decrease in MAP of ≥ 30 mmHg from baseline) at the discretion of the anesthesia provider. Dopamine infusion was always used whenever prolonged vasopressor support was indicated. As per local protocol, all recipients received intravenous (iv) furosemide 50 mg and mannitol 12.5 g 10 min prior to, as well as 10 min after reperfusion. In recipients of a high-risk allograft, as deemed by the transplant surgeon, a furosemide infusion of 20 mg/h was initiated shortly after the second 50mg bolus dose and continued in the postoperative unit. All patients received induction immunosuppression with three immunosuppressive agents each: iv basiliximab (20 mg, 2 doses), rabbit antithymocyte globulin (1 mg/kg daily, 3 doses), and methylprednisolone (500 mg, 3 doses)[23].

Intraoperative iv heparin was selectively administered to recipients deemed high risk for graft thrombosis by the transplant surgeon. Accordingly, seven patients received intraoperative IV bolus heparin with doses ranging between 1000-3000 units. Routine postoperative thromboprophylaxis consisted of heparin 5000 units subcutaneously twice daily. Surgical drains and ureteral stents were placed at surgeon discretion and not routinely utilized.

Statistical analysis

Categorical variables were expressed as percentages (%) and differences between the groups were assessed with chi-square or Fisher's exact test when appropriate. Continuous variables were expressed as median and interquartile ranges (25%-75%) and differences between the groups assessed with Wilcoxon rank-sum test. A bivariate analysis was performed to compare the groups with and without DGF regarding recipients', donors' and HMP pump variables, including recipient BMI, baseline MAP, donor terminal creatinine, cold ischemia time, cold storage time, and HMP pump flow rate and resistance. We subsequently determined the cut-off values for statistically significant continuous variables, using receiver operating characteristic analysis and Youden index[24]. A logistic regression model was then built for the cohort using a stepwise personality with a stopping rule P-value threshold of 0.10 for probability to enter or leave, conducted in a mixed direction, was performed to identify recipient, donor, HMP pump, and intraoperative predictors statistically associated with DGF. Clinically significant factors from Tables 1-3 were included as covariates to adjust for cofounders. Odds ratios (OR) and 95%CI were calculated. C-index was used to calculate the strength of the associations. The bootstrap method for 2500 iterations yielded bias-corrected C-index and 95%CI for the regression coefficients of the model[25]. Misclassification rates calculated the proportion of observations allocated to the incorrect group and represent the false-positive rate. Predictor's profiler and predictor's importance was explored for main and total effect. Main effect is the importance index that reflects the relative contribution of that factor alone and total effect is the importance index that reflects the relative contribution of that factor both alone and in combination with other factors[26]. Cochran-Armitage trend test was used to assess the association between a cut-off value of baseline MAP and intraoperative phenylephrine[27]. The statistical software used for all study calculations was JMP Pro 14.0 (SAS Institute Inc., Cary, NC, United States).

RESULTS

The incidence of the primary outcome DGF was 27% (79/294).

Preoperative

A descriptive analysis of preoperative clinical characteristics, stratified by DGF *vs* non-DGF, is shown in Table 1. Comorbidities associated with metabolic syndrome were more common in recipients with DGF when compared to non-DGF, including obesity with BMI ≥ 30 kg/m^2 [47% (37/79) *vs* 28% (60/215) respectively, OR 2.3, 95%CI: 1.335-3.878, χ^2 = 9.4, P = 0.002], diabetes [53% (42/79) *vs* 31% (66/215) respectively, OR 2.6, 95%CI: 1.510-4.347, χ^2 = 12.5, P = 0.001], dyslipidemia [72% (57/79) *vs* 47% (102/215) respectively, OR 2.9, 95%CI: 1.639-5.025, χ^2 = 14.2, P = 0.001], and coronary artery disease (CAD) [35% (28/79) *vs* 18% (39/215) respectively, OR 2.5, 95%CI: 1.391-4.411, χ^2 = 9.8, P = 0.002]. Dialysis-associated hypotension requiring oral vasopressor therapy with midodrine was recorded in 3% (8/294) of recipients with similar incidences in DGF and non-DGF groups [3% (2/79) *vs* 3% (6/215) respectively, OR 0.90, 95%CI: 0.178-4.578, χ^2 = 0.02, P = 0.90].

Intraoperative fluid and hemodynamic management

A descriptive analysis of intraoperative clinical characteristics, stratified by DGF *vs* non-DGF, is presented in Table 2. Administered crystalloids (type and volume), albumin, and blood products were similar in recipients with or without DGF. A clinically insignificant increase in estimated blood loss was observed in DGF recipients [150 *vs* 100 mL in non-DGF, χ^2 = 6.5; P = 0.01].

In a majority of recipients (70%, 206/294) the baseline MAP was ≥ 100 mmHg. Both baseline and first postoperative MAPs were slightly lower in the DGF group compared to non-DGF [107 mmHg *vs* 112 mmHg respectively, χ^2 = 3.1, P = 0.08 and 102 *vs* 105 respectively, χ^2 = 2.9, P = 0.09]. A cut-off baseline MAP < 110 mmHg was statistically associated with DGF (χ^2 = 4.6, P = 0.02; OR 1.8, 95%CI: 1.049-3.047]. MAPs at 5- and 30-min post-reperfusion were similar in DGF and non-DGF recipients. The targeted post-reperfusion MAP (≥ 100 mmHg) was achieved in only nearly 25% of recipients at 5 min (74/294) and 30 min (75/294) post reperfusion, and in 60% of patients (177/294) on arrival to the postoperative unit (Table 2), but similarly in recipients with or without DGF. Likewise, incidences of hypotension, with a decrease from baseline values in MAP ≥ 30 mmHg, at 5-min [24% (18/79) *vs* 26% (56/215) respectively, OR 0.83, 95%CI: 0.453-1.528, χ^2 = 0.35, P = 0.55] and on arrival to the postoperative unit

Table 1 Preoperative characteristics of recipients with and without delayed graft function

	All patients	DGF	No DGF	*P* value
	n = 294	*n* = 79	*n* = 215	
Transplant, yr, *n* (%)				0.18
2016	175 (60)	52 (66)	123 (57)	
2017	119 (40)	27 (34)	92 (43)	
Age, yr	56 (44-64)	58 (50-63)	54 (41-64)	0.06
Male, *n* (%)	186 (63)	50 (63)	136 (63)	0.99
Race, *n* (%)				0.35
Caucasian	48 (16)	8 (10)	40 (19)	
Afro-American	153 (52)	45 (57)	108 (50)	
Hispanic	88 (30)	25 (32)	63 (29)	
Other	5 (2)	1 (1)	4 (2)	
BMI, kg/m^2	28 (24-32)	29 (26-35)	27 (24-30)	0.001[a]
BMI ≥ 30 kg/m^2	97 (33)	37 (47)	60 (28)	0.002[a]
Redo transplant, *n* (%)	26 (8)	4 (5)	22 (10)	0.17
Dialysis type, *n* (%)				0.26
Peritoneal	24 (8)	6 (8)	18 (8)	
Hemodialysis	263 (90)	73 (92)	190 (88)	
Pre-dialysis	7 (2)	0 (0)	7 (3)	
Duration of dialysis, mo	67.4 (29.1-88.7)	67.4 (52.5-92.9)	67.1 (46.6-87.2)	0.37
Preoperative baseline laboratory				
WBC, × 10^3/μL	6.6 (5.5-8.2)	6.8 (5.7-8.5)	6.6 (5.4-8.1)	0.22
Hgb, g/dL	11.1 (10.2-12.1)	11.1 (10.2-12.9)	11.2 (10.1-12.2)	0.66
Hct, %	34.5 (31.0-37.6)	34.7 (31.2-37.0)	34.5 (30.9-37.8)	0.97
K^+, mmol/L	4.7 (4.3-5.2)	4.9 (4.4-5.4)	4.7 (4.3-5.1)	0.05
$HCO3^-$, mmol/L	26 (23-29)	26 (23-28)	26 (23-29)	0.36
Na^+, mmol/L	140 (138-142)	140 (138-143)	140 (138-142)	0.25
Creatinine, mg/dL	8.9 (6.7-11.2)	9.11 (7.1-11.1)	8.9 (6.7-11.2)	0.88
Medical history, *n* (%)				
Hypertension	285 (97)	77 (97)	208 (97)	0.75
Diabetes	108 (37)	42 (53)	66 (31)	0.001[a]
Dyslipidemia	159 (54)	57 (72)	102 (47)	0.001[a]
CAD	67 (23)	28 (35)	39 (18)	0.002[a]
Smoking	79 (27)	19 (24)	60 (28)	0.51
Preoperative medications, *n* (%)				
ACEi/ARB	99 (34)	19 (24)	80 (37)	0.03[a]
CC-blocker	134 (46)	35 (44)	99 (46)	0.79
Beta-blocker	168 (57)	47 (59)	121 (56)	0.62
Diuretic	33 (11)	12 (15)	21 (10)	0.19
Statin	107 (36)	43 (54)	64 (30)	0.001[a]
Aspirin	94 (32)	35 (44)	59 (27)	0.006[a]
Clopidogrel[1]	22 (7)	11 (14)	11 (5)	0.01[a]

Midodrine	8 (3)	2 (3)	6 (3)	0.9
Echocardiography				
LV EF < 50%, *n* (%)	8 (3)	3 (4)	5 (2)	0.49
DD Grade 2 or 3, *n* (%)	44 (15)	14 (18)	30 (14)	0.42
LVH, *n* (%)	183 (62)	55 (70)	128 (60)	0.11
RVSP, mmHg	28 (23-34)	27 (22-34)	28 (23-33)	0.91

Values are presented as medians with 25th and 75th percentiles, or as numbers (*n*) and percentages %.

[a]*P* < 0.05 denotes statistical significance.

[1]11 patients on both aspirin and clopidogrel.

BMI: Body mass index; DGF: Delayed graft function; WBC: White blood cell count; Hgb: Hemoglobin; Hct: Hematocrit; K^+: Potassium; NaHCO3: Sodium bicarbonate; Na^+: Sodium; CAD: Coronary artery disease; ACEi: Angiotensin-converting enzyme inhibitor; ARB: Angiotensin II receptor blocker; CC-blocker: Calcium channel blocker; LVEF: Left ventricular ejection fraction; DD: Diastolic dysfunction; LVH: Left ventricular hypertrophy; RVSP: Right ventricular systolic pressure.

[9% (7/79) *vs* 9% (20/215) respectively, OR 0.94, 95%CI: 0.383-2.324, χ^2 = 0.02, *P* = 0.90] were similar between DGF and non-DGF recipients. However, hypotension at 30 min post-reperfusion occurred more commonly in the non-DGF group 27% (57/215) *vs* 16% (13/79) in DGF group, but did not reach statistical significance (χ^2 = 3.2; *P* = 0.07).

Phenylephrine boluses were administered to 22% (64/294) of the cohort, and were statistically associated with DGF, insofar as 32% (25/79) of recipients with DGF received phenylephrine vs 18% (39/215) in recipients who did not develop DGF (OR 2.1, 95%CI: 1.161-3.759, χ^2 = 6.2; *P* = 0.01). An association between baseline MAP < 110 mmHg and intraoperative phenylephrine therapy was found in the Cochran-Armitage trend test (*Z* = 2.33, *P* = 0.02). Additionally, compared with untreated recipients, phenylephrine-treated recipients had lower MAPs at 5-min and 30-min post-reperfusion, and upon arrival to the PACU [103 *vs* 112 mmHg, χ^2 = 7.9, *P* = 0.005; 87 mmHg *vs* 91 mmHg, χ^2 = 4.1, *P* = 0.04; 87 mmHg *vs* 92 mmHg, χ^2 = 8.2, *P* = 0.01; and 97 mmHg *vs* 106 mmHg, χ^2 = 15.5; *P* < 0.001, respectively]. In 70 recipients (24%), the MAP 30 min post reperfusion was lower than baseline by more than 30 mmHg; 16 and 54 thereof were treated and not treated with phenylephrine, respectively. DGF occurred in 7 of the 16 (44%) and in 6 of the 54 (11%), respectively [OR 6.2, 95%CI: 1.691-22.882; χ^2 =8.7; *P* = 0.0032]. Of the 224 recipient without a similar decrease from baseline in MAP measured 30 min post reperfusion, 48 and 176 were treated and not treated with phenylephrine, respectively; DGF occurred in 18 of the 48 (38%) and 48 of the 176 (27%), respectively [OR 1.6, 95%CI: 0.810-3.109; χ^2 =1.8; *P* = 0.18].

Donor data

A descriptive analysis of donor and HMP pump data for recipients who did and did not develop DGF is presented in Table 3. Nearly half (46%) of kidney allografts used in our center were imports. A higher KDPI was recorded for imported *vs* local allografts [median 69% (42-86) *vs* 47% (23-68) respectively, χ^2 = 22, *P* = 0.001]. Cold ischemia and cold storage times were significantly longer in DGF *vs* non-DGF allografts, [30.6 h *vs* 26.4 h (χ^2 = 6.9; *P* =0.009); and 18.4 h *vs* 9.6 h (χ^2 = 9.9; *P* =0.002), respectively]. Similarly, HMP flows < 150 mL/min and resistance ≥ 0.23 mmHg/mL/min were recorded for allografts that developed DGF, see Table 3.

Postoperative and outcome data

A descriptive analysis of postoperative characteristics in DGF and non-DGF recipients is presented in Table 4. Based on the Clavien-Dindo classification, the overall surgical complication rate in the first month postoperatively was 19% (56/294), with a higher rate in recipients with DGF than in non-DGF recipients [32% (25/79) *vs* 14% (31/215) respectively, OR 2.7, 95%CI: 1.496-5.047; χ^2 = 11; *P* = 0.002]. Moreover, compared to non-DGF allografts, DGF was associated with significantly lower eGFR after six postoperative months, and higher incidence of 1-year graft failure [50.6 mL/min *vs* 73.3 mL/min (χ^2 = 31.8; *P* = 0.001), and 10% *vs* 1% (OR 8, 95%CI: 2.056-30.832, χ^2 = 12.2; *P* = 0.002), respectively]. The overall incidence of allograft failure at one year was 4% (11/294). Etiologies of graft failure were: (4) Rejection, (4) thrombosis within 1st post-transplant week, (1) chronic allograft nephropathy, and (2) deaths with a functioning graft (1 sepsis, and 1 cardiac event).

Table 2 Intraoperative characteristics for recipients with and without delayed graft function

	All patients	DGF	No DGF	*P* value
	n = 294	*n* = 79	*n* = 215	
Surgery time, h	2.7 (2.0-3.9)	2.5 (1.8-4.4)	2.8 (2.2-3.9)	0.03[a]
Warm ischemia time, min	29 (24-36)	27 (23-34)	29 (24-36)	0.08
Fluid and electrolytes				
Crystalloid, L	2.0 (1.5-2.5)	2.0 (1.5-2.2)	2.0 (1.5-2.5)	0.97
Plasmalyte/Isolyte, *n* (%)	94 (32)	23 (29)	71 (33)	0.82
Normal saline, *n* (%)	161 (55)	45 (57)	116 (54)	
Combined, *n* (%)	39 (13)	11 (14)	28 (13)	
Weight based crystalloid (mL/kg)	24 (19-32)	22 (18-31)	25 (19-33)	0.11
Albumin, grams	25 (12.5-50)	25 (25-50)	25 (12.5-50)	0.66
Packed red blood cells, *n* (%)				0.46
None	224 (76)	60 (76)	164 (76)	
1 unit	39 (13)	11 (14)	28 (13)	
2 units	25 (9)	8 (10)	17 (8)	
3+ units	6 (2)	0 (0)	6 (3)	
Fresh frozen plasma, *n* (%)				0.38
None	287 (98)	79 (100)	208 (97)	
1 unit	2 (1)	0 (0)	2 (1)	
2+ units	5 (2)	0 (0)	5 (2)	
Platelets, *n* (%)				0.58
None	290 (99)	79 (100)	211 (98)	
1 unit	4 (1)	0 (0)	4 (2)	
Estimated blood loss, mL	100 (95-200)	150 (100-300)	100 (50-200)	0.01[a]
NaHCO3, mEq	50 (50-112.5)	50 (50-100)	50 (50-150)	0.76
$CaCl_2$, *n* (%)	210 71)	59 (75)	151 (70)	0.56
$CaCl_2$, g	1 (0.75-1.5)	1 (0.75-1.25)	1 (0.75-1.5)	0.65
Furosemide infusion, *n* (%)	192 (65)	44 (56)	148 (69)	0.04[a]
$NaHCO_3$, *n* (%)	54 (18)	11 (14)	43 (20)	0.31
Urine output, mL	75 (15-200)	28 (5-80)	100 (20-250)	< 0.0001[a]
Hemodynamics and inotropes				
MAP at baseline, mmHg	109 (96-122)	107 (95-118)	112 (96-123)	0.08
Baseline MAP < 110 mmHg, *n* (%)	159 (54)	51 (65)	108 (50)	0.02[a]
MAP 5 min post-reperfusion, mmHg	90 (81-100)	91 (79-97)	90 (82-100)	0.45
5 min post-reperfusion MAP < 100 mmHg, *n* (%)	220 (75)	61 (77)	159 (74)	0.61
Drop in MAP ≥ 30 mmHg from baseline -5 min post-reperfusion, *n* (%)	74 (25)	18 (24)	56 (26)	0.55
MAP 30 min post-reperfusion, mmHg	91 (82-100)	92 (82-101)	91 (83-99)	0.85
30 min post-reperfusion MAP < 100 mmHg, *n* (%)	218 (74)	54 (68)	164 (77)	0.15
Drop in MAP ≥ 30 mmHg from baseline -30 min post-reperfusion, *n* (%)	70 (24)	13 (16)	57 (27)	0.07
MAP 1st post-operative, mmHg	104 (95-113)	102 (92-110)	105 (96-113)	0.09
1st post-operative MAP < 100 mmHg, *n* (%)	117 (40)	35 (44)	82 (38)	0.34
Drop in MAP ≥ 30 mmHg from baseline -1st post-operative, *n* (%)	27 (9)	7 (9)	20 (9)	0.9

Dopamine, *n* (%)	5 (2)	2 (3)	3 (1)	0.61
Ephedrine, *n* (%)	74 (25)	25 (32)	49 (23)	0.12
Ephedrine dose, mg	10 (5-20)	10 (5-20)	10 (5-18)	0.62
Phenylephrine, *n* (%)	64 (22)	25 (32)	39 (18)	0.01[a]
Phenylephrine dose, mcg	200 (100-400)	200 (125-400)	200 (100-400)	0.64
Phenylephrine timing:				
None, *n* (%)	230 (78)	54 (68)	176 (82)	0.06
Before reperfusion, *n* (%)	39 (14)	14 (18)	25 (12)	
After reperfusion, *n* (%)	10 (3)	4 (5)	6 (3)	
Both before and after, *n* (%)	15 (5)	7 (9)	8 (4)	
Phenylephrine and Ephedrine, *n* (%)	37 (13)	16 (20)	21 (10)	0.02[a]

Values are presented as medians with 25th and 75th percentiles, or as numbers (*n*) and percentages %.
[a]*P* < 0.05 denotes statistical significance.
DGF: Delayed graft function; MAP: Mean arterial blood pressure; NaHCO3: Sodium bicarbonate; $CaCl_2$: Calcium chloride; OR: Operating room.

Employing logistic regression, eight risk factors for DGF were identified (see Table 5): Recipient BMI ≥ 30 kg/m^2; Baseline MAP < 110 mmHg, intraoperative phenylephrine administration; Cold storage time ≥ 16 h; Donation after cardiac death, donor history of CAD, donor terminal creatinine ≥ 1.9 mg/dL, and HMP pump resistance ≥ 0.23 mmHg/mL/min. Supplementary Table 1 delineates the eight predictors in order of importance. The whole model was statistically significant in its entirety ($\chi^2 = 87$, $P = 0.001$), and a C-index of 0.83 was calculated for these risk factors with a bias-corrected C-index of 0.84 (95%CI: 0.76-0.88). The model's calculated misclassification rate of 19% reflects its ability to accurately predict DGF in 81 of 100 recipients.

DISCUSSION

Higher-risk donor allografts provide a way to increase the deceased-donor kidney transplant pool, but have been associated with DGF. In our cohort, the incidence of DGF was 27%, which is consistent with the previously reported incidence[13,28-30]. Optimization of modifiable perioperative risk factors for the development of DGF would allow for improved transplantation outcomes, particularly improved early graft function, without shrinking the donor pool. The important role of intraoperative renal blood flow on early postoperative renal function has been known since the 1970's[31,32], and intraoperative hemodynamic variables are the focus of several recent outcome studies[12-15].

A novel finding of this study is the identification of pre-induction MAP < 110 mmHg as an independent risk factor for the development of DGF. This observation underscores the need of the newly grafted kidney for optimal perfusion pressure that is higher than the traditional normal[33]. A complex interaction between donor's and recipient's comorbidities, pre-procurement ischemia, procurement and organ storage conditions, along with peri-transplant factors result in such a unique perfusion requirement of the allograft[10]. Suboptimal blood pressure has previously been explored as a potential risk factor in the development of DGF. Thomas *et al*[13] reported that half of the patients in their study with a post-reperfusion systolic BP of less than 120 mmHg experienced DGF. More recent data showed that patients with a MAP of < 80 mmHg at the time of reperfusion were 2.4 times more likely to develop DGF[12].

The optimal intraoperative hemodynamic management of recipients of renal allografts remains controversial. Since several studies reported a reduced incidence of DGF with fluid loading[14,34,35], in this study we carefully evaluated outcomes in relation to crystalloid volume, weight-based crystalloid administration, crystalloid type, colloid volume, and colloid type. Our finding of a lack of an association between fluids administered and DGF is in accord with others[12,36,37], and a recent multicenter study[38].

Vasopressors may be indicated when volume loading is insufficient to obtain optimal allograft perfusion. Reported outcomes of perioperative vasopressor use in

Table 3 Donor and hypothermic machine perfusion pump characteristics for recipients with and without delayed graft function

	All patients	DGF	No DGF	*P* value
	n = 294	*n* = 79	*n* = 215	
Donor characteristics				
Donor kidney				0.35
Left, *n* (%)	136 (46%)	33 (42%)	103 (48%)	
Right, *n* (%)	158 (54%)	46 (58%)	112 (52%)	
Donor location				0.001[a]
Local, *n* (%)	158 (54%)	27 (34%)	131 (61%)	
Import, *n* (%)	136 (46%)	52(66%)	84 (39%)	
Kidney donor profile index, %	53 (33-81)	61 (40-85)	49 (28-75)	0.006[a]
Donor age, yr	44 (32-56)	49 (36-56)	42 (30-55)	0.04[a]
Donor body mass index, kg/m^2	27 (23-31)	28 (25-33)	26 (23-31)	0.009[a]
Donation after cardiac death, *n* (%)	50 (17%)	23 (29%)	27 (13%)	0.001[a]
Donor cause of death				0.6
Anoxia, *n* (%)	119 (40%)	31 (39%)	88 (41%)	
Head trauma, *n* (%)	76 (26%)	18 (23%)	58 (27%)	
Stroke, *n* (%)	99 (34%)	30 (38%)	69 (32%)	
Donor cardiac arrest, *n* (%)	141 (48%)	40 (51%)	101 (47%)	0.58
Donor medical history				
Hypertension, *n* (%)	104 (35%)	32 (41%)	72 (33%)	0.28
Diabetes, *n* (%)	34 (12%)	12 (15%)	22 (10%)	0.24
Coronary artery disease, *n* (%)	27 (9%)	16 (20%)	11 (5%)	0.001[a]
Smoking, *n* (%)	70 (24%)	20 (25%)	50 (23%)	0.73
Heavy alcohol use, *n* (%)	65 (22%)	13 (16%)	52 (24%)	0.15
Admit creatinine, mg/dL	1.1 (0.9-1.4)	1.1 (0.9-1.5)	1.1 (0.9-1.30)	0.2
Terminal creatinine, mg/dL	1.0 (0.7-1.6)	1.3 (0.81-2.8)	0.9 (0.7-1.4)	0.001[a]
Terminal creatinine ≥ 1.9 mg/dL	63 (21%)	31 (39%)	32 (15%)	0.001[a]
Donor Biopsy: % glomerulosclerosis	3.9 (0-8.3)	4.6 (1.7-10)	3.4 (0-7.6)	0.14
HMP pump characteristics				
Cold ischemia time	28.5 (21.5-34.5)	30.6 (25.8-36.4)	26.4 (21.2-33.8)	0.009[a]
Cold ischemia time ≥ 26 h	172 (59%)	58 (73%)	114 (53%)	0.002[a]
Cold storage time, h	10.6 (6.8-20.6)	18.4 (7.1-24.7)	9.6 (6.8-18.9)	0.002[a]
Cold storage duration ≥ 16 h	120 (41%)	46 (58%)	74 (34%)	0.001[a]
Total pump time, h	13.3 (8.4-19.2)	13.1 (8.2-18.9)	13.4 (8.4-19.7)	0.37
Final pump parameters				
Flow, mL/min	141 (123-156)	127 (117-148)	142 (126-159)	0.001[a]
Resistance, mmHg/mL/min	0.20 (0.15-0.25)	0.24 (0.16-0.29)	0.19 (0.15-0.24)	0.001[a]
Systolic pressure, mmHg	34 (29-40)	35 (30-40)	33 (27-39)	0.009[a]
Diastolic pressure, mmHg	24 (18-29)	26 (19-30)	23 (18-29)	0.09
Pump flow < 150 mL/min	190 (65%)	65 (82%)	125 (58%)	0.001[a]
Pump resistance ≥ 0.23 mmHg/mL/min	115 (39%)	47 (59%)	68 (32%)	0.001[a]

Values are presented as medians with 25th and 75th percentiles, or as numbers (*n*) and percentages (%).
[a]*P* < 0.05 denotes significance.
DGF: Delayed graft function; HMP: Hypothermic machine perfusion.

Table 4 Postoperative characteristics for recipients with and without delayed graft function

	All patients	DGF	No DGF	*P* value
	n = 294	*n* = 79	*n* = 215	
Post-operative location, *n* (%)				0.95
PACU	230 (78)	62 (78)	168 (78)	
ICU	64 (22)	17 (22)	47 (22)	
Extubation in OR	282 (96)	74 (94)	208 (97)	0.24
Reintubation, *n* (%)				
Within 48 h	4 (1)	3 (4)	1 (0.5)	0.06
Within 1 wk	6 (2)	4 (5)	2 (1)	0.05
Pulmonary edema, *n* (%)				
Within 48 h	11 (4)	5 (6)	6 (3)	0.16
Within 1 wk	13 (4)	6 (8)	7 (3)	0.11
Adverse cardiac events, *n* (%)				
Within 48 h	10 (3)	2 (3)	8 (4)	0.62
Within 1 wk	15 (5)	3 (4)	12 (6)	0.54
Within 1 mo	17 (6)	4 (5)	13 (6)	0.1
Clavien-Dindo at 1 mo, *n* (%)[1]				
None	238 (81)	54 (68)	184 (86)	0.002[a]
Grade I	4 (1)	0 (0)	4 (2)	
Grade II	14 (5)	6 (8)	8 (4)	
Grade IIIa	19 (6)	11 (14)	8 (4)	
Grade IIIb	13 (4)	4 (5)	9 (4)	
Grade IVa	4 (1)	3 (4)	1 (0.5)	
Grade IVb	1 (1)	1 (1)	0 (0)	
Grade V	1 (1)	0 (0)	1 (0.5)	
Total complications	56 (19)	25 (32)	31 (14)	
Length of stay, d	6 (5-8)	8 (6-12)	6 (5-7)	0.001[a]
eGFR, 6 mo, mL/min	65.3 (48.4-81.6)	50.6 (36.2-71.0)	73.3 (58.6-89.5)	0.001[a]
eGFR < 60 mL/min at 6 mo, *n* (%)	120 (41)	51 (65)	69 (32)	0.001[a]
Graft survival at 1 yr, *n* (%)[2]	283 (96%)	71 (90)	212 (99)	0.002[a]
Patient survival at 1 yr, *n* (%)	292 (99)	79 (100)	213 (99)	0.34

Values are presented as medians with 25th and 75th percentiles, or as numbers (*n*) and percentages %.
[a]*P* < 0.05 denotes significance.
[1]Includes ultrasound evidence of 19 perinephric fluid collections not requiring intervention, and 32 perinephric fluid collections with intervention.
[2]4 graft failure attributed to thrombosis were due to technical difficulty: two allografts had single renal arteries and two allografts had two renal arteries, only one of which underwent arterial reconstruction in which the inferior portal artery was connected to the vein in a side-to-side anastomosis.
PACU: Post-anesthesia care unit; ICU: Intensive care unit; BP: Blood pressure; eGFR: Estimated glomerular filtration rate.

kidney transplant are incongruous. Day *et al*[39] suggested that postoperative phenylephrine administration was associated with the development of DGF, but was not implicated in allograft function by the time of hospital discharge. A recent multicenter study identified intraoperative ephedrine use, but not phenylephrine, as an independent predictor for the development of DGF[38]. These studies, however, did not assess whether the association between vasopressor use and DGF is due to an undesirable effect of the vasopressor on the outcome, or if vasopressor use solely serves as a surrogate of suboptimal perfusion and/or volume status. In the current study, we identified the use of phenylephrine intraoperatively, but not ephedrine, as an independent risk factor for the development of DGF. Further, we performed subgroup analyses to evaluate the hemodynamic and fluid resuscitation of phenylephrine-treated and untreated recipients (Supplementary Table 2). There were no statistically significant differences in terms of volume of crystalloid administered between recipients treated and not treated with phenylephrine. Phenylephrine, however, appears to be associated with an increase in DGF in all recipients, particularly in recipients whose MAP 30 min post-reperfusion was lower than baseline by more than 30 mmHg (OR of 6.2 and 1.6, with and without similar post reperfusion hypotension, respectively). Even so, it's unlikely that phenylephrine-induced vasoconstriction is the culprit[40], since the effect of a bolus dose is brief and the phenylephrine was administered before reperfusion in more than half of the recipients (Supplementary Table 2). Plausibly, intraoperative phenylephrine use is a surrogate of an unmeasured hemodynamic variable, *e.g.* postoperative allograft perfusion[12,13], or another clinical parameter that influences the outcome.

This study's non-modifiable predictors of DGF (Table 5) are consistent with previously reported risk factors[7,8,17,41-46]. Of note, we found over a 5-fold increase in incidence of DGF in allografts recovered from donors with a history of CAD. This study finding of poorer transplantation outcomes in recipients with DGF, such as postoperative reintubation, increased length of stay, and reduced graft function at 6 mo (Table 4), is in agreement with previous reports[9,47]. The association of DGF with reduced graft and recipient survival is contentious; as such, our findings of an association with reduced 1-year graft survival, but not with 1-year recipient survival (Table 4) are in accord with some but not all previous studies[9,47].

The limitations of this study include: (1) Its retrospective single transplant center nature and as such the results may not be readily extrapolated to other centers with diverse practices; (2) The timing of the most recent pre-transplant dialysis was not available; (3) The hemodynamic picture of the entire perioperative period was not captured; most importantly, the postoperative period was not assessed beyond the first set of vitals upon arrival to the post-anesthesia unit; (4) The study sample size was relatively small therefore limiting the possibility of separate analysis of outcome variables other than DGF, such as graft failure, which only occurred in 3.7% (11/294) of the population; and (5) Variations in individual patient adherence to immunosuppression regimens was not captured but may have contributed to graft outcomes.

CONCLUSION

In conclusion, this study identifies a baseline mean arterial pressure less than 110 mmHg and intraoperative phenylephrine therapy as predictive of DGF along with reaffirming other previously well-established risk factors. Further studies are needed to explore means to improve outcomes of recipients with suboptimal baseline or intraoperative blood pressure.

Table 5 Perioperative predictors associated with delayed graft function

	OR	95%CI	*P* value
Preoperative recipient risk factor			
Recipient BMI ≥ 30 kg/m^2	3.8	1.947-7.548	0.0001[a]
Intraoperative recipient risk factor			
Baseline MAP < 110 mmHg	2.2	1.098-4.326	0.0260[a]
Phenylephrine usage	2.2	1.040-4.820	0.0392[a]
Donor risk factors			
Cold storage time ≥ 16 h	2.8	1.378-5.666	0.0044[a]
Donation after cardiac death	4.4	1.872-10.225	0.0007[a]
Donor with history of CAD	5.8	2.133-16.033	0.0006[a]
Terminal creatinine ≥ 1.9 mg/dL	4.3	2.041-8.855	0.0001[a]
HMP pump risk factor			
Resistance ≥ 0.23 mmHg/mL/min	2.2	1.132-4.307	0.0201[a]

[a]*P* < 0.05 denotes significance.

OR: Odds ratio; BMI: Body mass index; MAP: Mean arterial pressure; CAD: Coronary artery disease; HMP: Hypothermic machine perfusion pump.

ARTICLE HIGHLIGHTS

Research background

There is a profound need to increase the availability of deceased donor kidney transplantation (DDKT) to address the high incidence of kidney failure. However, challenges exist in the utilization of higher risk donor organs into what appears to be increasingly complex recipients; thus the identification of modifiable risk factors associated with poor outcomes is paramount.

Research motivation

Higher-risk kidney allografts more frequently exhibit delayed graft function (DGF), which has previously been associated with adverse outcomes such as acute rejection, chronic allograft nephropathy, shorter allograft survival, and increased costs. Furthermore, prior studies have pointed to an association between recipients' blood pressure and the occurrence of DGF but have conflicted on the clinical setting and unique patient characteristics that may predispose to it.

Research objectives

A clear need exists for the identification and optimization of modifiable perioperative risk factors associated with DGF. We aim to identify risk factors associated with DGF, with a particular focus on perioperative hemodynamic factors, since these can be more readily optimized to improve graft and patient outcomes.

Research methods

Consecutive adults undergoing DDKT between January 2016 and July 2017 were identified with a study population of 294 patients. All donor data and recipients' demographic, comorbidities, preoperative medications, and echocardiographic data within one year prior to transplant, as well as laboratory evaluation upon admission and intraoperative data were recorded. The primary outcome was the occurrence of DGF.

Research results

The incidence of DGF was 27%. Under logistic regression, eight independent risk factors for DGF were identified including recipient body mass index ≥ 30 kg/m^2, baseline mean arterial pressure < 110 mmHg, intraoperative phenylephrine administration, cold storage time ≥ 16 h, donation after cardiac death, donor history of coronary artery disease, donor terminal creatinine ≥ 1.9 mg/dL, and a hypothermic machine perfusion (HMP) pump resistance ≥ 0.23 mmHg/mL/min.

Research conclusions

We delineate the association between DGF and recipient characteristics of pre-induction MAP below 110 mmHg, metabolic syndrome, donor-specific risk factors, HMP pump parameters, and intraoperative use of phenylephrine.

Research perspectives

Future studies with larger multicenter cohorts are needed to further explore means to improve outcomes of recipients with suboptimal baseline or intraoperative blood pressure.

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