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Machine perfusion following static cold storage preservation in kidney transplantation: donor-matched pair analysis of the prognostic impact of longer pump time

Gaetano Ciancio,[1,2] Jeffrey J. Gaynor,[1,2] Junichiro Sageshima,[1,2] David Roth,[3] Warren Kupin,[3] Giselle Guerra,[3] Lissett Tueros,[1,2] Alberto Zarak,[1,2] Lois Hanson,[1,2] Susan Ganz,[2] Linda Chen,[1,2] Phillip Ruiz,[1,4] Alan S. Livingstone,[2] and George W. Burke III[1,2]

1 The Lillian Jean Kaplan Renal Transplant Center, Leonard M. Miller School of Medicine, University of Miami, FL, USA
2 Division of Transplantation, Department of Surgery, Leonard M. Miller School of Medicine, University of Miami, FL, USA
3 Division of Nephrology, Department of Medicine, Leonard M. Miller School of Medicine, University of Miami, FL, USA
4 Department of Pathology, Leonard M. Miller School of Medicine, University of Miami, FL, USA

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Correspondence
Gaetano Ciancio MD, Department of Surgery, Division of Transplantation, University of Miami Miller School of Medicine, P.O. Box 012440 (R-440), Miami, FL 33101, USA. Tel.: +1 305 355 5111; fax: +1 305 355 5134; e-mail: gciancio@med.miami.edu

Conflicts of Interest
Representatives of Institut Georges Lopez (IGL) had no direct involvement in this study and did not prepare any part of the manuscript. None of the co-authors have any financial interest in IGL.

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Summary

The impact of machine perfusion (MP) time on kidney transplant outcome is mixed in previous studies using multivariable analyses. In an analysis of 66 pairs of donor-matched adult, first transplant recipients ($N = 132$) with identical donor characteristics except for pump time, tests of association of shorter versus longer pump time (first versus second kidney removed) by delayed graft function(DGF), slow graft function(SGF), and biopsy proven acute rejection (BPAR) were performed using McNemar's test. Freedom-from-BPAR, graft and patient survival, and renal function were also compared. Mean ± SD pump times for paired recipients with first and second kidneys were 22.7 ± 7.3 h and 31.2 ± 7.9 h, respectively (mean difference: 8.5 ± 4.5 h, $P < .000001$). There was no significant impact of pump time on DGF or SGF, with discordant pairs favoring less SGF with longer pump time (N.S.). The incidence of BPAR during the first 12 months post-transplant yielded a borderline difference favoring longer pump time ($P = .09$), and freedom-from-BPAR during the first 12 months was significantly more favorable for longer pump times (95% vs. 84%, $P = 0.04$). No differences were observed in graft and patient survival, and renal function. While offering significantly favorable protection from BPAR, this analysis of donor-matched recipient pairs corroborates longer MP (pump) times having no unfavorable effect on other clinical outcomes.

Introduction

For over 30 years at our single center, hypothermic machine perfusion (MP) has been used as the preservation method for all deceased-donor (DD) kidneys retrieved for transplantation. We recently reported favorable outcomes with MP and longer pump (duration of MP) times in an observational study of 339 adult, primary, DD kidney transplant recipients who were pooled across three distinct randomized clinical trials performed at our center since 2000 [1]. Exceptionally low rates of delayed graft function (DGF) and slow graft function

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(SGF) were reported, i.e., 4.4% (15/339) and 12.1% (41/339), with no unfavorable impact of a longer pump (MP) time. In fact, evidence to suggest a significantly lower rate of first biopsy-proven acute rejection (BPAR) among recipients with longer pump times was found. While a non-significant trend for improved death-censored graft survival was observed in patients with longer pump times [1], conflicting opinions/results exist regarding the prognostic impact of MP on graft survival [2].

To evaluate the prognostic impact of pump time on kidney transplant outcome without the effects of other donor-associated variables, we analyzed 66 pairs of recipients ($N = 132$) who received a DD kidney from the same donor to determine whether recipients with longer pump times within pairs had more favorable outcomes.

Methods

We analyzed three of our previously published, prospective, randomized immunosuppression trials in adult, primary kidney transplantation. Between May 2000 and December 2001, a randomized trial of 150 adult, primary kidney transplant recipients was performed comparing tacrolimus/sirolimus versus tacrolimus/mycophenolate mofetil(MMF) versus cyclosporine microemulsion/sirolimus (50 per arm) [3–5]. All patients received daclizumab induction and corticosteroids. Between November 2002 and September 2004, a randomized trial of 90 adult, primary kidney transplant recipients of DD kidneys was performed comparing induction with thymoglobulin versus alemtuzumab versus daclizumab (30 patients per arm) [6,7]. Tacrolimus, MMF, and corticosteroids were given in the thymoglobulin and daclizumab arms, whereas one-half the regular MMF dose, tacrolimus and no corticosteroids were scheduled in the alemtuzumab arm. Between December 2004 and February 2006, a randomized trial of 150 adult, primary kidney transplant recipients was performed comparing tacrolimus/MMF versus tacrolimus/enteric-coated mycophenolate sodium as maintenance, with an induction regimen consisting of both thymoglobulin and daclizumab, and early (1 week) discontinuation of corticosteroids (75 patients per arm) [8]. Among the study participants in these three randomized trials, there were 27, 14, and 25 pairs of recipients ($N = 54$, 28, and 50), respectively, who received DD kidneys from the same donor, yielding a total 66 donor-matched pairs of DD recipients for the present study. Minimum follow-up of 2 years post-transplant existed for each patient.

Each DD kidney pair was initially placed in static cold storage (CS) at retrieval (i.e., from the time of donor cross-clamp). Upon arrival at our medical center, each DD kidney pair was immediately placed on MP and remained there until time of transplant (Fig. 1). All transplanted DD kidneys received MP preservation with the RM3 Renal Preservation Machine (Waters Instruments Inc., Rochester, MN, USA), using a DCM-100 Cassette and Belzer-MPS (Machine Perfusion Solution, Trans-Med Corporation, Elk River, MN, USA) as the perfusate (set at 4°C). Additives included: mannitol (3.75 g/l), dexamethasone (16 mg/l), insulin (100 units/l), and ampicillin (250 mg/l). For adult kidneys, the initial perfusion pressure was set to 40 mmHg systolic, with the pressure being raised (if needed) to improve flow (by 5 mmHg increments up to 50 mmHg). Up to three additional doses of mannitol were added (generally, at 12 h apart) when the flow was suboptimal (<100 ml/min/100 g renal mass as a guide, but also at the discretion of the kidney transplant surgeon).

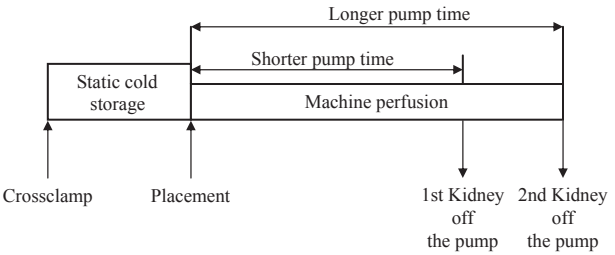

Figure 1 Flow diagram of kidney preservation at our center, displaying the timing of a deceased donor's first and second kidneys being removed from machine perfusion for transplantation.

Standard transplantation procedures were used in all patients: anastomosis of the renal artery and renal vein to the external iliac artery and external iliac vein, respectively, and vesico-ureteral anastomosis using an extravesical approach in most patients.

DGF was defined as the requirement for dialysis during the first week post-transplant. SGF was defined as DGF or a serum creatinine decreasing less than 0.5 mg/dl during the first 24 h post-transplant; a similar definition of SGF has been used by Ekberg *et al.* [9–11].

Statistical methods

Recipients of kidneys from the same DD had identical donor characteristics as well as static CS time; other than kidney location (right or left) the only other distinguishing donor characteristic within each pair was the length of pump time. Recipients with the longer pump time were identified, and tests of association of longer versus shorter pump time by baseline characteristics and the occurrence of DGF, SGF, and BPAR, respectively, were performed using paired *t*-tests and McNemar's test (the exact test was used if the total number of discordant pairs was <20). Comparisons of freedom-from-first BPAR, freedom-from-graft failure (censoring deaths and never

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functioning grafts), graft survival (death uncensored), and patient survival were performed using Kaplan-Meier curves and the log-rank test. Comparisons of tacrolimus trough levels, MMF doses, and estimated glomerular filtration rate (eGFR) (by the 4-variable MDRD equation) were performed using standard *t*-tests, as complete data was not available in all donor-matched pairs at all times (e.g., data was no longer obtained once a patient experienced graft failure). As a result of the relatively small number of donor-matched pairs in this study, implying that good statistical power would exist only for the detection of distinctly large differences, *P*-values < .05 (statistically significant) and <0.10 (trend towards statistical significance) were both considered meaningful in this study.

Results

Demographics

Mean donor age and static CS time ± SD for the 66 pairs of recipients were 36.9 ± 13.9 years and 4.8 ± 1.9 h, respectively. Median (range) of static CS times was 5 (2–12) h, with 95% (63/66) being ≤8 h; kidneys for all but one of the pairs were locally retrieved. One pair received donation after cardiac death (DCD) kidneys (thus, all other 65 pairs received donation after brain death (DBD) kidneys), and seven additional pairs received expanded criteria donor (ECD) kidneys. Distributions of selected baseline characteristics and induction therapy for recipients of donor-matched first and second kidneys off the pump (i.e., those with shorter versus longer pump times) are displayed in Table 1. By chance, mean recipient age was significantly older among recipients of the first kidney off the pump (those with shorter pump times): 53.8 ± 12.4 vs. 49.3 ± 12.8 among recipients of the second kidney ($P = .02$). As the mean recipient age was significantly younger among African-Americans in our cohort ($P = .02$), the percentage of African-American recipients was also lower among recipients who received the first versus second donor-matched kidney off the pump, 20% (13/66) vs. 35% (23/66), respectively ($P = .05$). As expected, there were no differences in induction therapy for recipients of shorter and longer pump times. In addition, the mean pump time and cold ischemia time (CIT, i.e., static CS time plus pump time) were significantly longer among recipients of the second kidneys, 22.7 ± 7.3 vs. 31.2 ± 7.9 for pump time (27.6 ± 7.7 vs. 36.0 ± 8.3 for CIT), with the mean difference ± SD being 8.45 ± 4.51 h ($P < .000001$). Median (range) pump time and CIT for recipients of first kidneys was 24 (1–38) h and 28 (7–43) h, respectively; median (range) pump time and CIT for recipients of second kidneys was 31 (8–54) h and 37 (14–59) h, respectively.

Table 1. Distributions of selected baseline characteristics and induction therapy for donor-matched recipients of 1st and 2nd kidneys off the pump.

	Mean ± SD if continuous, % if categorical		
Baseline characteristic	Received 1st kidney ($N = 66$)	Received 2nd kidney ($N = 66$)	*P*-value
Recipient age (years)	53.8 ± 12.4	49.3 ± 12.8	0.02
Race/ethnicity			
Caucasian	35% (23/66)	30% (20/66)	0.56
Hispanic	41% (27/66)	29% (19/66)	0.16
African-American	20% (13/66)	35% (23/66)	0.05
Other	4% (3/66)	6% (4/66)	
Sex			
Male	73% (48/66)	73% (48/66)	1.00
Female	27% (18/66)	27% (18/66)	
Pretransplant diabetes			
No	65% (43/66)	76% (50/66)	
Yes	35% (23/66)	24% (16/66)	0.16
Pump time (h)	22.7 ± 7.3	31.2 ± 7.9	<0.000001
CIT (h)	27.6 ± 7.7	36.0 ± 8.3	<0.000001
Induction therapy:			
DAC	53% (35/66)	45% (30/66)	0.18
ATG	4.5% (3/66)	9% (6/66)	0.51
C1H	4.5% (3/66)	8% (5/66)	0.63
ATG/DAC	38% (25/66)	38% (25/66)	1.00

SD, standard deviation; CIT, cold ischemia time; ATG, anti-thymocyte globulin (Thymoglobulin); DAC, daclizumab; C1H, Alemtuzumab (Campath-1H).

DGF and SGF

There was no significant impact of pump time on the incidences of DGF or SGF. For DGF, 63 pairs of recipients had no DGF, and one pair (both recipients) had DGF. Thus, there were two discordant pairs, with one pair favoring a longer pump time (recipient of the first kidney developed DGF) and one pair favoring a shorter pump time (recipient of the second kidney developed DGF) ($P = 1.0$). For SGF, 53 pairs of recipients had no SGF, and three pairs (both recipients) had SGF. Thus, there were 10 discordant pairs, with six pairs favoring a longer pump time (recipient of the first kidney developed SGF) and four pairs favoring a shorter pump time (recipient of the second kidney developed SGF) ($P = 0.75$).

Note that both recipients of the single DCD donor in this study developed DGF (static CS time was 5 h; pump times were 8 h and 14 h). Among the seven ECD pairs of recipients, 0/14 developed DGF, and 2/14 developed SGF (one each in patients with shorter and longer pump times, both discordant). Static CS and pump times in these 14 patients were similar to those in the whole cohort: median (range) was 5 (4–8) h for CS time, and

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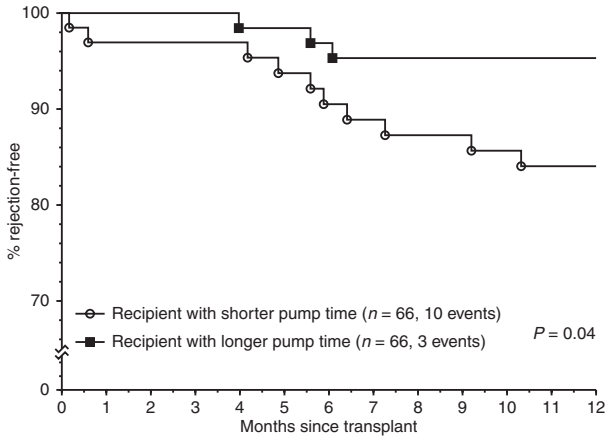

Figure 2 Comparison of freedom-from-first BPAR during the first 12 months post-transplant between donor-matched recipients with shorter versus longer pump times. Note that 52/66 and 59/66 patients in the shorter and longer pump time groups, respectively, were still at risk at 12 months post-transplant (i.e., alive with functioning grafts and no BPAR).

26 (13–38) h and 34 (22–54) h for first and second kidney recipient pump times, respectively. Finally, one patient in the longer pump time group (static CS time: 4 h; pump time: 36 h) received a graft that never functioned (primary nonfunction) – this patient was included as having both DGF and SGF.

First BPAR

Regarding BPAR incidence (14 vs. 8 patents developed BPAR in the donor-matched recipients with shorter versus longer pump times), a slight trend in favor of longer pump times was observed ($P = .24$, exact McNemar's test), and comparison of BPAR incidence during the first 12 months post-transplant yielded a borderline difference in favor of longer pump times ($P = .09$). Specifically, 53 pairs of recipients had no BPAR during the first 12 months post-transplant. There were 13 discordant pairs, with 10 pairs favoring a longer pump time (recipient of the first kidney developed BPAR), and three pairs favoring a shorter pump time (recipient of the second kidney developed BPAR). In fact, comparison of freedom-from-BPAR during the first 12 months post-transplant (when more immunologically active patients would develop BPAR) yielded a statistically significant difference in favor of longer pump times (Fig. 2), with BPAR-free survival at 12 months of 95% vs. 84% ($P = .04$, log-rank test).

Note that among the two recipients of the single DCD donor, one recipient (with the shorter pump time) developed BPAR during the first 12 months post-transplant. Among the seven ECD pairs of recipients, 3/7 and 0/7 who received the first and second kidneys, respectively, developed BPAR during the first 12 months post-transplant (all four BPAR's were discordant). Thus, while small in number, the BPAR outcomes among the DCD and ECD recipients favored those having longer pump times.

Table 2. Comparison of graft and patient survival between donor-matched recipients of 1st and 2nd kidneys off the pump.

	Number of events (failures)		
Clinical outcome	Received 1st kidney ($N = 66$)	Received 2nd kidney ($N = 66$)	Log-rank test *P*-value
Graft failure (death-censored & never functioning kidney-censored graft survival)	8	7	0.85
Graft survival (death-uncensored)	15	13	0.76
Patient survival	8	5	0.39

Graft and patient survival

There were no statistically significant differences between the two groups regarding graft survival (Table 2). Out of 66 transplants in each group, eight grafts were lost in the first kidney group versus seven in the second kidney group ($P = .85$) when deaths and never functioning kidneys were censored. Note that among patients who never developed versus developed a BPAR episode, the percentage subsequently developing graft failure (censoring deaths and never functioning kidneys) was 5.5% (6/110) vs. 40.9% (9/22), respectively ($P = .00002$). Thus, the strong association of BPAR incidence with a subsequently higher risk of graft failure did not translate into a meaningfully lower graft failure rate in the second kidney group. In addition, among the eight and seven patients in the first and second kidney groups that developed graft failure, the median (range) pump time was 18 (13–38) h and 30 (17–54) h, respectively – similar to the observed values among those not developing graft failure.

Graft survival (death uncensored) and patient survival comparisons between first and second kidney recipients were also similar, with 15 graft losses and eight deaths in the first kidney group and 13 graft losses and five deaths in the second kidney group ($P = .76$ and $P = .39$); the death-uncensored graft survival comparison is displayed in Fig. 3.

Tacrolimus trough levels and MMF doses

Tacrolimus trough levels and MMF doses were comparable between the groups at 12, 24, and 36 months post-

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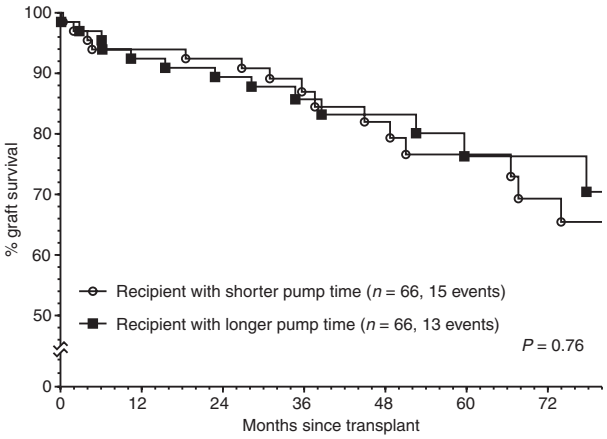

Figure 3 Graft survival (death-uncensored) comparison of donor-matched recipients with shorter versus longer pump times. As there was a minimum follow-up of 2 years in this study, with five and seven graft losses occurring during the first 2 years in the two groups, the number of patients still at risk at 2 years post-transplant was 61 and 58 in the first and second kidney groups, respectively.

transplant (Table 3). Renal function as indicated by estimated GFR were also not different between groups at 12, 24, and 36 months post-transplant (Table 3). Finally, type of induction therapy, tacrolimus trough level, and MMF dose were not associated with rejection and graft failure rates in this study (results not shown).

Discussion

We demonstrated in an analysis of 132 recipients from 66 donor-matched pairs that longer pump times were not associated with any unfavorable effect on DGF and SGF rates, graft and patient survival, or impaired renal function; in fact, they offered a significantly favorable protection from BPAR. These results corroborate what we found in our total cohort of 339 DD recipients (which included 207 nonmatched recipients) using stepwise logistic and Cox regression analyses [1]. In that study, a longer pump time had no unfavorable effect on DGF and SGF rates. In addition, pump time≥24 h was associated with a significantly more favorable freedom-from-BPAR, particularly among higher risk (having DGF, age <50 years, and nonwhite) patients [1]. A biological explanation for this observed favorable effect of longer pump time on BPAR rate is currently unknown – current theories include a better flushing of immunogenicity from the DD kidney, augmented or reduced oxidative and metabolic stress, cell senescence, and/or vascular injury. However, while BPAR occurrence is known to be associated with a significantly higher risk of subsequent graft failure, in both this study of 66 matched pairs and in our larger study of 339 DD recipients [1], we did not find a corresponding significant association of longer pump times with a more favorable (death-censored) graft failure rate.

Recently reported randomized trials of MP versus static CS preservation have also reported somewhat conflicting results regarding the prognostic impact of MP. In the randomized trial of Moers *et al.* [12] with 672 recipients of 336 matched paired DD (mostly DBD) kidneys, the MP arm had significantly lower rates of DGF and death-censored graft failure at 1 year post-transplant (versus the static CS arm) in both univariable and multivariable analyses. The favorable effect of MP preservation on DGF rate appeared to be consistent across standard criteria and expanded criteria donors in that study. A randomized trial by the same group among 164 recipients of 82 matched paired DCD kidneys [13] found a significantly

Table 3. Comparisons of mean TAC trough level, MMF dose, and eGFR at 12, 24, and 36 months post-transplant between donor-matched recipients of 1st and 2nd kidneys off the pump.

		Mean ± SE if continuous, % if categorical				
		Received 1st kidney		Received 2nd kidney		
Variable*	Post-transplant month	(*N*)	Mean ± SE	(*N*)	Mean ± SE	*P*-value
TAC level	12	(54)	7.67 ± 0.50	(55)	6.96 ± 0.34	0.24
TAC level	24	(52)	6.47 ± 0.26	(51)	6.52 ± 0.25	0.90
TAC level	36	(38)	6.46 ± 0.50	(41)	6.87 ± 0.31	0.49
MMF dose	12	(34)	1103 ± 75	(32)	1141 ± 88	0.75
MMF dose	24	(36)	1174 ± 60	(35)	1214 ± 82	0.69
MMF dose	36	(31)	1250 ± 75	(31)	1161 ± 84	0.43
eGFR	12	(61)	59.3 ± 2.4	(61)	62.4 ± 2.9	0.42
eGFR	24	(61)	57.4 ± 2.5	(59)	60.2 ± 2.5	0.43
eGFR	36	(54)	57.9 ± 3.2	(51)	62.9 ± 3.2	0.27

SE, standard error; TAC, tacrolimus; MMF, mycophenolate mofetil; eGFR, estimated glomerular filtration rate.

*Units of Measurement: TAC Level, ng/l; MMF Dose, mg; eGFR, ml/min/1.73 m^2.

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lower DGF rate in the MP arm but without a concomitant benefit in death-censored graft survival at 1 year, suggesting that the effect of DGF on subsequent graft failure risk may differ according to donor type (DBD or DCD). Lastly, a separately reported randomized trial of 90 recipients of 45 matched paired DCD kidneys [14] reported no advantage of MP over static CS, even for DGF rate. Although the Lifeport preservation machine was used in both of these DCD recipient studies, kidneys were immediately placed on MP in the Jochmans *et al.* study [13], whereas many of the MP kidneys in the Watson *et al.* study [14] were first placed in static CS at the time of retrieval, then transported and immediately placed on MP upon arrival at the transplant center (similar to the our center's approach, although using a different machine). Of note, the Watson *et al.* study[14] did report a trend for a lower BPAR rate in the MP arm at 3 months post-transplant ($P = 0.06$).

It is widely accepted that prolonged static CS times are associated with significantly higher DGF rates [15,16], and DGF is associated with significantly increased rates of early acute rejection[17,18], reduction in eGFR [19], and poorer graft survival [17,20]. Opelz *et al.* [21], in evaluating the collaborative transplant study of 91 674 kidney transplants in which static CS was the preservation method used in 97.4% of the kidneys, concluded that prolonged CIT >18 h significantly decreased kidney graft survival in mainly standard criteria donor(SCD) recipients,. No beneficial effect of MP on graft survival was observed in the small percentage of patients receiving MP; furthermore, within the subgroup of MP kidneys, an increasing CIT up to 36 h had no deleterious effect on graft outcome. Details on machine type and other MP parameters were not available in that study. Therefore, it is difficult to generalize the findings of Opelz *et al.* [21] to machine-preserved kidneys and the prognostic impact of longer MP (pump) time, as many MP-related variables (e.g., machine type, pressure/flow settings, and preservation solution) may affect kidney transplant outcome [1].

Similar to the present study, Giblin *et al.* [22] reported a comparison of graft survival rates between the first and second donor kidneys transplanted. While long-term graft survival in the study was significantly better for the first kidney transplanted compared with the second kidney, several differences existing between the Giblin *et al.* and current study may explain the different outcome. First and foremost, kidneys in the Giblin *et al.* study were exclusively (and for extended times) preserved by static CS, whereas our kidneys were preserved by MP following relatively short static CS times. Second, their kidneys were preserved in Euro-Collins solution, whereas our kidneys were initially preserved in Belzer (University of Wisconsin) solution followed by Belzer-MPS on the machine. Third, their recipients received cyclosporin-based immunosuppression, whereas our recipients received antibody induction and mainly tacrolimus-based immunosuppression.

The authors are aware of a few limitations of the current study. Although donor factors other than anatomical difference (i.e., right versus left kidney) and pump time were the same for paired recipients, there were some demographic differences in recipient variables. Specifically, mean recipient age among the first kidney recipients was significantly older than that of the second kidney recipients, and a correspondingly greater percentage of second kidney recipients were African-American (Table 1). While we believe that it is highly unlikely that any type of selection bias existed, we cannot completely rule out this possibility as recipients were not randomized to receive the first and second donor kidneys taken off the pump. Despite having more immunologically high-risk (i.e., younger and African-American) patients, recipients of the second kidney (i.e., those with longer pump times) demonstrated significantly more favorable freedom-from-BPAR (demonstrated in Fig. 2). Although the first and second kidneys from the same donor were always transplanted consecutively, the ongoing operating room scheduling issues at our busy county hospital necessitated the rather long pump times (and differences in pump times between first and second kidneys) at our center. A retrospective analysis of a limited number of patients from a single-center study may also carry other inherent (and unknown) limitations when applying its results to other patient cohorts. Further studies are warranted to validate our observation, including those with a larger number of donor-matched pairs of recipients with comparable backgrounds, mechanistic studies to explain these preliminary results using appropriate biochemical markers, and if appropriate, randomized trials.

In summary, the results of this donor-matched pairs analysis suggest that prolonged CIT (even longer than 36 h) using MP with a minimal static CS time may not negatively affect kidney graft outcome, when comparing recipients with longer versus shorter cold ischemia times from the same donor, and may possibly even protect kidney grafts from BPAR. This study supports continued use of MP, further investigation of the relationship between pump time and perfusion profile (flow rate, perfusion resistance, etc.), and further clinical studies of the potential benefits of DD kidney preservation with MP.

Authorship

GC, JJG, JS, DR, WK, GG, LC, and GWB: contributed to the research design. GC, JJG, JS, DR, WK, GG, LT, AZ, LH, SG, LC, PR, ASL, and GWB: participated in

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performance of the research. GC, JJG, JS, and GWB: analyzed the data. GC, JJG, JS, PR, ASL, and GWB: wrote the paper.

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