The prognostic value of time needed on dialysis in patients with delayed graft function

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Abstract

Introduction. We hypothesize that in patients with delayed graft function (DGF), the need for a longer time needed on dialysis (TND) post-kidney transplant is associated with poorer long-term function and an increase in complications.

Methods. This was a retrospective chart review involving collaboration between Western University (WU) Renal
Transplant Program of London, Ontario and the Saskatchewan renal transplant program (SRTP). A total of 774 patients (567 WU and 207 SRTP) received kidney transplants between 2004 and 2011, of which 83 patients with deceased donor transplants (59 WU and 24 SRTP) developed DGF, defined as the need for dialysis in the first week posttransplant.

**Results.** Patients with DGF were divided into three groups depending on TND [group 1: <7 days (n = 52), group 2: 7–14 days (n = 13) and group 3 (n = 18): >14 days]. The creatinine clearance (CrCl) at 30 days (42.5, 33.8, 20.0 cc/min; P < 0.001) and 1 year (56.7, 49.2, 37.3 cc/min, P = 0.031) were significantly different between the three groups. Multivariate regression analysis identified length of TND posttransplant (β = −0.5, P < 0.001) and donation after cardiac death (DCD) donor (β = 19.5, P < 0.001) as the most significant predictors of CrCl at 1 year in these patients with DGF. DCD kidneys with DGF had a higher CrCl at 1 year and fewer readmissions in the first year compared with non-DCD kidneys with DGF.

**Discussion.** Our study suggests that increased TND is associated with worse CrCl at 1 year. The data also support the hypothesis of a different mechanism for DGF in DCD and non-DCD kidneys.

**INTRODUCTION**

In the early posttransplant period, some kidneys recover quickly from delayed graft function (DGF), while others can take weeks before resuming function [1]. Overall, the long-term outcomes are less favorable for grafts that have initial DGF [2, 3]. Yet, little has been written about the long-term prognosis of those kidneys that take longer to ‘wake up’ after transplant, particularly in the era of donation after cardiac death (DCD) kidney transplants.

A review of the literature shows that only a few studies have examined time needed on dialysis (TND) as a factor in long-term graft function. An early study used a unique definition of DGF that was independent of the need for dialysis (time to attain an estimated glomerular filtration rate (eGFR) of ≥10 mL/min) [4]. In their study, kidneys requiring >6 days to cross this threshold of eGFR were shown to have a poorer long-term graft survival. In 2009, a small study suggested that serum creatinine at 1 year was adversely affected by a longer DGF duration [5]. A more recent study showed that the need for only a single dialysis treatment after transplant was not associated with the worse outcomes seen in patients requiring a longer duration of dialysis [6]. Our study differed from these previous studies in that it included patients receiving kidneys from DCD donors and more expanded criteria (ECD) donors than the early study, in keeping with the demographics of the donor population in most North American and European programs today.

We hypothesize that a longer length of TND portends a poorer prognosis for long-term renal function in terms of creatinine clearance (CrCl) at 1 year. Also, recent publications [7, 8] have documented a better prognosis for DCD kidneys with DGF than for non-DCD kidneys with DGF, and we wished to examine the effect of a longer TND on function in these DCD kidneys.

**MATERIALS AND METHODS**

This was a retrospective chart review involving collaboration between the Western University (WU) and the Saskatchewan renal transplant program (SRTP). Information about each recipient and their donor as well as investigations in the preoperative and postoperative course of these 83 patients with DGF was collected retrospectively. Patients were divided into three groups depending on TND [group 1: <7 days (n = 52), group 2: 7–14 days (n = 13) and group 3 (n = 18): >14 days], but analysis was also carried out using TND as a linear variable. Our main outcome of interest was the CrCl at 1 year, and secondary outcomes were adverse events.

CrCl was estimated using the Cockcroft–Gault equation. Complications examined included wound infection or leakage, reoperation, ICU admission, readmission or graft loss within less than a year. Wound infection was defined as the need for the incision to be reopened partially or completely and packed. Significant wound leakage was defined as a need for consultation to a specialized wound care team or the placement of a bag appliance. Reoperations for the purpose of our study included only those reoperations that required reopening the kidney transplant incision. Neither program performed routine protocol biopsies, but instead performed biopsies based on clinical indication; rejection episodes in this study were biopsy proven.

Univariate analysis of factors involved in CrCl at 1 year was carried out and factors with P < 0.20 were included in the multivariate analysis as per the classic method of Kleinbaum et al. [15].

The multivariate analysis was repeated to include variables that are generally considered classic confounders, including donor age [16], early acute rejection [17] and DCD donor, in addition to TND. Cold ischemic time (CIT), one of the traditional confounders, was not included because the range of CIT was very narrow and the difference between the donor kidneys with the longest and shortest CIT’s would not be expected to make a significant difference to renal function [18], and in order to keep the number of variables to an acceptable number. Medications used postoperatively were not included in the model because all but one patient received induction (61 thymoglobulin, 21 basiliximab, 1 patient refused); no differences were found between the two types of induction with respect to CrCl at 1 year. Finally, all but three of the patients received tacrolimus-based immunosuppression, precluding any meaningful analysis of the effect of immunosuppressive drugs as a confounder. Biopsy-proven early acute rejection was included as a possible confounder in one of the regression models because of a trend towards less early acute rejection in the DCD group and because of this well-documented factor in the outcome of kidney transplants. Due to concerns over collinearity between donor age and donor Cr (r = −0.206, P = 0.05), these two could not be included in any model at the same time, but were analyzed individually in

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separate multivariate models. TND was analyzed in multi-
variate regression models first as a continuous variable, then as a
categorical variable.

Data were analyzed using SPSS 20.0 (IBM Corporation,
Armonk, NY), including multivariate linear regression, the $\chi^2$
-test, ANOVA, and Student’s t-test with Bonferroni correction
for multiple comparisons. Ethics approval was obtained from
the Ethics Review Board at both institutions.

RESULTS

Between January 2004 and December 2011, there were 567
kidney transplants at WU Renal Transplant Program of
London, Ontario and 227 at SRTP, for a total of 774 trans-
plants. For the purposes of our study, multi-visceral, repeat
and en bloc kidney transplants were excluded. A total of 83
patients receiving deceased donor kidney transplants devel-
op DGF, which is defined as the need for dialysis in the
first week posttransplant. There were 59 cases of DGF at
WU and 24 cases of DGF at SRTP during this time period.
The two sites had similar practices and, aside from the fact
that the WU site has had a DCD program since 2006 and
the SRTP does not have a DCD program, the two sites
showed no significant differences in terms of donor or recipi-
ent age, dialysis modality, use of machine cold perfusion,
CIT rate of DGF, rate of early acute rejection and length of
stay.

Patient demographics are shown in Table 1. The 83 patients
with DGF were divided into three groups based on the
number of days postoperatively that dialysis was needed,
whether <7 days (group 1, $n = 52$), between 7 and 14 days
(group 2, $n = 13$) and >2 weeks (group 3, $n = 18$). The three
groups were similar in terms of recipient demographics, dialy-
sis modality, proportion of DCD transplants and CIT. The
CrCl at 30 days and at 1 year showed differences between the
three groups, with poorer function seen in patients having
longer TND. A greater proportion of patients with one or
more complications were seen in the groups of patients requir-
ing longer time on dialysis.

Univariate analysis of potential predictors of CrCl at 1 year
is shown in Table 2. A multivariate regression model of CrCl
at 1 year was constructed including the variables with $P$
-value < 0.20 on univariate analysis (donor age, DCD kidneys
and TND). TND and DCD donor emerged as highly

| Table 1. Demographics and outcomes for the three groups of patients, divided according to TND |
|---------------------------------------------|----------------|----------------|----------------|----------------|
|                                           | Group 1 (<7 days) $n = 52$ | Group 2 (7–14 days) $n = 13$ | Group 3 (>14 days) $n = 18$ | P-value |
| M:F                                       | 41:11                        | 12:1                        | 12:6                        | 0.24$^a$ |
| Recipient age (±SEM)                      | 54.5 ± 1.8                   | 53.9 ± 3.7                  | 56.1 ± 3.0                  | 0.88$^b$ |
| Donor age (±SEM)                          | 47.1 ± 2.0                   | 41.4 ± 4.3                  | 52.8 ± 2.9                  | 0.097$^b$ |
| Type of RRT (HD:PD)                       | 39 : 13                      | 11 : 2                      | 15 : 3                      | 0.87$^a$ |
| DCD kidney                                | 24 (46%)                     | 5 (38%)                     | 6 (33%)                     | 0.62$^a$ |
| Machine cold perfusion                    | 18 (35%)                     | 3 (28%)                     | 7 (39%)                     | 0.64$^a$ |
| CIT (min ±SEM)                            | 788 ± 56                     | 700 ± 109                   | 740 ± 69                    | 0.73$^b$ |
| TND (days ± SEM)                          | 3.7 ± 0.3                    | 10.1 ± 0.6                  | 32.4 ± 5.6                  | <0.001$^c$ |
| Number of dialysis runs                   | 2.3 ± 0.2                    | 5.2 ± 0.6                   | 12.8 ± 2.4                  | <0.001$^b$ |
| Length of stay (days ± SEM)               | 15.3 ± 1.0                   | 19.6 ± 3.2                  | 23.5 ± 3.4                  | 0.01$^b$ |
| One or more complications$^d$             | 13 (25%)                     | 7 (54%)                     | 13 (72%)                    | 0.001 |
| CrCl at 30 days (cc/min ± SEM)            | 42.5 ± 2.5                   | 33.8 ± 5.0                  | 20.0 ± 2.2                  | <0.001$^b$ |
| CrCl at 1 year (cc/min ± SEM)             | 56.7 ± 2.8                   | 49.2 ± 4.8                  | 37.3 ± 2.3                  | 0.031$^b$ |

RRT, renal replacement therapy.
$^a$Calculated using the $\chi^2$-test.
$^b$Calculated using ANOVA.
$^c$Calculated using ANOVA, Kaplan Meier, and Krushkal–Wallis. The result was the same for all three tests.
$^d$Composite of wound leak, wound infection, ICU admission, reoperation, graft loss under 1 year and death <1 year posttransplant.
In our study of patients with DGF, the length of TND before the resolution of DGF was shown to be a factor predictive of CrCl at 1 year. Also, patients with DGF whose kidney transplants came from DCD donors had better CrCl at 1 year compared with patients with DGF whose kidneys did not come from DCD donors.

Although DCD kidneys have a high incidence of DGF, it is becoming clear that DCD kidneys with DGF have similar creatinine at 1 year compared with standard criteria donors or DCD donor transplants that did not experience DGF [9, 10]. Markedly lower readmission rates were seen for recipients of DCD kidneys and (although not statistically significant), we saw trends towards less TND, lower early acute rejection, lower complication rates and lower readmission rates for the DCD group, similar to that in previous reports and arguing in favor of different mechanisms for DGF in the two groups.

One possibility is that DCD donors are more carefully selected, but our data in Table 4 shows the DCD and non-DCD kidneys to have similar demographics. It has been hypothesized that there exist different mechanisms for the injury that leads to DGF whether a kidney is from a DCD donor or a donation after brain death (DBD) donor. In the case of DBD, inflammatory mediators and cytokines released due to the mechanism of death may increase inflammation and tissue injury [11]. Early diminished allograft reserve may then explain the long-term diminished GFR. On the other hand, the ischemic injury that occurs to DCD kidneys may be less likely to provoke immune attack and early acute rejection and more likely to be reversible.

The reason for the association of prolonged TND with worse long-term function could be that more dialysis is somehow detrimental to long-term renal function, either because of transient hypotension that occurs with hemodialysis or to inflammatory reactions to dialysis membranes or dialysate [12, 13]. In our study, there was no difference in CrCl at 1 year between patients dialyzed postoperatively with peritoneal dialysis or with hemodialysis (56.0 ± 6.3 cc/min versus 53.1 ± 2.5 cc/min, P = 0.27). An earlier study found that a single dialysis run in the early postoperative period resulted in no detrimental effect to long-term kidney function [6].

Instead, it seems more likely that the association between prolonged TND and decreased long-term function is due to the fact that kidneys with worse baseline function also have less functional reserve or perhaps fewer glomeruli [14] and hence require more support in terms of dialysis. The fact that increased donor age is associated with worse function at 1 year is in keeping with this possibility [7].

Our study is limited by the somewhat subjective nature of the definition of DGF. If and when to initiate dialysis as well as when to stop doing dialysis on these patients is somewhat of a subjective judgment call of the treating transplant physician, but is thought to be similar between the two sites. Thus, the number of days needed on dialysis (TND) is a rough measure at best, yet there is no denying that a patient who ‘needed’ dialysis for the first 14 days postoperatively needed...
significantly more support than a patient who needed 5 days, for example. When the kidney 'wakes up' out of DGF, however, it generally does so quite convincingly and it is likely that two transplant physicians might differ only by one dialysis treatment, if there was a difference at all.

We used well-documented variables to construct our regression models, in order to control for known factors, yet any regression study is limited by the fact that a number of variables are likely unknown. CIT, one of the usual known factors, for example, did not emerge as a significant predictor likely because the average CIT’s was quite reasonable and the range of CIT’s was quite narrow. Early acute rejection, a classic confounder, did not emerge as a statistically significant confounder, and this may be related to the fact that neither center does protocol biopsies nor is there a protocol dictating how many days of lack of return of function warrants a biopsy. Only 30 out of 83 (36%) of the patients in our study had a transplant biopsy, with 12 done in the first week, 10 in the second week, and 8 after a period of ≥2 weeks from the time of the transplant. The incidence of early acute rejection may have been underestimated in our study as a result. A trend towards more early acute rejection in the non-DCD transplants in our study and literature showing significant differences between non-DCD and DCD transplants in terms of early acute rejection [13] further emphasizes the need for inclusion of early acute rejection in a multivariate analysis model.

The proportion of patients experiencing one or more complications seems to increase with increased TND. Whether this is a cause or an effect of the increased TND cannot be discerned in this study, but it is nonetheless an interesting finding. In both centers, DGF is an indication to hold off the use of calcineurin inhibitors and to use thymoglobulin in the initial postoperative period. The use of thymoglobulin has been associated with leaky capillaries, hypotension, respiratory embarrassment and an increased risk of ICU admission, all of which may contribute to prolonging DGF. One of our earlier studies found that a large number of patients requiring ICU admission after transplant had received thymoglobulin [8]. The dosing and duration of thymoglobulin administration are protocol based and, according to our data, there is no difference in dose received whether someone had DGF for 5 or 21 days.

The length of time it takes for a kidney to recover from DGF can provide useful prognostic information about long-term function, and it seems that the need for prolonged dialysis is more likely an effect than a cause of a reduced function kidney. DGF that lasts >2 weeks results in a markedly poorer function at 1 year. As the length of time on dialysis seems to

| Table 4. Comparison of patients with DGF who received a DCD kidney transplant or a non-DCD kidney transplant |
|-------------------------------------------------|------------------|------------------|------------------|
| Non-DCD (n = 48) | DCD (n = 35) | P-value |
| Recipient age (±SEM) | 53.8 ± 2.0 | 56.0 ± 1.9 | 0.45<sup>a</sup> |
| Donor age (±SEM) | 47.7 ± 2.2 | 47.1 ± 2.2 | 0.86<sup>a</sup> |
| ECD | 18 (38%) | 9 (26%) | 0.26<sup>b</sup> |
| Machine cold perfusion | 12 (25%) | 16 (46%) | 0.05<sup>b</sup> |
| CIT (min) | 660 ± 41 | 547 ± 39 | 0.08<sup>a</sup> |
| TND (days ± SEM) | 12.5 ± 2.4 | 8.8 ± 2.5 | 0.15<sup>a</sup> |
| Number of dialysis runs | 5.1 ± 0.8 | 4.8 ± 1.2 | 0.95<sup>a</sup> |
| Length of Stay (days ± SEM) | 18.4 ± 1.8 | 16.8 ± 1.2 | 0.48<sup>a</sup> |
| CrCl at 30 days (cc/min ± SEM) | 38.0 ± 2.6 | 34.7 ± 3.4 | 0.43<sup>a</sup> |
| CrCl at 1 year (cc/min ± SEM) | 45.7 ± 2.4 | 63.7 ± 4.0 | <0.001<sup>a</sup> |
| Dialysis dependence at 30 days | 8 (17%) | 1 (3%) | 0.10<sup>b</sup> |
| Rejection in first 30 days | 9 (19%) | 2 (6%) | 0.06<sup>b</sup> |
| Readmission in first 6 months | 24 (50%) | 4 (11%) | 0.001<sup>b</sup> |
| Graft Loss before 1 year | 4 (8%) | 0 | 0.22<sup>b</sup> |
| Death before 1 year | 2 (4%) | 1 (3%) | 0.78<sup>b</sup> |
| One or more complications<sup>c</sup> | 23 (48%) | 10 (29%) | 0.08<sup>b</sup> |

DCD, donation after cardiac death; CIT, cold ischemic time.
<sup>a</sup>Calculated using Student’s <i>t</i>-test.
<sup>b</sup>Calculated using the <i>χ</i><sup>2</sup>-test.
<sup>c</sup>Composite of wound leak, wound infection, ICU admission, reoperation, graft loss under 1 year and death <1 year posttransplant.
be an effect rather than a cause of decreased function, early weaning from dialysis prior to definite return of renal function would not be expected to lead to an improvement in renal function. The differences between patients with DGF from DCD and non-DCD kidneys suggest a different mechanism of injury between the two types of organs and perhaps looking at interventions aimed at reducing the inflammatory response that occurs at the time of procurement of non-DCD kidneys should be pursued.

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AUTHOR’S CONTRIBUTION

C.M. participated in study design, data collection, data analysis and writing of the paper. B.T. participated in study design, data collection, data analysis and writing of the paper. A.S. participated in study design and writing of the paper. P.P.L. participated in study design, data analysis and writing of the paper. M.A.J.M. participated in study design, data collection, data analysis and writing of the paper.

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