ORIGINAL ARTICLE

Impact of delayed graft function on renal function and graft survival in deceased kidney transplantation

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Objectives To define the risk factors for delayed graft function and study the impact of such delays on renal function and long-term allograft survival in renal transplant recipients.

Design Single-centre retrospective study.

Setting Regional hospital, Hong Kong.

Patients Records of 118 Chinese renal transplant recipients from 1 July 1997 to 31 July 2005 were reviewed, and categorised into delayed and immediate graft function groups.

Results Delayed graft function was observed in about 19% of patients, for which cold ischaemic time was an important independent predictor. For each additional hour of cold ischaemic time, the odds ratio increased for delayed function by 0.002 (95% confidence interval, 0.001-0.003; P=0.03). Multivariate analysis revealed that neither cold ischaemic time nor delayed graft function was associated with acute rejection. On the other hand, at 1 year both delayed graft function (odds ratio=18.5; 95% confidence interval, 2.6-130.5; P=0.003) and donor age (1.2; 1.1-1.3; P=0.003) were related to a glomerular filtration rate of less than 30 mL/min. When renal function between patients with and without delayed graft function during the first 3 years was compared, it was significantly better in those without delayed graft function. However, there was no significant difference in death-censored graft survival between delayed graft function and immediate graft function groups.

Conclusions Delayed graft function has a significant adverse effect on graft function at 1 year. Limiting cold ischaemic time is important as it is an independent predictor of delayed graft function.

Introduction

Delayed graft function (DGF) and acute rejection are the two main early adverse events in renal transplantation. The rate of DGF varies between 23 and 34% among different centres.[1-5] The impact of DGF on long-term graft survival is controversial. Some studies have associated DGF with reduced graft survival rates,[2,4-7] whilst others failed to find such relationship.[1,3] With universal organ donor shortage and subsequent inclusion of the so-called 'marginal donor', there may be even higher rates of DGF. Moreover, acute rejection has also been associated with reduced long-term graft survival.[4] Some, though not all, evidence suggests that DGF may increase the frequency of acute rejection and thus reduce long-term survival.[1,8,9] Most of the available data, however, were derived a decade earlier. With the increasing use of newer immunosuppressive agents (tacrolimus, interleukin-2 receptor antagonist, and mycophenolate mofetil), there is a significant reduction of acute rejection episodes and prolongation of graft survival. Nowadays therefore, the relationship between DGF, acute rejection and long-term graft outcome may be different. Moreover, there is lack of data concerning DGF in Chinese patients in the literature. We therefore decided to revisit this topic in our cadaveric renal transplant recipients.

In this single-centre retrospective study, we first defined the various risk factors for DGF. The impact of DGF on renal function and long-term renal allograft survival was then studied.

Key words
Cold ischemia; Graft rejection; Graft survival; Kidney transplantation; Treatment outcome

Hong Kong Med J 2010;16:378-82

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Methods

Between 1 July 1997 and 31 July 2005, 125 Chinese patients received cadaveric kidney transplantation in Queen Elizabeth Hospital, Hong Kong. Seven were excluded due to technical complications during the first postoperative month, leaving 118 patients whose data were analysed. All organs from deceased donors were harvested while the heart was beating. Euro-Collins was the preservation fluid used during the entire study period. Follow-up data were analysed until 31 March 2008.

Patients were categorised into two groups, namely: DGF and immediate graft function (IGF). Delayed graft function was defined as the need for renal replacement therapy more than 7 days post-transplantation. Graft survival was defined as the time interval from transplantation until death, return to dialysis, or re-transplantation. Glomerular filtration rate (GFR) was estimated by the abbreviated MDRD Study (Modification of Diet in Renal Disease Study) equation.[10] Baseline body mass index (BMI; defined as the weight in kilograms divided by height in metres squared) was ascertained at the time of kidney transplantation. The ratio of donor kidney weight to recipient body weight (KW/BW) was used to estimate the donor/recipient size mismatch,[11] and expressed as grams per kilogram. Acute rejection was classified according to Banff 97 classification,[12] after assessment by local pathologists.

Immunosuppressive regimens

Our patients basically received triple immunosuppressive therapy with (i) either tacrolimus (Prograf; Astellas, Japan) or cyclosporine (Neoral; Novartis, Switzerland) as the calcineurin inhibitor (CNI), (ii) prednisolone, and (iii) azathioprine. They all received 500 mg of methylprednisolone at induction, followed by intravenous hydrocortisone 100 mg every 6 hours for 3 days and then oral prednisolone 30 mg daily. After the first month, the dose of prednisolone was gradually tapered at a rate of 2.5 mg every 2 weeks and eventually maintained at 7.5 mg daily. Azathioprine was given at a dose of 1.5 mg/kg daily from day 1 after the transplant. Cyclosporine was initially administered orally as a loading dose (10 mg/kg within 12 hours of surgery) and then 5 mg/kg twice daily. In our centre, an abbreviated formula based on a limited sampling strategy was used to estimate the cyclosporine area under 12-hour concentration-time curve (AUC_{0-12}).[13] On the other hand, tacrolimus was administered orally as a loading dose of 0.3 mg/kg within 12 hours of surgery, and then 0.15 mg/kg twice daily. Abbreviated tacrolimus AUC_{0-12} monitoring was also used.[14] Since 2001, some of our patients received either basiliximab (Simulect; Novartis, Switzerland) or daclizumab (Zenapax; Roche [NJ], US) during induction therapy.

屍體腎移植中腎功能延遲恢復對腎臟功能及移植物存活率的影響

目的 探討移植腎功能延遲恢復的風險因素，並研究接受腎移植的病人中，腎功能延遲恢復對腎臟功能及移植物長期存活的影響。

設計 一所中心的回顧研究。

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患者 回顧1997年7月1日至2005年7月31日期間118位接受腎移植病人的病歷紀錄，並把他們分成腎功能延遲恢復和立即恢復兩組。

結果 腎移植病人中約19%出現腎功能延遲恢復，而移植腎的冷缺血時間是一項重要的獨立指標。移植腎的冷缺血時間每增加1小時，腎功能延遲恢復的比值比會增加0.002（95%置信區間：0.001-0.003；P=0.03）。多元變數分析顯示移植腎的冷缺血時間和腎功能延遲恢復都與急性排斥無關。另一方面，移植手術後1年腎功能延遲恢復（比值比=18.5；95%置信區間：2.6-130.5；P=0.003）及捐腎者年齡（1.2；1.1-1.3；P=0.003）均與腎小球過濾速率少於每分鐘30 mL相關。比較移植手術後首3年，腎功能延遲恢復和立即恢復的兩組病人，發現立即恢復的病人的腎功能明顯較佳，但病人死亡時移植物存活率卻沒有顯著分別。

結論 移植手術後1年，腎功能延遲恢復會對移植物功能有顯著的不良影響。由於移植腎的冷缺血時間是腎功能延遲恢復的一項獨立指標，所以盡量減少移植腎的冷缺血時間相當重要。

Statistical analyses

Statistical software (SPSS 15.0, Inc, Chicago [IL], US) was used to perform the analyses. Continuous data were analysed by independent sample *t* tests to assess difference between groups; categorical data were analysed by the Chi squared or Fisher's exact tests. Kaplan-Meier survival curves were constructed for death-censored graft survival, which were compared using the log rank test. Associations between the clinical variables and the development of DGF, acute rejection, and renal function at 1 year were estimated using univariate analysis and multivariate logistic regression analysis. The model incorporated a backward and stepwise elimination method, using variables with a P value of less than 0.25 from the univariate analysis. A P value of less than 0.05 was defined as statistically significant.

Results

In our cohort, the median follow-up duration was 76 (range, 7-136) months. Delayed graft function was observed in 23 (19%) of the 118 patients. Demographic patient data are shown in Table 1. In the univariate analysis, only cold ischaemic time (CIT) was associated with the development of DGF. The

TABLE 1. Demographics and risk factors in patients with and without delayed graft function*

Demographics/risk factor†	Immediate graft function (n=95)	Delayed graft function (n=23)	P value
Age of recipients (years)	40 ± 11	42 ± 12	0.318
Recipient gender (male)	52 (55)	13 (57)	0.877
Recipient BMI (kg/m^2)	21.6 ± 3.9	23.1 ± 4.8	0.123
First transplant	89 (94)	21 (91)	0.653
PRA (%)	23.6 ± 31.3	18.8 ± 30.8	0.513
AB mismatch	2.3 ± 1.2	2.5 ± 1.1	0.593
DR mismatch	1.1 ± 0.7	1.1 ± 0.8	0.987
Anastomotic time (min)	48 ± 12	52 ± 15	0.195
Cold ischaemic time (hours)	8.7 ± 5.3	11.8 ± 5.8	0.020
Use of CNI			0.326
Tacrolimus	48 (51)	9 (39)	
Cyclosporine	47 (49)	14 (61)	
Use of IL-2RA	57 (60)	11 (48)	0.289
KW/BW (g/kg)	3.3 ± 0.9	2.9 ± 0.7	0.129
Donor age (years)	47.0 ± 13.5	51.0 ± 9.7	0.318
Acute rejection	26 (27)	8 (35)	0.481

* Data are shown as No. (%) or mean ± standard deviation

† BMI denotes body mass index, PRA panel reactive antibody, CNI calcineurin inhibitor, IL-2RA interleukin-2 receptor antagonist, and KW/BW ratio of donor kidney weight to recipient body weight

TABLE 2. Patient demographics and risk factors for acute rejection*

Demographics/risk factor†	Acute rejection absent (n=84)	Acute rejection present (n=34)	P value
Age of recipients (years)	40 ± 11	41 ± 12	0.456
Recipient gender (male)	45 (54)	20 (59)	0.603
First transplant	80 (95)	30 (88)	0.225
PRA (%)	24.2 ± 32.7	18.7 ± 27.1	0.381
AB mismatch	2.3 ± 1.3	2.5 ± 1.1	0.415
DR mismatch	1.0 ± 0.7	1.3 ± 0.7	0.045
Anastomotic time (min)	49 ± 12	49 ± 14	0.869
Cold ischaemic time (hours)	9.6 ± 5.7	8.5 ± 4.9	0.357
Use of CNI			0.009
Tacrolimus	47 (56)	10 (29)	
Cyclosporine	37 (44)	24 (71)	
Use of IL-2RA	48 (57)	20 (59)	0.867
DGF	15 (18)	8 (24)	0.481

* Data are shown as No. (%) or mean ± standard deviation

† PRA denotes panel reactive antibody, CNI calcineurin inhibitor, IL-2RA interleukin-2 receptor antagonist, and DGF delayed graft function

frequency of DGF was similar in patients receiving tacrolimus and cyclosporine (16% vs 23%, P=0.326). There was no significant increase in DGF frequency among patients having second transplants or at higher immunological risk. In the multivariate model incorporating recipient BMIs, anastomotic time and CIT, once again DGF was associated only with CIT. The odds ratio (OR) for DGF increased by 0.002 (95% confidence interval [CI], 0.001-0.003) for each hour of CIT (P=0.03).

During the study period, acute graft rejection occurred in 34 (29%) of the patients. Univariate analysis showed that only the DR mismatch (P=0.045) and use of cyclosporine-based immunosuppression (P=0.009) were associated with acute rejection (Table 2). These features were subsequently entered in a multivariate analysis, whereupon only cyclosporine use as the initial CNI (OR=2.88; 95% CI, 1.21-6.86; P=0.016) remained statistically significant. In our cohort, neither CIT nor DGF were associated with acute rejection (P=0.357 and 0.481, respectively).

To study the impact of DGF and other risk factors on graft function after 1 year, we used a GFR of more or less than 30 mL/min as the dependent variable. Five grafts were lost within the first year of transplant. Regarding the 113 patients with surviving grafts at 1 year, their demographic data are shown in Table 3. In univariate analysis, DGF was a significant risk factor for suboptimal graft function (GFR <30 mL/min). Other risk factors in recipients included: acute rejection, high BMI at transplantation, pre-transplant diabetes mellitus, older age, older donor age, longer anastomotic time, lower KW/BW, and use of cyclosporine as the initial CNI. When all the above variables were entered into the multivariate analysis, only DGF (OR=18.5; 95% CI, 2.6-130.5; P=0.003) and donor age (OR=1.2; 95% CI, 1.1-1.3; P=0.003) remained significantly related to a GFR of less than 30 mL/min at 1 year. When we compared the renal function in patients with and without DGF during the first 3 years post-transplant, it was significantly better in those not enduring DGF (Table 4).

When censored for death, a total of eight grafts were lost during the study period. Seven belonged to the IGF group, while one was in the DGF group. A Kaplan-Meier curve revealed that there was no significant difference in death-censored graft survival between DGF and IGF groups (P=0.68, Figure).

Discussion

The frequency of DGF varies in different centres.[1-5] In our cohort, it was 19%. A key risk factor for DGF was CIT. Data from the United States Renal Data system showed that for every 6 hours of CIT, the risk increased by 23%.[4] In our study, CIT was also a significant independent predictor of DGF, as revealed by multivariate analysis, which was consistent with many previous studies.[5,8,15,16] However, Pieringer and Biesenbach[17] failed to detect such a significant relationship. They postulated that the effect of CIT on DGF was profound only if it was longer than 24 hours and was even more so when reaching 36 hours, whereas their cohort entailed only a few grafts with a CIT exceeding 24 hours. The mean CIT in our

cohort was also very short (9.3 vs >24 hours in other published studies). The short CIT, together with the better quality of donor kidneys (from heart-beating donors) might explain why our renal transplant recipients had a lower frequency of DGF. However, our results also showed that despite the CITs being so short, an impact on DGF was nevertheless evident.

The association between DGF and acute rejection is controversial.[1,17,18] Different studies showed that CIT was associated with both an increased frequency of DGF as well as acute rejection.[19] The pathophysiology of cold ischaemia–induced DGF and rejection is very similar.[20] The rate of acute rejection was also higher in patients enduring DGF (27% in those without DGF vs 35% in those with DGF) but this difference was not statistically significant. In our cohort moreover, neither CIT nor DGF were predictors of acute rejection. A possible explanation was that subclinical rejection might be underdiagnosed, because biopsy is not a routine part of the protocol in our centre.

In addition to risk factors, we also examined the prognostic impact of DGF in our renal transplant recipients. Different studies mainly focused on patient and graft survival as the outcome. However, study of renal function is also very important as graft function at 1 year is a strong surrogate marker of late graft outcome.[21] We found that both DGF and donor age correlated independently with graft function at 1 year. A possible mechanism for decreased GFR in DGF seems related to ischaemia-reperfusion injury to the graft. The impact of DGF on long-term graft outcome, however, is more controversial. A multivariate analysis showed that compared to IGF, DGF was an independent predictor of graft loss with a relative risk of 2.9.[22] The importance of DGF on long-term graft outcome was further supported by a study reporting that the half-life of kidneys with no DGF was 12 years, compared with 7 years in those with DGF.[23] On the other hand, some investigators found that DGF is associated with increased graft loss in the first 6 to 12 months, but not subsequently.[24,25] In our cohort, there was no significant difference in death-censored graft survival between DGF and IGF groups. A possible explanation was the small sample size of our cohort, which was also a major limitation in this study. As a result, the analyses were subject to potential bias due to type 2 error. In our cohort, renal function at 1 year was probably a more important determinant of late graft loss, which was also suggested in the Collaborative Transplant Study.[26]

In conclusion, CIT is an important independent predictor of DGF. Efforts should therefore be directed to reduce CIT. Moreover, DGF has a significant adverse effect on graft function at 1 year. In this analysis however, we could not demonstrate any association between DGF and acute rejection episodes and graft loss.

TABLE 3. Patient demographics and risk factors for glomerular filtration rate (GFR) at 1 year*

Demographics/risk factor†	GFR ≥30 mL/min (n=88)	GFR <30 mL/min (n=25)	P value
Age of recipients (years)	38 ± 10	45 ± 10	0.003
Recipient gender (male)	47 (53)	16 (64)	0.347
Recipient BMI >25 kg/m^2	6 (7)	8 (32)	0.002
Pre-transplant diabetes mellitus	5 (6)	6 (24)	0.014
First transplant	82 (93)	23 (92)	1.000
PRA (%)	21.1 ± 29.7	22.7 ± 31.0	0.810
AB mismatch	2.3 ± 1.3	2.5 ± 1.0	0.535
DR mismatch	1.1 ± 0.7	0.9 ± 0.7	0.295
Anastomotic time (min)	48 ± 11	55 ± 14	0.013
Cold ischaemic time (hours)	9.3 ± 5.6	9.0 ± 5.3	0.826
Use of CNI			0.019
Tacrolimus	48 (55)	7 (28)	
Cyclosporine	40 (45)	18 (72)	
Use of IL-2RA	51 (58)	14 (56)	0.861
DGF	11 (13)	10 (40)	0.006
KW/BW (g/kg)	3.3 ± 0.9	2.8 ± 0.7	0.008
Donor age (years)	44.5 ± 12.1	56.5 ± 10.1	0.001
Acute rejection	18 (20)	13 (56)	<0.001

* Data are shown as No. (%) or mean ± standard deviation

† BMI denotes body mass index, PRA panel reactive antibody, CNI calcineurin inhibitor, IL-2RA interleukin-2 receptor antagonist, DGF delayed graft function, and KW/BW ratio of donor kidney weight to recipient body weight

TABLE 4. Changes of glomerular filtration rate (GFR) over time in patients with and without delayed graft function

Time	GFR (mL/min), mean ± standard deviation		P value
	Immediate graft function	Delayed graft function	
6-Month	44 ± 16 (n=93)	33 ± 13 (n=22)	0.002
12-Month	46 ± 15 (n=92)	37 ± 15 (n=21)	0.026
24-Month	45 ± 18 (n=92)	37 ± 13 (n=21)	0.026
36-Month	46 ± 18 (n=89)	38 ± 15 (n=19)	0.046

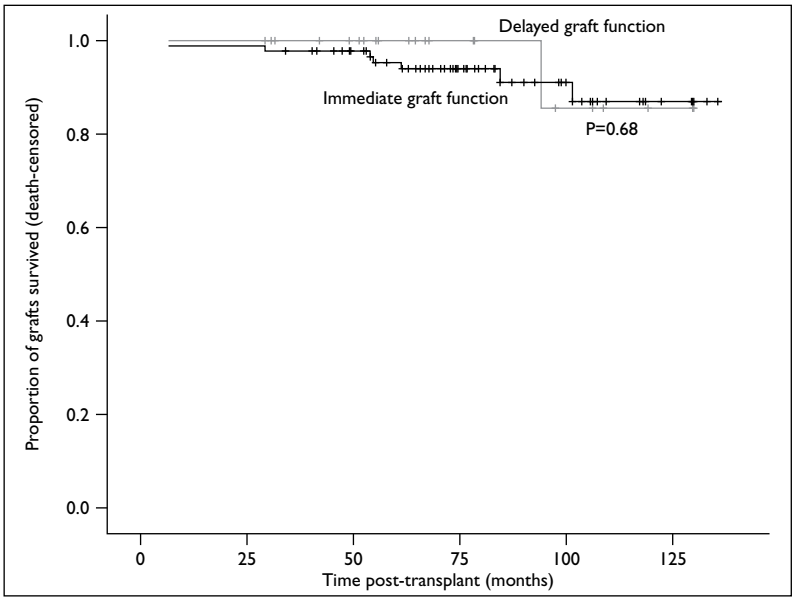

FIG. Death-censored graft survival in patients with and without delayed graft function

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