Risk Factors for Delayed Graft Function Defined as Need for Dialysis or Failure of Creatinine to Fall by 10% in the First 24 Hours After Transplant

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Abstract

Objectives: **Delayed graft function after deceased-donor transplant remains a significant clinical problem. The conventional definition of delayed graft function is the requirement of dialysis within the first week after transplant, but this criterion has many problems that have led to many controversies including those of incidence and significance. Therefore, we sought to identify the possible risk factors of delayed graft function and to investigate their effect on short-term graft survival, according to a composite criterion.**

Materials and Methods: **We reviewed the records of 94 renal transplants obtained from heart-beating deceased donors done at our center during a 2-year period. Variables related to the donor, recipient, and graft were retrospectively collected. Follow-up was 12 months. Delayed graft function was defined as the need for dialysis or the failure of the creatinine level to fall by 10% during the first 24 hours after transplant. To confirm suspected rejection, protocol biopsies were done, irrespective of graft function, on the seventh and 28th days after transplant, or when indicated to confirm suspected rejection.**

Results: **The overall incidence of delayed graft function was 31.9%. Multivariate analysis showed donor age as a significant independent predictor of delayed graft function (OR=1.05, *P* = .03, 95% CI: 1.01-1.09), whereas donor hypotension was the only independent risk factor associated with a worse 1-year graft survival rate (OR=4.6, *P* = .021, 95% CI: 1.3-16.5). No association could be established between delayed graft function, acute rejection, and graft survival.**

Conclusions: **Advanced donor age is a predictor of delayed graft function defined as the need for dialysis or the failure of creatinine to fall by 10% during the first 24 hours after transplant. Preventing hemodynamic instability should be an important aspect of donor care.**

Key words: *Renal transplantation, Graft survival, Acute rejection, Donor age, Deceased donor*

The lack of acceptable autonomous function in a kidney after renal transplant is known as delayed graft function (DGF). It is a common complication after renal transplant that makes managing patients more complicated and diagnosing rejection more difficult; it also prolongs hospital stay and increases the cost of transplant (1, 2). Most authors use "need for dialysis within the first week" as the diagnostic inclusion criterion; however, this does not differentiate the various causes of DGF such as ischemia-reperfusion injury or early acute rejection (3).

Several donor factors (ie, increased age, hypertension for longer than 10 years, hypotension, creatinine clearance lower than 80 mL/min, vascular sclerosis, obesity, and female gender), recipient factors (ie, presensitization, black ethnicity, pretransplant anuria, pretransplant mean arterial pressure below 100 mm Hg, and American Society of Anesthesiology physical status category IV) and transplant procedural factors (ie, prolonged cold ischemia time, time to do the anastomoses, and selection of preservation solution) have been associated with this complication (4, 5). However, the exact causes remain to be clarified.

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Experimental and Clinical Transplantation (2008) 1: 37-41

In this study, we analyzed the risk factors of DGF defined by the composite criterion: the need for dialysis or the failure of the creatinine level to fall by 10% in the first 24 hours after transplant. We also investigate the influence of DGF and other possible risk factors on short-term graft outcome.

Materials and Methods

Between June 2001 and May 2003, a total of 112 renal transplants from heart-beating deceased donors were done at the Oxford Transplant Centre in Oxford, United Kingdom. We excluded 18 transplants because these patients had been enrolled in a randomized trial of Belatacept (n=8), had received a simultaneous kidney-pancreas transplant (n=8), had an early vascular complication (n=1), or were lost to follow-up (n=1). The remaining 94 patients were included in the analysis. The follow-up was 12 months.

All patients received baseline immunosuppression according to a protocol introduced in 2001 (Table 1). In this protocol, patients were stratified into 3 groups at the time of transplant, according to immunologic risk. For immunosuppression, highest-risk patients (ie, those with panel reactive antibodies > 85%, serious crossmatch concern, or 5-6 HLA mismatches) received basiliximab induction, tacrolimus, mycophenolate mofetil, and prednisolone. Those patients of medium risk (ie, those with a previously rejected graft, 3-4 HLA mismatches, or 2 DR mismatches) were given cyclosporine, mycophenolate mofetil, and prednisolone. Low-risk patients (all others) were given cyclosporine, azathioprine, and prednisolone.

Protocol biopsies were obtained in all patients, irrespective of graft function, on the seventh and 28th days after transplant, or when indicated to confirm suspected rejection. All episodes of acute rejection were biopsy proven. DGF was defined as the need for dialysis or the failure of the creatinine level to fall by 10% in the first 24 hours after transplant.

Donor data (ie, age, serum creatinine, hemodynamic instability; hypotension, hypertension, and use of vasoactive drugs), recipient data (ie, age, hypersensitization with > 50% panel reactive antibodies, previous transplants, and serum creatinine levels at 1 year), transplant variables (ie, length of warm ischemia, length of cold ischemia, time to do the anastamoses, HLA mismatches, number of graft arteries or patches, immunologic risk, number of rejections, borderline changes and donor vascular disease confirmed with biopsy, and peak cyclosporine and tacrolimus levels within the first week after transplant), and graft and patient outcomes at 1 year were retrospectively collected.

Table 1. Recipients are stratified into 3 groups before transplant according to immunologic risk.

Risk group	Immediate function	DGF	DGF > 7d
High risk PRA > 85% Serious crossmatch concern 5-6 HLA mismatches	Basiliximab tacrolimus mycophenolate prednisolone†	1/2 level tacrolimus	Stop tacrolimus* Weekly biopsy
Medium risk Previously rejected graft 3-4 HLA mismatches or 2 DR mismatches	Cyclosporin mycophenolate 3-6/12‡ prednisolone†	1/2 level cyclosporin	Stop CyA* start ATG§ Biopsy at end of ATG course, then weekly until function improves
Low risk All others	Cyclosporin azathioprine prednisolone†	1/2 level cyclosporin; stop azathioprine and start mycophenolate 3-6/12‡	Stop CyA* start ATG§ Biopsy at end of ATG course, then weekly until function improves

Abbreviations: ATG, antithymocyte globulin; CyA, cyclosporine; DGF, delayed graft function; PRA, panel reactive antibodies

*Providing renal function is restored and patient is off dialysis, reintroduce calcineurin inhibitor at full dose (aiming for CyA levels 150-300 ng/mL or tacrolimus levels of 10-15 ng/mL) 3 days before stopping ATG. If patient is still dialysis dependent at the end of the ATG course, then continue on dual therapy; mycophenolate mofetil (MMF) and steroids. Monitor closely with FNAs (fine needle aspirations) every 3 days and weekly tru-cut biopsies. Reintroduce calcineurin inhibitor at full dose (aiming for CyA levels of 150-300 ng/mL or tacrolimus levels of 10-15 ng/mL) only when renal function is restored and patient is off dialysis.

†Prednisolone dose: 20 mg od (patients > 60 kg) or 15 mg od (patients ≤ 60 kg). This dose is used for the first 2 months after transplant, then steroid reduction is commenced, unless there have been major rejection episodes in that time. A steroid reduction program reduces the dose at 2 months posttransplant by 2.5 mg every 4 weeks until 5 mg od is achieved. The patient then remains on this dose until seen in the medical transplant clinic at 1 year; at this time a decision is made whether to continue with steroid withdrawal or leave the patient on 5 mg.

‡Continue MMF for 3 of 12 months, then convert to azathioprine (1.5 mg/kg od). However, if the patient has experienced a rejection episode during these first 3 months, then the course of MMF must be extended to 6 months, and at 6 months convert to azathioprine.

§Start ATG 2 mg/kg, 10-to-14-day course (depending on patient response). Give ATG dose when absolute T cell count > 50.

Donor, recipient, and procedural factors, as well as biopsy results, were compared between patients who developed DGF and those who did not. All of the variables were examined to determine whether they affect DGF and 1-year graft survival.

Differences among groups were examined with the *t* test or the nonparametric Mann-Whitney U test for nonnormally distributed data. Also, the Mann-Whitney *U* test was used to compare ordinal categorical data. The Pearson chi-square test or the Fisher's exact test, when appropriate, was used for percentage comparisons. A multiple, backwards, stepwise, logistic regression model was used to

determine the independent relation of the examined variables to DGF and graft survival. Only significant variables (ie, donor age, serum creatinine at 1 year, cold ischemia time, and donor hypotensive episodes) in the previously done univariate analysis and acute rejection episodes were included into the model. For all tests, values for *P* less than .05 were considered statistically significant.

Results

The incidence of DGF was 31.9% (30 grafts). The characteristics of the donors, recipients, and transplants in the 2 study groups with immediate graft function and with DGF are summarized in Table 2. The occurrence of DGF was associated with increased donor age (*t* test, $P = .038$) and with high serum creatinine levels at 1 year after transplant (Mann-Whitney *U* test, $P = .017$). One-year graft survival was affected by a longer cold ischemia time (Mann-Whitney *U* test, $P = .014$) and hypotensive episodes in the donor (Fisher's exact test, $P = .022$).

Table 2. Donors, recipients, and transplants variables and clinical evolution in the 2 groups with IGF and DGF.

Variables	IGF (n=64)	DGF (n=30)	*P* value
Recipient age (y)	46.5 ± 13.3	49.9 ± 12.5	ns
Transplant (1/2/3)	58/5/1	23/5/2	ns
HLA A mismatches	0.90 ± 0.63	0.63 ± 0.66	ns
HLA B mismatches	0.96 ± 0.64	0.76 ± 0.62	ns
HLA C mismatches	0.32 ± 0.47	0.33 ± 0.47	ns
Total HLA mismatches	2.20 ± 1.12	1.73 ± 1.33	ns
Donor age (y)	44.2 ± 14.9	51.1 ± 14.6	.038
Donor serum creatinine level (µmol/L)	82.6 ± 29.8	100.1 ± 56.7	ns
Number of arteries, n (1/2/3/aorta)	50/11/1/2	23/6/1/0	ns
Number of patches, n (0/1/2/aorta)	1/60/1/2	1/29/0/0	ns
Donor hypotension, n (%)	42 (65.6)	19 (63.3)	ns
Donor hypertension, n (%)	34 (53.1)	21 (70)	ns
Use of vasoactive drugs, n (%)	56 (87.5)	23 (76.6)	ns
Hypersensitization (PRA > 50%), n (%)	4 (6.2)	4 (13.3)	ns
Warm ischemia time (min)	0.03 ± 0.17	0.46 ± 1.63	ns
Cold ischemia time (h)	16.8 ± 5.3	16.7 ± 4.8	ns
Anastomotic time (min)	44.4 ± 12.5	44.6 ± 12.2	ns
Risk group (low/medium/high)	29/30/5	13/13/4	ns
Biopsy-proven acute rejection, n (%)	22 (34.37)	15 (50)	ns
Subclinical rejection in protocol biopsies, n (%)	3 (4.6)	1 (3.3)	ns
Borderline changes, n (%)	15 (23.43)	4 (13.3)	ns
Donor vascular disease, n (%)	23 (35.93)	12 (40)	ns
Peak cyclosporine (1st week) (ng/mL)	452.5 ± 231.2	405.6 ± 199.3	ns
Peak tacrolimus levels (1st week) (ng/mL)	18.8 ± 7.7	25.5 ± 4.1	ns
Creatinine level at 1 year (µmol/L)	162.6 ± 123.3	229.2 ± 1 78.2	.017
1-year graft survival, n (%)	57 (89)	25 (83.3)	ns
1-year patient survival, n (%)	59 (92.1)	27 (90)	ns

Abbreviations: DGF, Delayed graft function; IGF, Immediate graft function; ns, not significant; PRA, Panel reactive antibodies; Pt nr, Patient number; statistical measure of variation = standard deviation

To further identify which variables could independently predict DGF and 1-year graft survival, we analyzed data with a multiple, backwards, stepwise, logistic regression model. In this analysis, donor age was an independent predictor of DGF (OR=1.05, $P = .03$, 95% CI: 1.01-1.09). Donor hypotension was the only independent risk factor associated with poorer graft outcome at 1 year after transplant (OR=4.6, $P = .021$, 95% CI: 1.3-16.5). No association between DGF, acute rejection, and graft survival could be established. There was no significant difference in 1-year graft survival rates between recipients who had DGF with or without acute rejection (73.3% and 93.3% respectively, $P = .329$), as well as between patients who had immediate graft function with or without acute rejection (88% and 90.9% respectively, $P = 1.00$).

Discussion

In deceased-donor kidney transplant, DGF usually ranges between 20% and 30%, although some centers have reported an incidence of up to 50% (3). Because of the inability to define DGF by a measurable factor, there is wide variation in its reported incidence. As people attempt to redefine the parameters of DGF, they influence its rate of presentation. The factors that predispose the patient to DGF also differ among centers, and this contributes to the variation.

The rate of DGF (31.9%) seen in the present study was comparable to that reported by other authors. The sample size may have influenced these results, but the criteria used to define DGF also might have done so. Different criteria and different definitions of DGF may change associated risk factors and transplant outcomes. The most frequent definition of DGF is the requirement for dialysis during the first week after transplant, but this has its limitations (the "criteria for dialysis" requirement can vary among nephrologists, and making a diagnosis of DGF may be delayed by up to 1 week). The imprecision of the definition explains why there is so much variation among different clinical studies.

The introduction of new immunosuppressive drugs (ie, tacrolimus, rapamycin, and monoclonal antibodies) may allow clinicians to change therapies until renal function improves and to individualize therapy in those patients who develop DGF. Developing criteria with which to diagnose DGF at a time earlier than 1 week can facilitate this alternative strategy.

Govani and associates developed a definition of DGF that uses a creatinine reduction ratio on the second day after transplant; the authors found that serum creatinine level and the rate of acute rejection were significantly higher in recipients with severe DGF compared with recipients with immediate graft function (6). Other centers use a definition of DGF based on the creatinine reduction ratio the second day after transplant (3) or the serum creatinine level on day 5 (7). Authors at these centers found that older donor age and longer cold ischemia times are the main risk factors for DGF. In their study, Boom and associates diagnosed DGF when serum creatinine levels increased, remained unchanged, or decreased by less than 10% per day for 3 consecutive days during the first week after transplant.

Several risk factors for DGF were identified including advanced donor age, low recipient pretransplant mean arterial blood pressure, prolonged cold ischemia time, transplant of kidneys from female donors to male recipients, and peak panel reactive antibodies of over 50% (8). Gonwa and associates designed a protocol that would identify patients at risk for DGF in the first 6 hours after transplant based on urine output (< 300 cc) or rising serum creatinine level, but they did not analyze the risk factors for DGF (9).

We used a composite definition of DGF that included the need for dialysis or the failure of the creatinine level to fall by 10% during the first 24 hours after transplant. In this study, donor age and renal function at 1 year (as assessed by serum creatinine level) were associated with DGF. Although serum creatinine level is not independent of other factors such as rejection, it is the standard test for assessing renal function and could be used to identify patients to be targeted for intervention.

On multivariate analysis, we identified only 1 well-known independent risk factor for DGF: advanced donor age. Donor age greater than 50 years previously had been reported as a major risk factor for DGF (1, 4, 8). The persistent shortage of donors stimulated different strategies to increase the donor pool. Aged or non–heart-beating donors are frequently included in the category of deceased donors. The need to expand the organ donor pool means that we cannot exclude older donors. However, advanced donor age is clearly associated with increased risk of DGF (1, 3, 8). Furthermore, in our study, we showed that short-term graft survival was influenced by cold ischemia time and donor hypotension. On multivariate analysis, we observed that donor hypotension was the only independent predictor of graft outcome. There were no adverse effects associated with any of the other donor factors. The lack of an effect of matching on graft survival was not surprising because we had a relatively well-matched population (the mean total number of mismatches was 2.03).

It still is not clear how much influence DGF has on graft and patient survival. The effect of DGF on graft survival has been the subject of considerable debate, with a negative impact on graft survival having been found by some studies (1, 3, 7, 10, 11) but not others (4, 8, 12, 13). This may be related to different criteria used to define DGF or to differences in data analyses. In a study by Giral-Classe and associates, the influence of DGF on graft survival was different according to the criteria for DGF used (14). Other authors found that DGF was an independent risk factor for graft loss in the first 6 months but not after 6 months (15). Another study showed that DGF was not associated with graft loss in the first year but that it was associated with graft loss after 1 year (9). In general, multicenter database studies demonstrate a clear link between DGF and graft survival, but the results of many single centers do not (16). It is unknown whether efforts to further improve early renal function will favorably influence graft outcome. This question cannot be answered from a retrospective study.

The evidence that DGF may be associated with an increased risk of early acute rejection is also contradictory (1, 4, 9-13, 17). Examining possible reasons for these conflicting observations provides insight into the problems of studying DGF. Some authors suggest that the relation between DGF and acute rejection is of paramount importance, and that intense DGF surveillance, such as a weekly biopsy to detect and treat acute rejection, is required (2). Detecting subtle renal injury using an earlier definition (ie, diagnose DGF at a time earlier than 1 week) may suggest the need to take routine or earlier biopsies or modify immunosuppressive therapy. Other reports have shown that graft survival in patients with or without DGF is the same if no acute rejection episode occurs, but lower in patients with both DGF and acute rejection when compared with patients with DGF alone (12, 18). However, these results are controversial; other studies have reported acute rejection episodes and DGF to be independent risk factors for allograft loss (10, 19).

Our data contradict this and show that graft survival at 1 year after transplant was not adversely affected by DGF or acute rejection. The lack of an effect of acute rejection on 1-year graft survival is surprising but not unexpected (9, 13). In part, this may be explained by our strategy to do a routine transplant biopsy every 7 days to exclude acute rejection in kidneys with DGF until function is established and by our policy to do protocol biopsies in all patients (irrespective of graft function) on the seventh and 28th day after transplant, or when indicated to confirm suspected rejection. Moreover, fine-needle aspirations were done routinely to monitor the level of infiltration in the graft in recipients with DGF. We believe that diagnosing DGF earlier than 1 week in our group of recipients who had been stratified according to immunologic risk before transplant helped graft recovery, while calcineurin inhibitors were reduced, aiming for half levels. Further, high-risk recipients were treated with basiliximab as induction therapy, which could account partly for the good results for these patients; this is because reports suggest that antibody therapy helps prevent graft loss in high-risk patients (9).

In conclusion, advanced donor age is the main risk factor for postoperative DGF defined by a composite criterion as the need for dialysis or the failure of the creatinine level to fall by 10% during the first 24 hours after transplant. Careful monitoring and maintenance of donor hemodynamic stability is of paramount importance to improve the prognosis for short-term graft survival.

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