Kidney International, Vol. 58 (2000), pp. 859–866

Delayed graft function influences renal function, but not survival

Henk Boom, Marko J.K. Mallat, Johan W. de Fijter, Aeilko H. Zwinderman, and Leendert C. Paul

Departments of Nephrology and Medical Statistics, Leiden University Medical Center, Leiden, The Netherlands

Delayed graft function influences renal function, but not survival.

Background. In renal transplantation, the impact of delayed graft function (DGF) on prognosis is controversial. We analyzed the risk factors of DGF and its impact on graft function and prognosis.

Methods. Seven hundred thirty-four cadaveric renal transplants performed between 1983 and 1997 were analyzed. DGF was diagnosed when serum creatinine levels increased, remained unchanged, or decreased less than 10% per day in three consecutive days in the first week after transplantation. Creatinine clearances of more or less than 50 or 30 mL/min at one year were used as cut-off points for optimal and suboptimal graft function, respectively. The logistic regression model was used to identify independent risk factor related to DGF and renal function one year after transplantation. The Cox regression model was used to examine the influence of DGF on long-term graft survival.

Results. Multivariate analysis revealed the following risk factors for DGF: recipient pretransplantation mean arterial blood pressure of less than 100 mm Hg (OR = 2.08, 95% CI, 1.43 to 3.03), female donor to male recipient combination (OR = 1.55, 95% CI, 1.02 to 2.35), donor age of more than 50 years (OR = 2.21, 95% CI, 1.49 to 3.26), cold ischemia time of more than 28 hours (OR = 1.78, 95% CI, 1.19 to 2.63), and peak panel reactive antibodies of more than 50% (OR = 1.7, 95% CI, 1.15 to 2.55). The incidence of DGF was one of the independent risk factors for suboptimal graft function at one year (OR = 1.68, 95% CI, 1.14 to 2.48), together with donor age of more than 50 years (OR = 2.39, 95% CI, 1.61 to 3.57), female donor gender (OR = 1.99, 95% CI, 1.42 to 2.78), the occurrence of acute rejection episodes (OR = 2.66, 95% CI, 1.87 to 3.78), peak panel-reactive antibodies of more than 50% (OR = 1.67, 95% CI, 1.15 to 2.47), and sharing of 1 to 3 versus 4 to 8 cross-reactive antigens groups (OR = 1.65, 95% CI, 1.09 to 2.49). Moreover, DGF was one of the two independent risk factors for acute rejection episodes, but it had no independent effect on graft survival.

Conclusion. Several risk factors for DGF were identified, of which a low recipient pretransplant mean arterial blood pressure, the transplantation of kidneys from female donors to male recipients, and a prolonged cold ischemia time are potentially avoidable. Although DGF is one of the several risk factors of acute rejection and suboptimal function at one year, it is not independently associated with an increased rate of graft loss.

Key words: transplantation, cadaveric renal transplantation, ischemia-reperfusion injury, acute graft rejection, kidney graft function.

Received for publication December 6, 1999
and in revised form February 15, 2000
Accepted for publication March 10, 2000

In renal transplantation, there is controversy regarding the impact of delayed graft function (DGF) on long-term outcome. This may relate to different criteria used to define DGF or to differences in data analysis. Most authors use the need for dialysis within the first week as the diagnostic inclusion criterion, but this does not differentiate the various causes of DGF such as ischemia-reperfusion injury or early acute rejection episodes. In addition, the degree of renal damage is often not taken into consideration. In the UNOS registry, DGF, defined as the need for dialysis in the first week after transplantation, had a significant and independent impact on graft half-life. This effect was distinct from cold ischemia time (CIT), occurrence of acute rejection episodes, donor age, and serum creatinine levels [1, 2]. Others found a detrimental effect of DGF, also defined as the need for dialysis in the first week, on graft survival only when it was complicated by one or more acute rejection episodes [3, 4]. Using the time required to reach a Cockroft renal clearance of more than 10 mL/min, DGF lasting for more than six days had a deleterious effect on graft survival, whereas DGF of shorter duration did not influence graft survival [5]. In the present study, we analyzed the risk factors of DGF defined by stringent criteria, independent from the need of dialysis. Moreover, as graft function at one year is a strong surrogate marker of late graft outcome [6, 7], we also studied the impact of DGF on one-year graft function, graft loss, and long-term prognosis.

METHODS

Patients

All patients who received a cadaveric renal transplant in our center between April 1983 and December 1996

were included in the study. Kidneys were allocated according to the matching and allocation criteria of Eurotransplant. We aimed to accept kidneys with no more than two human lymphocyte antigen (HLA) mismatches with a priority for HLA-DR matching.

Immunosuppressive regimen

The standard immunosuppressive regimen consisted of prednisone and cyclosporine A [Sandimmune (CsA)]. Sixty-two patients (8.4%) did not receive CsA and were initially treated with azathioprine (Aza) in a dosage of 2 mg/kg/day. Two hundred seven (28%) patients initially treated with CsA were randomly or on clinical grounds converted to Aza within the first six post-transplant months. CsA was administered intravenously in a dose of 3 mg/kg/day for the first 48 hours, starting at the onset of surgery. The initial oral dose of CsA was 10 mg/kg/day from day 2 onward, divided in three daily doses, and subsequently tapered. Doses were adjusted according to CsA trough levels. After six weeks, the total dose was given as a once daily dose. In the first three months, the target 24-hour CsA trough level was between 250 and 500 mg/L. We targeted to a 24-hour trough level range after three months between 50 and 150 mg/L. All patients received 20 mg of prednisone starting on day 1; this dose was reduced by 2.5 mg every fortnight until a daily maintenance dose of 10 mg was reached. Rejection episodes were treated with 1 g of methylprednisolone intravenously for 3 days or rabbit antithymocyte globulin for 10 days, as previously described [8].

Definitions

To exclude patients who were dialyzed for reasons other than impaired graft function, we diagnosed DGF retrospectively if the serum creatinine level increased, remained unchanged, or decreased by less than 10% per day immediately after surgery during three consecutive days for more than one week. If a graft biopsy taken within the first post-transplant week showed rejection, it was assumed that the graft did not have DGF, and it was categorized as primary function (PF). Primary nonfunction (PNF) was defined as the absence of a decrease in the serum creatinine level that ultimately resulted in graft nephrectomy. PF was defined as a decrease of the serum creatinine level of more than 10% per day over three consecutive days within the first week after surgery.

Graft loss was defined as resumption of dialysis treatments. Early graft loss was defined as graft loss within the first year after transplantation. Graft survival was censored for patient death with functioning graft. Renal function at one year was calculated using the Cockroft-Gault formula [9]:

$$\text{Creatinine clearance} = [(140 - \text{age}) \times \text{weight (kg)} \times (\text{A})/(\text{serum creatinine (mmol/L)} \times 0.8)]$$

in which A = 1 in males and A = 0.85 in females.

Study design

Risk factors of DGF and the impact of DGF on renal function within the first year were analyzed and compared with grafts experiencing PF. Moreover, a broad spectrum of donor-, recipient-and transplantation-related variables was studied (Table 1). Acute rejection episodes were diagnosed on clinical grounds and confirmed by biopsy, unless a biopsy could not be obtained. Rejections were classified as predominantly interstitial or vascular, although most vascular rejections had variable degrees of interstitial inflammation. Mean arterial blood pressure (MAP) was calculated using the following formula:

$$\text{MAP} = (\text{diastolic blood pressure} \times 2 + \text{systolic blood pressure})/3$$

Cross-reactive groups (CREGs) were defined as the HLA public epitopes of the class I MHC-antigens, based on the amino acid residue system as proposed for UNOS allocation [10]. Not only the degree of mismatching, but also the effect of sharing between donor and recipient of HLA antigens was studied. The term "mismatch" was used for the number of HLA antigens that donor and recipient did not have in common, whereas the term "shares" was used for the number of corresponding HLA antigens between donor and recipient.

In our study population, the mean endogenous creatinine clearance at one year was approximately 50 mL/min (Fig. 1). Arithmetical graft half-life was 70 years for grafts with a creatinine clearance of more than 50 mL/min and 18.5 years for grafts with a one-year creatinine clearance of less than 50 mL/min. Therefore, patients having a creatinine clearance of more or less than 50 mL/min were categorized as optimal or suboptimal function, respectively. We furthermore analyzed the data using a graft function of more or less than 30 mL/min as the dependent variable. This cut-off point represents the mean minus one standard deviation and is a more stringent outcome parameter. Arithmetical graft half-life was 53 years for grafts with a creatinine clearance of more than 30 mL/min and seven years for grafts with a one-year creatinine clearance of less than 30 mL/min. To predict outcome at one year, patients experiencing graft loss within this year were categorized as having suboptimal function at one year. To study the additional impact of DGF on outcome after the first year, we analyzed its effect in different strata of renal function after one year.

Table 1. Characteristics at time of transplantation

Risk factor	Total (N = 734)	PF N = 551 (75.1%)	DGF N = 183 (24.9%)
Recipient			
Age *years*	46 ± 13	46 ± 12	47 ± 14
Gender % *female*	38	38	39
Peak panel reactive antibodies (PRAH) %	31 ± 32	29 ± 31	36 ± 35
Current panel reactive antibodies (PRAC) %	12 ± 23	11 ± 22	14 ± 26
MAP before transplantation *mm Hg*	109 ± 16	110 ± 17	106 ± 16
Donor			
Age *years*	37 ± 14	36 ± 14	42 ± 14
Gender % *female*	41.7	44.9	40.5
Cause of death			
Trauma/cardiovascular %	47.5/52.5	49.5/50.5	41.8/58.2
Transplantation related			
Gender mismatch			
No mismatch %	54	56	46
Donor male-recipient female %	21	20	24
Donor female-recipient male %	25	23	30
Transplant status			
First transplant %	83	76	79
>1 transplant %	17	24	21
Cold ischemia time *hours*	29 ± 7	28 ± 7	30 ± 7
Warm ischemia time *minutes*	28 ± 9	28 ± 9	28 ± 9
Immunosuppression at transplantation			
Aza/pred. %	8	9	6
Immunosuppression at 6 months			
Aza/pred. %	28.1	29.6	23.5
HLA			
Mismatch	1.9 ± 1.1	1.9 ± 1.1	1.9 ± 1.2
Shares	3.7 ± 1.0	3.6 ± 1.0	3.6 ± 1.1
CREG			
Mismatch	1.2 ± 1.1	1.2 ± 1.1	1.1 ± 1.0
Shares	4.5 ± 1.2	4.5 ± 1.2	4.5 ± 1.1
Number of rejection episodes <1 year			
1 %	23	23	24
2 %	23	20	30
>2 %	11	10	13
Type of rejection <1 year			
Interstitial %	36	34	41
Vascular %	14	12	21
Clinical %	8	8	7
Graft loss within 1 year %	13	11	19
Clearance at 1 year *mL/min*	53 ± 20	55 ± 20	47 ± 21

Data are expressed as mean ± SD unless otherwise stated.

Statistical analysis

The logistic regression model was used to determine the factors significantly related to DGF, early graft loss, acute rejection, and renal function at one year in an univariate way. The significant predictors of each parameter of renal function were next fitted in a multivariate model. Step forward selection techniques were used to determine significant risk factors. The risk is expressed as odds ratio (OR) + 95% CI. The impact of a suboptimal Cockroft clearance at one year on late graft loss was studied using the Cox regression model. By using this model, we were able to correct for the time of follow-up to graft loss. The risk is expressed as a relative risk (RR) + 95% CI. We used the Kaplan–Meier survival analysis (log-rank test) to compare graft failure in the different strata of Cockroft clearance at one year. The SPSS software package (9.0) was used for all analyses.

RESULTS

Seven hundred ninety patients were included in the study; 24 (3.0%) were not analyzed because of PNF and 32 (4.1%) because of missing data on DGF. Demographic data are shown in Table 1. DGF was diagnosed if the serum creatinine level increased, remained unchanged, or decreased less than 10% per day immediately after surgery during three consecutive days for more than one week. Twenty-eight (11.8%) of the patients experiencing renal dysfunction in the first week, making dialysis treatment necessary, had a biopsy-proven acute rejection episode and were classified as PF.

Risk factors for delayed graft function

In an univariate analysis, donor age of more than 50 years, MAP of less than 100 mm Hg, cold ischemia time (CIT) of over 28 hours, transplantation of a kidney from

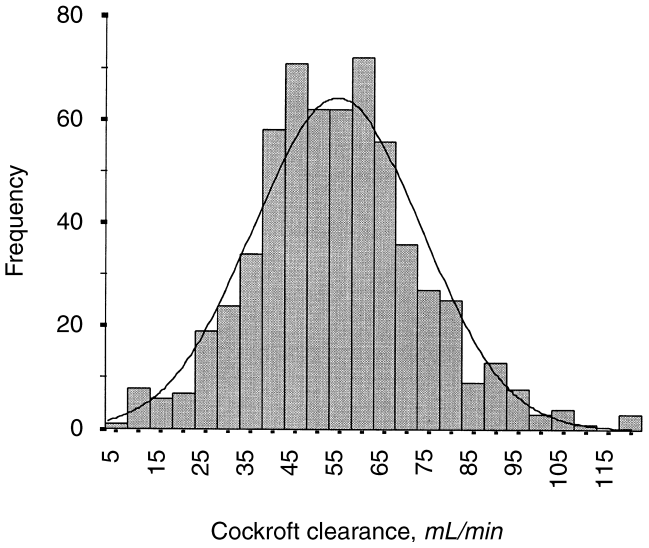

Fig. 1. Frequency-distribution curve of the Cockroft clearances at one year in 604 transplant patients.

Table 2. Risk factors for delayed graft function[a]

Variable	Odds ratio	95% CI[b]
Donor age		
>50 years	2.21	1.49–3.26
Recipient MAP before transplantation		
<100 mm Hg	2.08	1.43–3.03
Cold ischemia time		
>28 hours	1.78	1.19–2.63
Gender mismatch		
No mismatch	1	
Donor male-recipient female	1.09	0.69–1.73
Donor female-recipient male	1.55	1.02–2.35
Peak panel reactive antibodies		
>50%	1.7	1.15–2.55

[a] Multivariate analysis
[b] 95% confidence interval

a female donor to a male recipient, and peak panel reactive antibodies of over 50% were associated with DGF. All of these factors were subsequently entered in a multivariate analysis and remained significant (Table 2).

Risk factors for suboptimal graft function after one year

To analyze the impact of DGF and other factors on graft function after one year, we used the creatinine clearance of more or less than 50 mL/min as the dependent variable. The univariate analysis revealed DGF as a risk factor for a suboptimal graft function after one year. Other risk factors for suboptimal function included donor age of more than 50 years, female donor gender, donor cause of death (cardiovascular vs. trauma), total warm ischemia time, peak panel reactive antibodies of more than 50%, current panel reactive antibodies, sharing of less than three CREGs, and the number of acute rejection episodes within the first year. All of these factors were entered in a multivariate analysis and, as shown in Table 3, remained significant with the exception of donor cause of death and the warm ischemia time.

Table 3. Risk factors for suboptimal function (creatinine clearance <50 mL/min) at one year after transplantation, including graft loss in the first year[a]

Variable	Odds ratio	95% CI[b]
Delayed graft function	1.68	1.14–2.48
Donor age		
>50 years	2.39	1.61–3.57
CREG-sharing		
1–3 shares versus 4–8 shares	1.65	1.09–2.49
Number of acute rejection episodes		
>1	2.66	1.87–3.78
Donor gender		
Female versus male	1.99	1.42–2.78
Peak panel reactive antibodies		
>50%	1.67	1.15–2.47

[a] Multivariate analysis
[b] 95% confidence interval

Table 4. Risk factors for a one-year creatinine clearance <30 mL/min including graft loss within one year[a]

Variable	Odds ratio	95% CI[b]
Delayed graft function	1.81	1.17–2.81
Donor age		
>50 years	2.11	1.35–3.29
Immuno-suppressive regimen at time of transplantation		
Aza/Pred. vs. CsA/Pred.	2.53	1.32–4.83
CREG-sharing		
1–3 vs. 4–8 shares	2.53	1.30–3.35
Number of acute rejection episodes		
≥1	4.00	2.41–5.65

[a] Multivariate analysis
[b] 95% confidence interval

As a creatinine clearance of 30 mL/min was a more stringent outcome variable for graft function, we also analyzed 30 mL/min at one year as the dependent variable. In the univariate analysis, DGF remained a significant risk factor, as were donor age of more than 50 years, female donor gender, and sharing of three or less CREGs. The use of an initial Aza-based immunosuppressive regimen, the occurrence of acute rejection episodes, and vascular rejection, were all associated with suboptimal outcome. Table 4 shows the results of the multivariate analysis. The incidence of DGF (OR = 1.81, 95% CI, 1.17 to 2.81), the use of kidneys from donors older than 50 years (OR = 2.11, 95% CI, 1.35 to 3.29), the initial use of an Aza-based immunosuppressive regimen (OR = 2.53, 95% CI, 1.32 to 4.83), the sharing of three or less CREGs (OR = 2.53, 95% CI, 1.30 to 3.35), and the incidence of acute rejection episodes (OR = 4.00, 95% CI, 2.41 to 5.65) remained significantly and independently related to a graft function of less than 30 mL/

Table 5. Risk factors for the occurrence of acute rejection episodes within one year[a]

Variable	Odds ratio	95% CI[b]
Delayed graft function	1.61	1.11–2.33
Mismatch HLA DR ≥1	2.36	1.68–3.31
Peak panel reactive antibodies >50%	1.60	1.12–2.30

[a] Multivariate analysis
[b] 95% confidence interval

min after one year. We were not able to analyze the recipient's age, weight, and gender as risk factors because these variables were used in the Cockroft–Gault method to estimate graft function.

Occurrence of acute rejection episodes within one year after transplantation

Delayed graft function was associated with an increasing likelihood of acute rejection episodes in an univariate analysis, as were female donor gender, HLA-DR mismatch, peak panel reactive antibodies of more than 50%, and retransplant status of the recipient. HLA-sharing correlated inversely with the incidence of acute rejection episodes. Table 5 shows the independent risk factors for acute rejection in the first year in the multivariate analysis. The incidence of acute rejection episodes was independently associated with DGF (OR = 1.61, 95% CI, 1.11 to 2.33), an increase of HLA-DR mismatch (OR = 2.36, 95% CI, 1.68 to 3.31), and peak panel reactive antibodies of more than 50% (OR = 1.60, 95% CI, 1.12 to 2.30).

Influence of DGF on graft loss

Figure 2 shows the univariate Kaplan–Meier graft survival estimates of patients with PF and patients with DGF. There was a significantly decreased graft survival in patients with DGF, with an arithmetical graft half-life of 12.8 years, compared with 21.7 years for patients not experiencing DGF. The main effect of DGF on graft loss seemed to take place in the first year, whereas after the first year, especially after six years, there was no difference in outcome (data not shown). The short- and long-term graft losses were analyzed separately.

In a univariate analysis, DGF was correlated with graft loss within the first year, as were female donor gender, an Aza-based immunosuppressive regimen, CIT of more than 24 hours, and the number and type of rejection episodes. Sharing of HLA class-1 antigens correlated inversely with graft loss. However, when the data were entered in a multivariate analysis, neither DGF (OR = 1.52, 95% CI, 0.92 to 2.53) nor cold ischemic time (OR = 1.17, 95% CI, 0.72 to 1.88) remained a risk factor for graft-loss within the first year. Acute rejection episodes,

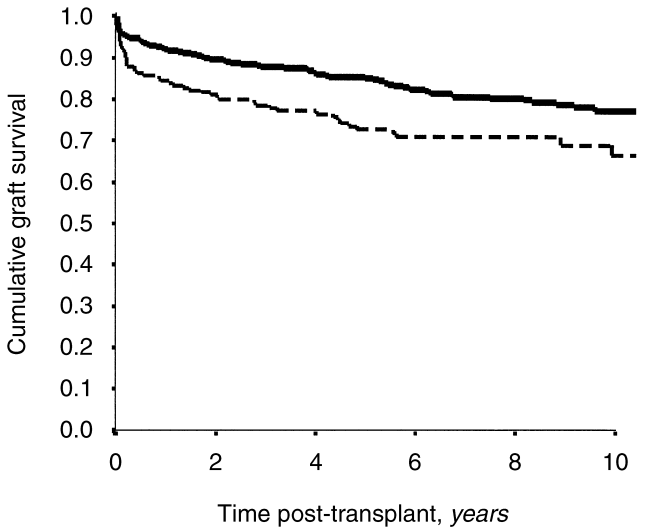

Fig. 2. Graft survival according to the incidence of delayed graft function (DGF). Kaplan–Meier estimates for transplants experiencing primary function (PF; ——, $N = 550$; half-life 21.7 years) and experiencing DGF (– – –, $N = 183$; arithmetical half-life 12.8 years). Log-rank test, $P = 0.0005$.

Table 6. Risk factors for graft loss within one year[a]

Variable	Odds Ratio	95% CI[b]
Donor related		
Gender of donor	1	
Female vs. male	1.70	1.07–2.68
Transplantation related		
Immunosuppressive regimen		
Aza/Pred. vs. CsA/Pred.	2.07	1.05–4.09
Type of rejection <1 year		
No	1	
Interstitial	2.64	1.33–5.22
Vascular	9.32	4.77–18.2
Clinical (no biopsy)	3.61	1.45–8.99

[a] Multivariate analysis
[b] 95% confidence interval

especially vascular rejection (OR = 9.32, 95% CI, 4.77 to 18.2), female donor gender (OR = 1.70, 95% CI, 1.07 to 2.68), and an Aza-based immunosuppressive regimen (OR = 2.07, 95% CI, 1.05 to 4.09) remained independently associated with graft loss within the first year (Table 6).

Graft loss after the first year was associated in a univariate analysis with recipient age of less than 50 years and donor age of more than 50 years, the occurrence of acute rejection episodes in the first year, and a CIT of more than 34 hours. Increased sharing of HLA antigens, sharing of four to eight versus three or less CREGs, and higher creatinine clearance at one year correlated inversely with graft loss. DGF was not an independent risk factor for graft loss after the first year (OR = 1.58, 95% CI, 0.98 to 2.54). Table 7 shows the results of the multivariate analysis. The occurrence of acute rejection

Table 7. Risk factors of graft loss after one year[a]

Variable	Relative risk	95% CI[b]
Recipient age		
<50 years	1.70	1.00–2.86
Cold ischemia time		
>34 hours	1.91	1.20–3.05
Occurrence of acute rejection episodes	1.38	1.11–1.71

[a] Multivariate analysis
[b] 95% confidence interval

episodes (OR = 1.38, 95% CI, 1.11 to 1.71), recipient age of less than 50 years (OR = 1.70, 95% CI, 1.00 to 2.86), and a CIT of more than 34 hours (OR = 1.90, 95% CI, 1.20 to 3.05) were all independent risk factors for late graft loss. As soon as the Cockroft clearance after one year was fitted in the model as a continuous parameter, CIT and recipient age were no risk factors anymore. Therefore, graft function at one year was a strong predictor of late graft outcome (RR 0.96, 95% CI, 0.95 to 0.97 per mL/min). When graft function after one year was divided in four strata of clearance of >50 mL/min, clearance of 40 to 50 mL/min, clearance of 30 to 40 mL/min, and clearance of <30 mL/min, DGF had no additional effect on graft survival in any stratum (Fig. 3).

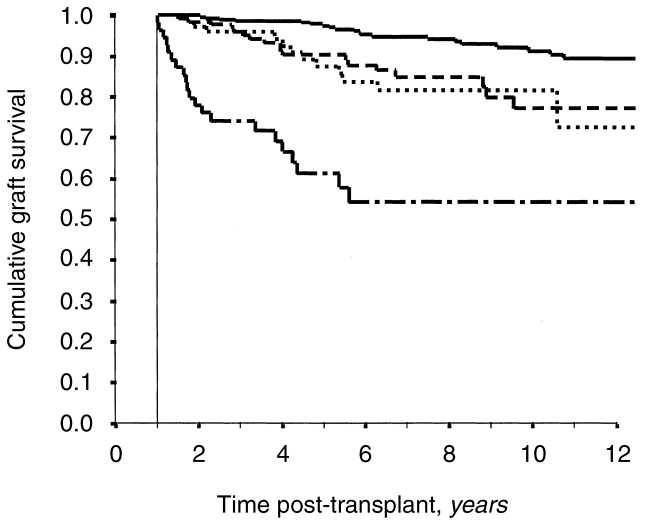

Fig. 3. Graft survival according to graft function one year after transplantation. Kaplan-Meier estimates for transplants experiencing a one-year creatinine clearance of >50 mL/min [(——; $N = 339$) and arithmetical half-life of 70 years]; 40 to 50 mL/min [(– – –; $N = 135$) and arithmetical half-life of 30 years]; 30 to 40 mL/min [(····· ; $N = 79$) and arithmetical half-life of 25 years]; <30 mL/min [(–·–·–·; $N = 56$) and arithmetical half-life 7 years]. Log-rank test: $P = 0.009$, > 50 mL/min vs. 40 to 50 mL/min; $P < 0.001$, >50 mL/min vs. 30 to 40 mL/min; $P < 0.001$, >50 mL/min vs. <30 mL/min; $P = 0.67$, 40 to 50 mL/min vs. 30 to 40 mL/min; $P < 0.001$, 40 to 50 mL/min vs. <30 mL/min; $P = 0.003$, 30 to 40 mL/min vs. <30 mL/min.

DISCUSSION

In this retrospective study, we examined the risk factors and prognostic significance of DGF in renal transplantation. In contrast to most other studies examining these parameters, we used a more stringent definition of DGF and analyzed the effect of DGF on graft function and survival independently. When DGF was diagnosed, if the serum creatinine level increased, remained unchanged, or decreased less than 10% per day immediately after surgery during three consecutive days for more than 1 week, 183 (23.2%) patients experienced DGF, and 551 (69.7%) had primary graft function. If DGF was defined as the need of dialysis in the first week, 244 (33.9%) of the patients would have been classified as having DGF. This means that 26% of patients who were dialyzed postoperatively required dialysis treatment for other reasons than DGF and that 10% of the patients experiencing DGF did not need dialysis treatment.

Studies on transplant outcomes have traditionally focused on patient and graft survival as end points, without consideration of graft function. Although graft loss is the worst type of graft dysfunction, grafts with an impaired function require the most intense follow-up and therapeutic management and are economically most costly [11]. For this reason, graft function as a parameter in studies on outcome of kidney transplantation should be considered.

One of the possible mechanisms of the decreased glomerular filtration rate in DGF seems related to tubular damage resulting from ischemia/reperfusion injury. Tubular epithelial cell degeneration, tubular cell exfoliation, interstitial edema, and interstitial cellular infiltration are usually observed in biopsies in DGF [12]. In the early phase, tubular obstruction by exfoliated tubular cells results in a low net filtration pressure [13]. Later, decreased sodium reabsorption results in afferent vasoconstriction and diminished glomerular filtration pressures through the tubuloglomerular feedback mechanism [14]. Another factor related to DGF is brain death [15], but all the patients studied received a cadaveric transplant.

In the present study, we found that DGF was significantly associated with the use of kidneys from older donors, particularly donors of more than 50 years of age, with the use of female donor kidneys transplanted into male recipients, a CIT of more than 28 hours, historic panel reactive antibodies of more than 50%, and a recipient's pretransplant MAP of less than 100 mm Hg. Other authors have also reported an increased incidence of DGF in grafts from older donors [1, 16–18]. In human adults, total metabolism and renal function in terms of glomerular filtration rate and renal blood flow decrease

with age. This is associated with a decrease in the number of glomeruli, a decrease in the mean glomerular volume [19], and interstitial fibrosis [20, 21]. It is conceivable that such kidneys are more susceptible to additional insults such as brain death and the transplantation procedure.

The higher incidence of DGF in female donor to male recipient combinations could be explained by the absence of estrogens in the male environment. In vitro studies have shown that the administration of estrogens leads to dilation of aortic rings [22], as has been described in vivo in human coronary arteries [23]. It is therefore conceivable that, when transplanted into a male environment, female kidneys experience more vasoconstriction and thus are more prone to DGF. An interesting observation is the finding that a low pretransplant blood pressure level in the recipient confers a significant risk to DGF (Table 2). A stable hemodynamic condition and possibly some degree of extracellular volume expansion are associated with good perfusion of the graft immediately after recirculation [24, 25]. Moreover, invasive hemodynamic studies have shown that a high pulmonary artery [26] or central venous pressures [27] before, during, and after the transplantation surgery correlate inversely with the incidence of DGF. As ischemia-reperfusion injury results in the loss of autoregulation [28], the beneficial effect of hypervolemia may result in an increased glomerular perfusion flow and pressure. It is unknown whether the reduced incidence of DGF in patients treated with peritoneal dialysis, as found by some authors [29, 30], is also based on an increased total extracellular fluid volume. A CIT of longer than 28 hours was also independently associated with an increased risk of DGF, as found by others [31–34]. This is probably also the result of increased vasoconstriction [35] and renal damage as a result of ischemic injury. Peak panel-reactive antibodies constitute another independent risk factor for DGF, as was noted by others [5]. In studies in which DGF was defined as the need of dialysis within the first week after transplantation, DGF could theoretically have included acute rejection episodes. Although we corrected for acute rejection episodes, peak panel-reactive antibodies remained independently correlated with DGF. It is thus conceivable that we missed some very early rejection episodes, as we did not biopsy every graft experiencing DGF, within one week. In contrast to another study [5], we found no effect of the initial immunosuppressive regimen on early graft function.

The transplanted nephron mass and subsequent graft damage determine renal function, and many of the risk factors for graft loss very likely operate through these factors [36, 37]. We found that the number of acute rejection episodes, donor age, donor gender, DGF, and decreased sharing of CREGs is correlated independently with graft function at one year. Using either 50 or 30 mL/min as the cut-off point, DGF remained a risk factor for poor graft function at one year. Although DGF is a strong risk factor for acute rejection episodes (OR = 1.63, 95% CI, 1.11 to 2.33), the effect of DGF on graft function was independent from the number of rejection episodes. Long-term follow-up studies of native kidneys that have experienced acute tubular necrosis (ATN) suggested a decrease in renal function in most cases, although it was not associated with chronic failure [38, 39]. However, experimental studies in rats have shown that ischemia added to ongoing injury results in more severe tissue damage [40]. Some authors found an effect of DGF on graft survival only in combination with acute rejection episodes [3, 4, 41]. In our model, DGF had no influence on graft loss at one year or after the first year. Renal function at one year is probably a more important determinant for late graft loss, as suggested in the Collaborative Transplant Study [42]. To study the effect of DGF on late outcome further, we stratified renal function after one year in four strata (Fig. 3), and demonstrated that renal function at one year is a risk factor of late graft loss. When the contribution of DGF on late graft loss was analyzed in these strata, there was no additional effect of DGF on outcome.

In this retrospective study, we found that DGF, defined as the absence of a decline in serum creatinine of 10% or more in three consecutive days for more than one week after transplantation, has an independent effect on graft function at one year as well as on the incidence of acute rejection episodes, but it does not seem to influence early or late graft loss. Graft survival after one year is mainly determined by the creatinine clearance at one year, which suggests that the influence of DGF on graft survival is through graft function at one year. We also found that the incidence of DGF is related to pretransplantation MAP, probably as a marker for the effective circulating volume. Furthermore, the use of kidneys from older donors or from female donors transplanted into male recipients increases the risk for DGF. It remains to be seen whether changing these risk factors improves the rate of DGF as well as long-term function.

Reprint requests to Henk Boom, M.D., Department of Nephrology, Leiden University Medical Center, P.O. Box 9600, 2300 RC, Leiden, The Netherlands.
E-mail: hboom@nephrology.azl.nl

REFERENCES

1. Ojo AO, Wolfe RA, Held PHJ, Port FK, Schmouder RL: Delayed graft function: Risk factors and implications for renal allograft survival. *Transplantation* 63:968–974, 1997
2. Shoskes DA, Cecka JM: Deleterious effects of delayed graft function in cadaveric renal transplant recipients independent of acute rejection. *Transplantation* 66:1697–1701, 1998
3. Troppmann C, Gillingham KJ, Gruessner RWG, Dunn DL, Payne WD, Najarian JS, Matas AJ: Delayed graft function in the absence of rejection has no long-term impact. *Transplantation* 61:1331–1337, 1996

4. Lehtonen SRK, Isoniemi HM, Salmela KT, Taskinen EI, Von Willebrand EO, Ahonen JP: Long-term graft outcome is not necessarily affected by delayed onset of graft function and early acute rejection. *Transplantation* 64:103–107, 1997
5. Giralclasse M, Hourmant M, Cantarovich D, Dantal J, Blancho G, Daguin P, Ancelet D, Soulillou JP: Delayed graft function of more than six days strongly decreases long-term survival of transplanted kidneys. *Kidney Int* 54:972–978, 1998
6. Woo YM, Jardine AG, Clark AF, MacGregor MS, Bowman AW, Macpherson SG, Briggs JD, Junor BJ, McMillan MA, Rodger RS: Early graft function and patient survival following cadaveric renal transplantation. *Kidney Int* 55:692–699, 1999
7. Sund S, Reisaeter AV, Fauchald P, Bentdal O, Hall KS, Hovig T: Living donor kidney transplants: A biopsy study 1 year after transplantation, compared with baseline changes and correlation to kidney function at 1 and 3 years. *Nephrol Dial Transplant* 14:2445–2454, 1999
8. Kooijmans-Coutinho MF, Hermans J, Schrama E, Ringers J, Daha MR, Bruijn JA, van der Woude FJ: Interstitial rejection, vascular rejection, and diffuse thrombosis of renal allografts: Predisposing factors, histology, immunohistochemistry, and relation to outcome. *Transplantation* 61:1338–1344, 1996
9. Cockcroft DW, Gault MH: Prediction of creatinine clearance from serum creatinine. *Nephron* 16:31–41, 1976
10. Truong L, Shappell S, Solez K: Adhesion molecules as markers of acute cellular rejection of renal allografts. *Transplant Proc* 28:519–522, 1996
11. Anonymous: The high cost of delayed graft function in cadaveric transplantation. *Transplantation* 51:1115–1118, 1991
12. Marcussen N, Lai R, Olsen S, Solez K: Morphometric and immunohistochemical investigation of renal biopsies from patients with transplant ATN, native ATN or acute graft rejection. *Transplant Proc* 28:470–476, 1996
13. Donohoe JF, Venkatachalam MA, Bernard DB, Levinsky NG: Tubular leakage and obstruction after renal ischemia: Structural-functional correlations. *Kidney Int* 13:208–222, 1978
14. Alejandro VS, Nelson WJ, Huie P, Sibley RK, Dafoe D, Kuo P, Scandling JDJ, Myers BD: Postischemic injury, delayed function and $Na^+/K(^+)$-ATPase distribution in the transplanted kidney. *Kidney Int* 48:1308–1315, 1995
15. Van der Hoeven JA, Ploeg RJ, Postema F, Molema I, de Vos P, Girbes AR, van Suylichem PT, van Schilfgaarde R, Ter Horst GJ: Induction of organ dysfunction and up-regulation of inflammatory markers in the liver and kidneys of hypotensive brain dead rats: A model to study marginal organ donors. *Transplantation* 68:1884–1890, 1999
16. Pfaff WW, Howard RJ, Patton PR, Adams VR, Rosen CB, Reed AI: Delayed graft function after renal transplantation. *Transplantation* 65:219–223, 1998
17. Koning OHJ, Ploeg RJ, van Bockel JH, Groenewegen M, van der Woude FJ, Persijn GG, Hermans J: Risk factors for delayed graft function in cadaveric kidney transplantation: A prospective study of renal function and graft survival after preservation with University of Wisconsin solution in multi-organ donors. *Transplantation* 63:1620–1628, 1997
18. Terasaki P, Gjertson DW, Cecka JM, Cho YW: Significance of the donor age effect on kidney transplants. *Clin Transplant* 11:366–372, 1997
19. Nyengaard JR, Bendtsen TF: Glomerular number and size in relation to age, kidney weight, and body surface in normal man. *Anat Rec* 232:194–201, 1992
20. Seron D, Carrera M, Grino JM, Castelao AM, Lopez-Costea MA, Riera L, Alsina J: Relationship between donor renal interstitial surface and post-transplant function. *Nephrol Dial Transplant* 8:539–543, 1993
21. Rodriguez-Puyol D: The aging kidney. *Kidney Int* 54:2247–2265, 1998
22. Ma L, Yu Z, Xiao S, Thadani U, Robinson CP, Patterson E: Supersensitivity to serotonin- and histamine-induced arterial contraction following ovariectomy. *Eur J Pharmacol* 23:191–200, 1998
23. Reis SE, Holubkov R, Zell KA, Smith AJ, Cohen HA, Feldman MD, Blumenthal RS: Estrogen acutely abolishes abnormal cold-induced coronary constriction in men. *Chest* 114:1556–1561, 1998
24. Toth M, Reti V, Gondos T: Effect of recipients' peri-operative parameters on the outcome of kidney transplantation. *Clin Transplant* 12:511–517, 1998
25. Dawidson IJ, Sandor ZF, Coorpender L, Palmer B, Peters P, Lu C, Sagalowsky A, Risser R, Willms C: Intraoperative albumin administration affects the outcome of cadaver renal transplantation. *Transplantation* 53:774–782, 1992
26. Carlier M, Squifflet JP, Pirson Y, Gribomont B, Alexandre GPJ: Maximal hydration during anesthesia increases PAP and improves early function of human renal transplants. *Transplantation* 34:201–204, 1982
27. Thomsen HS, Lokkegaard H, Munck O: Influence of normal central venous pressure on onset of function in renal allografts. *Scand J Urol Nephrol* 21:143–145, 1987
28. Morita K, Seki T, Nonomura K, Koyanagi T, Yoshioka M, Saito H: Changes in renal blood flow in response to sympathomimetics in the rat transplanted and denervated kidney. *Int J Urol* 6:24–32, 1999
29. Vanholder R, Heering P, Vanloo A, Vanbiesen W, Lambert MC, Hesse U, Vandervennet M, Grabensee B, Lameire N: Reduced incidence of acute renal graft failure in patients treated with peritoneal dialysis compared with hemodialysis. *Am J Kidney Dis* 33:934–940, 1999
30. Velasquez MT, Lew SQ, von Albertini B, Mishkin GJ, Bosch JP: Control of hypertension is better during hemodialysis than during continuous ambulatory peritoneal dialysis in ESRD patients. *Clin Nephrol* 48:341–345, 1997
31. Lechevallier E, Dussol B, Luccioni A, Thirion X, Vachercopomat H, Jaber K, Brunet P, Leonetti F, Lavelle O, Coulange C, Berland Y: Posttransplantation acute tubular necrosis: Risk factors and implications for graft survival. *Am J Kidney Dis* 32:984–991, 1998
32. Jacobs U, Niese D, Klein B, Paar D, Miersch WD, Klehr HU: Cold ischemia, histocompatibility, donor and recipients age: Impact on early lymphocyte subsets and transplant outcome. *Transplant Proc* 28:3251–3252, 1996
33. Peters THG, Shaver TR, Ames JE, Santiago-Delpin EA, Jones KW, Blanton JW: Cold ischemia and outcome in 17,937 cadaveric kidney transplants. *Transplant Immunol* 59:191–196, 1995
34. Kahan B, Mickey R, Flechner SM, Lorber MI, Wideman CA, Kerman R, Terasaki P, Buren Van CT: Multivariate analysis of risk factors impacting on immediate and eventual cadaver allograft survival in cyclosporine-treated recipients. *Transplantation* 43:65–70, 1987
35. Conger J, Weil JV: Abnormal vascular function following ischemia-reperfusion injury. *J Invest Med* 43:431–442, 1995
36. Azuma H, Nadeau K, Takada M, Mackenzie HS, Tilney NL: Cellular and molecular predictors of chronic renal dysfunction after initial ischemic/reperfusion injury of a single kidney. *Transplantation* 64:190–197, 1997
37. Hostetter TH, Olson JL, Rennke HG, Venkatachalam MA, Brenner BM: Hyperfiltration in remnant nephrons: A potentially adverse response to renal ablation. *Am J Physiol* 241:F85–F93, 1981
38. Briggs JD, Kennedy AC, Young LN, Luke RG, Gray M: Renal function after acute tubular necrosis. *Br Med J* 3:513–516, 1967
39. Lewers DT, Mathew TH, Maher JF, Schreiner GE: Long-term follow-up of renal function and histology after acute tubular necrosis. *Ann Intern Med* 73:523–529, 1970
40. Yilmaz S, Paavonen T, Hayry P: Chronic rejection of rat renal allografts. II. The impact of prolonged ischemia time on transplant histology. *Transplantation* 53:823–827, 1992
41. Troppmann C, Gillingham KJ, Benedetti E, Almond PS, Gruessner RWG, Najarian JS, Matas AJ: Delayed graft function, acute rejection and outcome after cadaveral renal transplantation. *Transplantation* 59:962–968, 1995
42. Opelz G: Immunosuppression with FK 506 does not improve kidney graft survival: Collaborative Transplant Study. *Transplant Proc* 31:1147–1148, 1999