Transplant International

Transplant International ISSN 0934-0874

ORIGINAL ARTICLE

How important is the duration of the brain death period for the outcome in kidney transplantation?

Willemijn N. Nijboer,[1,2] Cyril Moers,[1,2] Henri G. D. Leuvenink[1] and Rutger J. Ploeg[2]

1 Department of Surgery, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands
2 Department of Surgery, Surgery Research Laboratory, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands

Keywords
brain death duration, DGF, donor, kidney transplantation.

Correspondence
Willemijn N. Nijboer MD, PhD, University Medical Center Groningen, Department of Surgery, Hanzeplein 1, 9713 GZ Groningen, The Netherlands. Tel.: 31 50 361 1976; fax: 31 50 363 2796; e-mail: w.n.nijboer@chir.umcg.nl

Received: 16 March 2010
Revision requested: 6 April 2010
Accepted: 14 July 2010
Published online: 31 August 2010

doi:10.1111/j.1432-2277.2010.01150.x

Summary

In kidney transplantation, graft survival using grafts from donation after brain death (DBD) donors is inferior to results after living donation. However, little is known about the effect of the duration of brain death (BDdur) on outcome after transplantation. This is a retrospective Organ Procurement and Transplant Network analysis using kidney donor and recipient data from 1994 to 2006. BDdur was calculated as the period between brain death declaration and aortic cross clamp. Effects of BDdur on delayed graft function (DGF), acute rejection and graft failure were calculated using binary logistic regression and Cox regression models. Median BDdur was 23.8 h. Longer BDdur decreased the risk for DGF and 1- and 3-year graft failure slightly, but not for acute rejection. In multivariate analysis, donor age and acute rejection were confounders. However, in a multivariate subgroup analysis of donors aged ≤55 years BDdur independently predicted DGF; each hour of BDdur decreasing the risk of DGF with 0.4% ($P = 0.008$). Longer BDdur is not detrimental and in fact slightly beneficial in DBD donors ≤55 years of age, reducing the chance of DGF in the recipient. This finding may have an impact on organ retrieval procedures, as no rush but rather an improved donor management prior to retrieval will benefit donor kidney viability.

Introduction

To date, because of the persistent donor organ shortage, increasing numbers of living donors (LD) and donors after cardiac death are used in kidney transplantation. The majority of donor organs, however, are still retrieved from heart beating donation after brain death (DBD). Living (un)related grafts are associated with better survival and lower rates of delayed graft function (DGF) than kidneys retrieved from DBD [1,2]. This difference in success can be attributed to pathophysiological changes which take place during the phase of brain death in the donor and the injury related to other factors such as warm and cold ischemia times or HLA mismatches [3,4]. The combination of risk factors including brain death may result in an increased risk for (vascular) rejection and lower graft survival (GS) [5].

A number of studies have analyzed the detrimental effects of brain death on potential grafts, but only few studies have evaluated the impact of the duration of the brain death process on the outcome after kidney transplantation. In an animal model, our group has shown that prolonged duration of brain death leads to progressive organ dysfunction, and that the pro-inflammatory and pro-coagulatory responses which underly this effect are more pronounced in the presence of hemodynamic instability [6]. Thus, longer duration of brain death might lead to more extensive damage, as organs are longer exposed to the detrimental influences of cerebral injury and the subsequent hemodynamic consequences.

On the other hand, we and others have found that longer duration of brain death will also allow organs to recover and initiate reparative processes after the initial event that caused the cerebral injury [7]. Avlonitis *et al.* [8] demonstrated a decreased pulmonary vascular resistance after a prolonged period of brain death, which according to their explanation may have been triggered by the recovery of the lung from hemodynamic injury sustained during induction of brain death.

Studies addressing the issue of the importance of the duration of brain death in human organ donation are rare, which is remarkable as their outcome could have a major impact on donation logistics. Kunzendorf *et al.* suggested in their analysis of 1106 DBD kidney transplants that grafts retrieved from donors with a long duration of brain death (BDdur) (>470 min) had a lower incidence of DGF and a better GS rate compared with kidneys retrieved after a BDdur of <470 min. Unfortunately, their validation study remained inconclusive and no multivariate analyses were performed to determine whether (longer) BDdur was an independent predictor for successful transplantation, or that this effect was influenced by some confounding factor [9].

Thus, the question whether the length of the period of brain death is a risk factor for outcome after kidney transplantation still remains unsolved. This situation has lead to a difference in approach between European countries and the US; while in Europe we try to recover donor organs as fast as possible, in the US donors have often longer periods of brain death, and recovery procedures are typically performed during office hours. The outcome of a proper analysis regarding transplantation success after a certain duration of brain death could have significant consequences for donor management and logistics affecting the decision to either 'rush and retrieve' or 'relax and repair.' We have therefore studied the effect of BDdur on the incidence of DGF, acute rejection, and 1- and 3-year GS after kidney transplantation using the large transplantation database of the US Organ Procurement and Transplant Network (OPTN) for this comparison.

Patients and methods

Dataset

A June 2007 extract of the OPTN database was used. The study population consisted of DBD single-kidney recipients who were transplanted between 1 April 1994 and 11 June 2007. We chose 1994 as the lower limit of this cohort, as several important donor variables had not been collected before this year. Consecutive donor–recipient combinations were included when the following variables were known: date and time of brain death declaration, date and time of cross clamping, and data about the occurrence of DGF, rejection in the first year after transplantation and GS 1 and 3 years after transplantation.

Endpoints

The endpoint for short-term outcome after kidney transplantation was DGF, defined as any dialysis requirement in the first week after transplantation. To assess the incidence of acute rejection, any treatment for rejection in the first year after transplantation was scored. GS at 1 and 3 years post-transplant served as long-term outcome measures. Graft failure was defined as permanent return to maintenance dialysis and was censored upon death with a functioning graft.

Statistical analysis

Donor and recipient demographics as well as graft related factors were calculated for the study cohort. BDdur was defined as the interval between declaration of brain death and the time point of aortic clamping just prior to the start of systemic perfusion during organ retrieval [9]. In several cases, brain death declaration time was recorded, but brain death declaration date was unknown. If, in these cases, the date of donor admission to the hospital was identical to the date of cross clamping, the date of hospital admission was used to calculate BDdur. Otherwise, cases were excluded from the analysis. Outcomes are expressed as median (25th–75th percentile). Differences between groups were analyzed using the Mann–Whitney *U*-test.

Binary logistic regression models including pertinent donor-, preservation-, and recipient-related risk factors were employed to identify whether BDdur was an independent risk factor for DGF and acute rejection.

Cox regression models were constructed with relevant donor-, preservation-, and recipient-related risk factors as covariates to examine whether BDdur significantly contributed to the risk of graft failure at 1 and 3 years post-transplant. Statistical analyses were conducted using SPSS software, version 14 (SPSS Inc., Chicago, IL, USA). Two-sided *P*-values of <0.05 were considered statistically significance.

Results

Demographics and data management

Between April 1, 1994 and June 11, 2007 22 205 deceased heart beating donor (DBD) single-kidney transplants were performed in the USA with recorded data of BDdur in the donor. In this group, 1432 recipients were lost to follow up, leaving 20 773 donor-recipient pairs for analysis. As data regarding BDdur in the donor were not routinely

Table 1. Donor, recipient, and graft-related factors for the study cohort.

Donor demographics (n = 20 773)	
Donor age* (year)	40 (23–51)
Female donor (%)	40.7
ECD donor (%)	18.3
Traumatic cause of death (%)	43.1
Donor history of hypertension (%)	26.1
Donor history of diabetes mellitus (%)	6.5
Donor use of inotropic medication (%)	61.9
Recipient demographics	
Recipient age* (year)	52 (40–61)
Female recipient (%)	39.4
Total time spent on the wait list* (year)	1.56 (0.64–2.97)
Previous transplants (% ≥1)	11.6
DGF (%)	21.9
Rejection treatment (<1-year post Tx) (%)	12
Graft survival at 1 year (%)	92.7
Graft survival at 3 years (%)	90.6
Graft related factors	
HLA mismatches*	4 (3–5)
Cold ischemic time* (h)	17.5 (12.0–23.3)

*Median (25th–75th percentile).

entered into the database before 2004, only 206 out of 20 773 (1%) donor-recipient pairs were included from the period 1994–2003. Table 1 shows the basic demographic characterization for the study population. There was no difference in donor or recipient demographics between the period 1994–2003 and 2004–2007. In this dataset, the median time interval between declaration of brain death and aortic cross clamp was 23.8 h (17.8–31.0). In 95.5% BDdur was <48 h. Figure 1 shows the number of kidney transplant recipients according to distribution of donor BDdur.

Differences in BDdur between groups

Recipients who suffered from DGF had donors with a median BDdur of 23.20 h (17.1–30.4), while grafts transplanted into recipients with immediate graft function had sustained a median BDdur of 23.8 h (17.9–31.1) ($P < 0.001$). No statistical difference in donor BDdur was found between recipients who needed treatment for rejection within 1 year after transplantation and rejection-free recipients. Recipients with functioning grafts at 1 year after transplantation (92.7%) had kidneys from donors with a median BDdur of 23.9 h (17.9–31.2), while recipients with graft failure at 1 year had donors with a median BDdur of 22.4 h (16.6–29.5) ($P < 0.001$). Similarly, at 3 years after transplantation, median BDdur of functioning grafts (90.6%) was 24.0 h (17.9–31.3) compared to 21.9 h (16.5–29.0) for failed grafts ($P < 0.001$).

BDdur and risk of DGF

In a univariate binary logistic regression model, BDdur decreased the risk of DGF with an odds ratio (OR) of 0.995. This indicates that for each hour increase of BDdur, the odds for DGF in the recipient decreased by 0.5% [95% confidence interval (CI) 0.992–0.998, $P = 0.001$]. In a multivariate regression analysis, which included several donor-, graft-, preservation- and recipient related covariates which are known to influence the

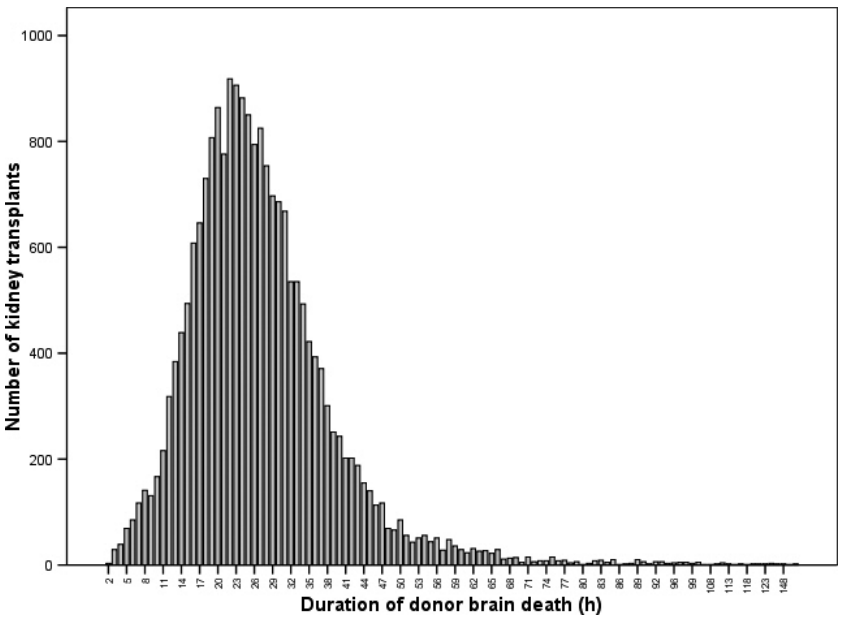

Figure 1 Distribution of donor BDdur in hours.

Table 2. Multivariate risk analysis for delayed graft function.

Delayed graft function: variable	Odds ratio (95% CI)	*P*-value
Duration of brain death (h)	0.998 (0.995–1.001)	0.156
Donor age (year)	1.013 (1.010–1.016)	<0.0005
Donor ethnicity: African-American	1.042 (0.942–1.153)	0.421
ECD donor versus non-ECD donor	0.739 (0.663–0.810)	<0.0005
Donor cause of death: CVA	0.964 (0.869–1.070)	0.495
Donor cause of death: trauma	0.732 (0.663–0.810)	<0.0005
Donor history of hypertension	1.446 (1.322–1.581)	<0.0005
Donor history of diabetes mellitus	1.061 (0.929–1.211)	0.383
Donor use of inotropic medication	1.019 (0.948–1.094)	0.614
Cold ischemic time (h)	1.035 (1.031–1.039)	<0.0005
Number of HLA mismatches	1.056 (1.035–1.077)	<0.0005
Recipient age (year)	1.002 (1.000–1.005)	0.088
Total time spent on the wait list (day)	1.116 (1.096–1.136)	<0.0005
Number of previous kidney transplants	1.155 (1.052–1.269)	0.003

ECD, extended criteria donor; CVA, cerebrovascular accident.

risk of DGF, BDdur was not an independent risk factor for DGF ($P = 0.156$). Table 2 shows the covariates included in the multivariate analysis.

After entering each covariate separately into the regression model, we found donor age to be the only factor that significantly influences BDdur. We then tested the correlation between donor age and BDdur. These variables were correlated with a Pearson's coefficient of −0.118 ($P < 0.001$), indicating that older donors had a shorter BDdur. We performed a *post hoc* subgroup analysis to study the effect of BDdur on 'young donors,' defined as donors ≤55 years of age [10,11]. In our study cohort, this group concerned 81.4% of the total population. In a multivariate regression analysis for this subgroup, BDdur did significantly decrease the risk of DGF with an adjusted OR of 0.996 (95% CI 0.992–0.999, $P = 0.008$).

As Kunzendorf *et al.* [9] showed a difference in DGF and GS after dividing their study population into donors with 'short BDdur' (the lower half of BDdur values in his dataset, with BDdur <470 min) and donors with 'long BDdur' (>470 min), we decided to do the same with our data. Following this method, we found in both univariate and multivariate analyses 'short BDdur' to be an independent risk factor for DGF, not influenced by donor age (adjusted OR 1.313, 95% CI 1.084–1.590, $P = 0.005$). In our study cohort, donors with 'short BDdur' concerned 2.8% of the total population.

BDdur and risk of rejection in the first year post-transplant

In a univariate logistic regression analysis, BDdur had no effect on the incidence of anti-rejection treatment in the first year after transplantation ($P = 0.112$).

BDdur and GS

Using Cox proportional hazards analysis, the influence of BDdur on 1- and 3-year GS was determined. In a univariate analysis, BDdur significantly lowered the risk of graft failure at 1 year with a hazard ratio (HR) of 0.995 ($P = 0.018$). In a multivariate Cox model, BDdur was not an independent risk factor for graft failure at

Table 3. Multivariate risk analysis for graft failure at 1 and 3 years after transplantation.

	Hazard ratio (95% CI)			
Graft failure: variable*	1 year	*P*-value	3 years	*P*-value
Duration of donor brain death (h)	1.005 (0.994–1.017)	0.370	1.006 (0.998–1.014)	0.127
Donor age (year)	1.011 (0.999–1.023)	0.070	1.012 (1.004–1.020)	0.002
Donor ethnicity: African-American	1.225 (0.845–1.775)	0.283	1.548 (1.234–1.942)	<0.0005
ECD donor versus non-ECD donor	0.880 (0.571–1.357)	0.563	0.975 (0.741–1.283)	0.855
Donor cause of death: CVA	1.254 (0.807–1.948)	0.314	1.083 (0.823–1.424)	0.569
Donor cause of death: trauma	1.133 (0.736–1.745)	0.570	0.981 (0.749–1.285)	0.889
Donor history of hypertension	1.145 (0.808–1.623)	0.447	1.116 (0.896–1.392)	0.328
Donor history of diabetes mellitus	1.561 (0.983–2.477)	0.059	1.703 (1.266–2.291)	<0.0005
Donor use of inotropic medication	1.271 (0.946–1.707)	0.111	0.968 (0.807–1.161)	0.725
Cold ischemic time (h)	1.002 (0.985–1.018)	0.857	0.996 (0.985–1.007)	0.462
Number of HLA mismatches	1.069 (0.985–1.160)	0.110	1.076 (1.020–1.134)	0.007
Recipient age (year)	0.996 (0.987–1.006)	0.473	0.999 (0.993–1.005)	0.760
Total time spent on the wait list (day)	1.000 (1.000–1.000)	0.037	1.000 (1.000–1.000)	0.083
Rejection treatment (<1-year post Tx) (%)	2.940 (2.195–3.937)	<0.0005	2.680 (2.218–3.236)	<0.0005
Number of previous kidney transplants	1.167 (0.818–1.665)	0.395	1.173 (0.929–1.481)	0.181
DGF in recipient	2.627 (1.985–3.476)	<0.0005	1.787 (1.486–2.149)	<0.0005

*Censored upon death with a functioning graft.

DGF, delayed graft function; ECD, extended criteria donor; CVA, cerebrovascular accident.

1 year ($P = 0.370$). Confounding factors for this effect were donor age and recipient treatment for rejection in the first year after transplantation. Division of BDdur into a 'short BDdur' group with BDdur <470 min and a 'long BDdur' group with BDdur >470 min did not alter these outcomes; neither did a subgroup analysis including only donors ≤55 years of age.

For 3-year GS, similar results were found. In a univariate Cox model, BDdur significantly lowered the risk of graft failure 3 years after transplantation with an HR of 0.996 ($P = 0.034$), but in the multivariate model BDdur was not an independent risk factor for graft failure ($P = 0.127$). Confounding factors were again donor age and recipient treatment for rejection in the first year. Moreover, in a subgroup analysis for donors ≤55 years of age, BDdur was no independent predictor of graft loss. Table 3 shows results for all covariates entered into the multivariate models.

Discussion

In this retrospective OPTN database analysis, we have shown for a large group of donor–recipient combinations that longer duration of brain death (BDdur) in the donor after cerebral injury is not detrimental and as a matter of fact may have a positive effect on outcome after kidney transplantation. In univariate analyses, a longer BDdur yielded lower odds for the development of DGF, and it improved 1- and 3-year GS. In addition, we performed a multivariate analysis including several donor-, preservation-, graft- and recipient-related factors that have all been shown in the previous studies to have an independent effect on outcome after kidney transplantation [12–18] and which had a significant prevalence in the database. Of course, there are more factors known to have an effect on outcome after kidney transplantation, e.g. machine perfusion of the kidney after retrieval [19,20], but these data either had a very low prevalence in the studied cohort or are not related to BDdur. Moreover, in the timeframe of this study, there were no major differences in organ preservation methods or immunosuppressive regimens, which might have otherwise affected the outcomes of this study. In this multivariate analysis, the positive effect of BDdur on lower DGF incidence was not an independent effect, but could be explained by donor age. Similarly, the positive effect of BDdur on GS could be explained by donor age and chance of antirejection therapy in the first year after transplantation.

In the subgroup of donors aged ≤55 years, however, BDdur did have an independent negative effect on the odds for developing DGF. Although the odds ratio seems rather close to 1.0 at first sight (0.996), it should be noted that BDdur was included in the model as a continuous variable, in contrast to the previously published study of Kunzendorf *et al.* [9] in which BDdur was a binary variable classified as 'long BDdur' or 'short BDdur.' Our model shows that for all DBD donors aged ≤55 years, each hour increase of BDdur in the donor reduces the odds of developing DGF in the recipient by 0.4%. Therefore, based on this study, we would carefully recommend not to rush with organ recovery procedures in DBD donors ≤55 years of age.

To our surprise the median BDdur in this US cohort was 23.8 h. In Kunzendorf's European study, performed within the Eurotransplant organ sharing network, the median BDdur was 470 min, or 7.8 h. When we simulated his analysis in our OPTN dataset, dividing the population into donors with BDdur <470 min and donors with BDdur >470 min, we could reproduce his findings with respect to DGF, but not for GS. However, in our study population donors with BDdur <470 min comprised only 582 donors (2.8%) of the total population. We could not find a satisfactory explanation for this difference between American OPTN data and European data, but we found that median donor BDdur times from kidneys allocated to our transplant center in Groningen, The Netherlands, were also only 10.5 h. From personal communication with US procurement coordinators, we found that the difference can be explained by two factors. First, in the US more time is spent with the donor's relatives to obtain consent for donation, thus lengthening the period between declaration of brain death and the preparations for organ retrieval. Second, the donor operation is usually scheduled to take place during office hours, whereas in Europe, the donor operation is often performed as soon as possible, and even in the middle of the night. As organs are recovered early, recipients also have to be found as quickly as possible. This may lead to more complicated logistics, with transplant centers under higher pressure to accept an organ offer.

As BDdur is much longer in our study population when compared with Kunzendorf's series, a pitfall in our analysis could be a 'stable donor' selection bias: Donors with longer BDdur have a prolonged ICU stay, which increases the risk of hemodynamical instability. This may lead to higher numbers of organs that are not retrieved and more organs that are discarded after recovery. As a result, a selection bias could be present in our study cohort, as we have only investigated donors of kidneys that have actually been transplanted. To evaluate this, we compared American and German kidney donor nonutilization as well as kidney discard rates. Donor nonutilization rate was defined as the number of reported organ donors from whom organs were not removed because of a medical contraindication after consent for donation had been obtained. Kidney discard rate was defined as the

number of kidneys that were recovered and subsequently found to be unsuitable for transplantation. Data were obtained from the OPTN/SRTR Annual Report, tables 2.2, 3.2 and 3.3 1996–2005 for American figures, and from the Kidney balance statistics for 1999–2000 from the Eurotransplant website for German figures. In the US, donor nonutilization rate was 7.8% and kidney discard rate was 11.8%. For Germany, these numbers were 6.1% and 9.7%, respectively, which lies in the same order of magnitude. Thus, we suggest that a longer average BDdur of 23.8 h neither leads to more donor nonutilization nor to a higher kidney discard rate.

The positive effect of longer BDdur on outcome after kidney transplantation seems somewhat counter-intuitive. However, it should be considered that a prolonged period of appropriate donor resuscitation and appropriate management in the ICU may have positive effects on organ function and recovery. Giral *et al.* have demonstrated that a long stay in intensive care and colloid transfusion of >1250 ml correlate with a lower risk of DGF in the recipient [21]. These effects may originate from the cellular processes observed during brain death. Experimental animal models, as well as human studies not only show an activation of inflammatory processes during brain death but also a time dependent effect of brain death on gene expression and protein production of several protective proteins in the graft [22,23]. As a result of brain death, several heat shock proteins as well as other chaperone molecules are upregulated, which can help organs to protect themselves during prolonged periods of cellular stress [7]. In addition, ICU treatment modalities may have a direct (innate) immunological effect on the future graft [24]. Hoeger showed that treatment with dopamine causes a reduction of monocyte infiltration of the kidney, a reduction of several pro-inflammatory molecules and an increase of the heat shock protein heme oxygenase-1 [25]. In human kidney donation, dopamine treatment of the donor resulted in reduced dialysis requirement in the recipient [26].

An interesting observation of our study is the negative correlation between BDdur and donor age. This can be explained either by an increased hemodynamic instability in older donors, as older donors have been exposed to more concomitant morbidity than their younger counterparts [27] leading to earlier retrieval procedures, or shorter donor work up times in older donors, as more often only the kidneys are offered for donation and transplantation. To test the first hypothesis, we took the need for inotropic medication as a surrogate marker for hemodynamic instability. When this factor was added as a covariate into the model, however, we found no effect on BDdur. We then calculated the deceased donor kidney recovery rate as a percentage of the total organ recovery rate for the period 1994–2007 using the OPTN data. In this period, kidney recovery constituted 44.1% of total organ recovery in donors aged 18–34 years. For the donor age group of 35–49 years, this increased to 51.2%. For the age group 50–64 years it was 60.9%, and for 65+ donors kidney recovery comprised 63.1% of the total organ recovery. Hence, the phenomenon of shorter donor workup times in older donors may explain the correlation between BDdur and donor age, as well as it explains why donor age is a confounding factor for the effect of BDdur in our multivariate analyses.

In conclusion, our results show that longer BDdur has a modest beneficial effect on the odds for immediate graft function and 1- and 3-year GS after kidney transplantation. BDdur has no influence on acute rejection in the first year after transplantation. In multivariate analyses, the positive effect of BDdur on outcome can be attributed to the effect of donor age and the occurrence of acute rejection in the recipient. However, for donors ≤55 years of age, BDdur is an independent predictor of DGF in the recipient, and the odds for developing DGF decrease by 0.4% for each additional hour of brain death. The pathophysiological mechanisms underlying this effect are currently unknown and will need further study. Longer BDdur, as seen in the US when compared with Europe, does not lead to increased numbers of donor nonutilization or kidney discard and longer BDdur has no detrimental influence on kidney graft quality. Based on these data, we recommend a meticulous but unhurried and high quality ICU donor management before DBD organ retrieval, as there is no need to 'rush and retrieve,' but rather time to 'relax and repair.'

Authorship

WNN: designed study, collected data, analyzed data and wrote the paper. CM: helped designing the study and writing the manuscript, and set up the major part of the statistical analyses. HGDL: helped designing the study and corrected the paper. RJP: supervised the study and corrected the paper.

Funding

No external funding sources were used for this work.

Acknowledgements

The authors thank Mrs G Vulgamott, RN, BSN, CPTC, from the Midwest Transplant Network, Westwood, and Mr JE Buiter, transplant coordinator from the University Medical Center Groningen, The Netherlands, for their advice and discussion about the current practice of deceased

donor organ retrieval in the USA and Eurotransplant. This work was supported in part by Health Resources and Services Administration contract 234–2005–37011C. The content is the responsibility of the authors alone and does not necessarily reflect the views or policies of the Department of Health and Human Services nor does mention of trade names, commercial products, or organizations imply endorsement by the US government.

References

1. Terasaki PI, Cecka JM, Gjertson DW, Takemoto S. High survival rates of kidney transplants from spousal and living unrelated donors. *N Engl J Med* 1995; **333**: 333.
2. Matas AJ, Gillingham KJ, Humar A, Dunn DL, Sutherland DE, Najarian JS. Immunologic and nonimmunologic factors: different risks for cadaver and living donor transplantation. *Transplantation* 2000; **69**: 54.
3. Roodnat JI, van Riemsdijk IC, Mulder PG, *et al.* The superior results of living-donor renal transplantation are not completely caused by selection or short cold ischemia time: a single-center, multivariate analysis. *Transplantation* 2003; **75**: 2014.
4. Jones JW Jr, Gillingham KJ, Sutherland DE, *et al.* Successful long-term outcome with 0-haplotype-matched living-related kidney donors. *Transplantation* 1994; **57**: 512.
5. Sanchez-Fructuoso AI, Prats D, Marques M, *et al.* Does donor brain death influence acute vascular rejection in the kidney transplant? *Transplantation* 2004; **78**: 142.
6. van der Hoeven JA, Molema G, Ter Horst GJ, *et al.* Relationship between duration of brain death and hemodynamic (in)stability on progressive dysfunction and increased immunologic activation of donor kidneys. *Kidney Int* 2003; **64**: 1874.
7. Bos EM, Schuurs TA, Kraan M, *et al.* Renal expression of heat shock proteins after brain death induction in rats. *Transplant Proc* 2005; **37**: 359.
8. Avlonitis VS, Wigfield CH, Golledge HD, Kirby JA, Dark JH. Early hemodynamic injury during donor brain death determines the severity of primary graft dysfunction after lung transplantation. *Am J Transplant* 2007; **7**: 83.
9. Kunzendorf U, Hohenstein B, Oberbarnscheid M, *et al.* Duration of donor brain death and its influence on kidney graft function. *Am J Transplant* 2002; **2**: 292.
10. Morrissey PE, Gohh R, Yango A, Gautam A, Monaco AP. Renal transplant survival from older donors: a single center experience. *Arch Surg* 2004; **139**: 384.
11. Kasiske BL, Snyder J. Matching older kidneys with older patients does not improve allograft survival. *J Am Soc Nephrol* 2002; **13**: 1067.
12. Goldfarb-Rumyantzev AS, Scandling JD, Pappas L, Smout RJ, Horn S. Prediction of 3-yr cadaveric graft survival based on pre-transplant variables in a large national dataset. *Clin Transplant* 2003; **17**: 485.
13. Issa N, Stephany B, Fatica R, *et al.* Donor factors influencing graft outcomes in live donor kidney transplantation. *Transplantation* 2007; **83**: 593.
14. Salahudeen AK, Haider N, May W. Cold ischemia and the reduced long-term survival of cadaveric renal allografts. *Kidney Int* 2004; **65**: 713.
15. McLaren AJ, Jassem W, Gray DW, Fuggle SV, Welsh KI, Morris PJ. Delayed graft function: risk factors and the relative effects of early function and acute rejection on long-term survival in cadaveric renal transplantation. *Clin Transplant* 1999; **13**: 266.
16. Neylan JF. Racial differences in renal transplantation after immunosuppression with tacrolimus versus cyclosporine FK506 Kidney Transplant Study Group. *Transplantation* 1998; **65**: 515.
17. Merion RM, Ashby VB, Wolfe RA, *et al.* Deceased-donor characteristics and the survival benefit of kidney transplantation. *JAMA* 2005; **294**: 2726.
18. Ojo AO, Leichtman AB, Punch JD, *et al.* Impact of pre-existing donor hypertension and diabetes mellitus on cadaveric renal transplant outcomes. *Am J Kidney Dis* 2000; **36**: 153.
19. Moers C, Smits JM, Maathuis MH, *et al.* Machine perfusion or cold storage in deceased-donor kidney transplantation. *N Engl J Med* 2009; **360**: 7.
20. Schold JD, Kaplan B, Howard RJ, Reed AI, Foley DP, Meier-Kriesche HU. Are we frozen in time? Analysis of the utilization and efficacy of pulsatile perfusion in renal transplantation. *Am J Transplant* 2005; **5**: 1681.
21. Giral M, Bertola JP, Foucher Y, *et al.* Effect of brain-dead donor resuscitation on delayed graft function: results of a monocentric analysis. *Transplantation* 2007; **83**: 1174.
22. Nijboer WN, Schuurs TA, van der Hoeven JA, *et al.* Effect of brain death on gene expression and tissue activation in human donor kidneys. *Transplantation* 2004; **78**: 978.
23. Kusaka M, Yamada K, Kuroyanagi Y, *et al.* Gene expression profile in rat renal isografts from brain dead donors. *Transplant Proc* 2005; **37**: 364.
24. Bos EM, Leuvenink HG, van Goor H, Ploeg RJ. Kidney grafts from brain dead donors: inferior quality or opportunity for improvement? *Kidney Int* 2007; **72**: 797.
25. Hoeger S, Reisenbuechler A, Gottmann U, *et al.* Donor dopamine treatment in brain dead rats is associated with an improvement in renal function early after transplantation and a reduction in renal inflammation. *Transpl Int* 2008; **21**: 1072.
26. Schnuelle P, Gottmann U, Hoeger S, *et al.* Effects of donor pretreatment with dopamine on graft function after kidney transplantation: a randomized controlled trial. *JAMA* 2009; **302**: 1067.
27. Cohen B, D'Amaro J, De MJ, Persijn GG. Changing patterns in organ donation in Eurotransplant, 1990–1994. *Transpl Int* 1997; **10**: 1.