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Early effects of brain death on kidney injury and outcome after transplantation

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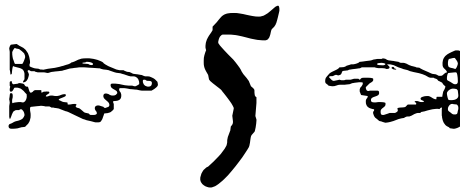
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CHAPTER



HOW IMPORTANT IS THE DURATION OF THE BRAIN DEATH PERIOD FOR THE OUTCOME IN KIDNEY TRANSPLANTATION?

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Submitted

- ABSTRACT -

Main problem:

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.

Methods:

Retrospective OPTN analysis using kidney donor and recipient data from 1994-2006. 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.

Results: Median BDdur was 23.8h. 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. Yet, in a multivariate subgroup analysis of donors ≤ 55 years BDdur independently predicted DGF; each hour of BDdur decreasing the risk of DGF with 0.4% ($P=0.008$).

Conclusion:

Longer BDdur is not detrimental and in fact slightly beneficial in DBD donors ≤ 55 years, reducing the chance of DGF in the recipient. This finding may have 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, due to the persistent donor organ shortage, increasing numbers of living donors (LD) and donors after cardiac death (DCD) are used in kidney transplantation. The majority of donor organs, however, is 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 (5).

A number of studies has 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 and colleagues 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 (8).

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 and co-workers suggested in their analysis of 1,106 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 graft survival rate compared to kidneys retrieved after a BDdur < 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, is still unsolved yet. This situation has led to a difference in approach between European countries and the U.S.: while in Europe we try to recover

donor organs as fast as possible, in the U.S. 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 one- and three-year graft survival after kidney transplantation using the large transplantation database of the U.S. 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 graft survival one and three years after transplantation.

Endpoints

The endpoint for short-term outcome after kidney transplantation was delayed graft function (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. Graft survival (GS) at one and three years posttransplant 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. Outcomes are expressed as median (range). Differences between groups were analyzed using Student's T-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 one and three years posttransplant. Statistical analyses were conducted using SPSS software, version 14 (SPSS Inc., Chicago, IL). Two-sided P-values of less than 0.05 were considered to indicate statistical significance.

- RESULTS -

Demographics and data management

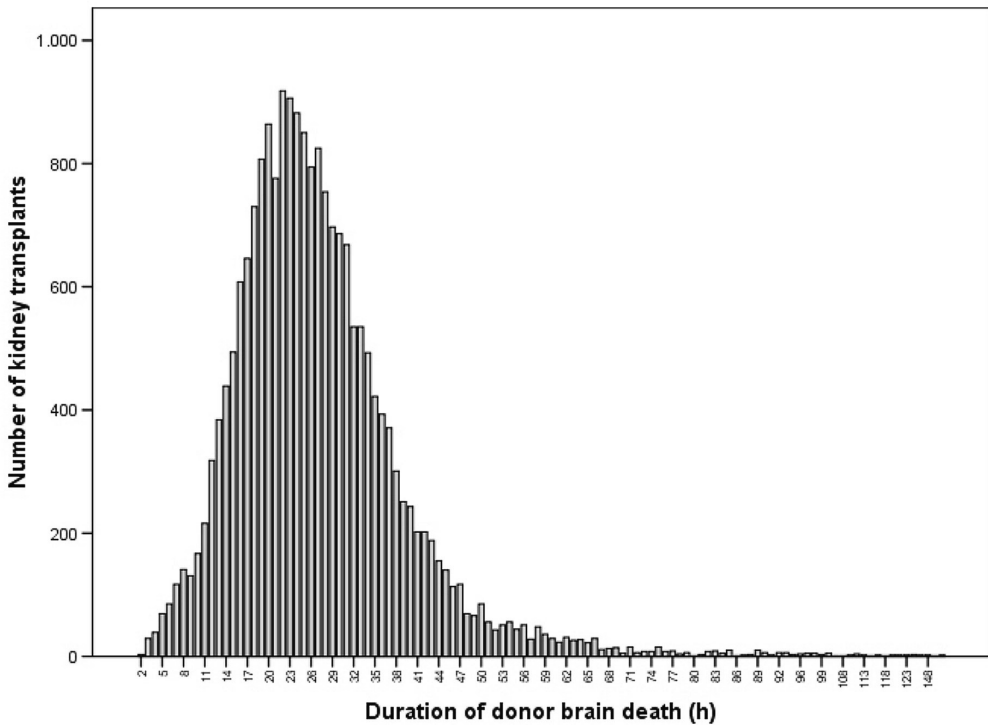
Between April 1, 1994 and June 11, 2007 20,773 deceased heart beating donor (DBD) single-kidney transplants were performed in the USA with recorded data of BDdur in the donor and available recipient outcome data. Table 1 shows the basic demographic characterisation for the study population. In this dataset, the median time interval between declaration of brain death and aortic cross clamp was 23.8h (1.0-189.9). In 95.5% BDdur was less than 48h. Figure 1 shows the number of kidney transplant recipients according to distribution of donor BDdur.

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

Donor demographics (N = 20,773)	
Donor age ^a (y)	40 (0-82)
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
Recipient demographics	
Recipient age ^a (y)	52 (0-86)
Female recipient (%)	39.4
Total time spent on the wait list ^a (yr)	1.6 (0-17.8)
Previous transplants (% ≥1)	11.6
DGF (%)	21.9
Rejection treatment (<1 y post Tx) (%)	12
Graft survival at 1 year (%)	92.7
Graft survival at 3 years (%)	90.6
Graft related factors	
HLA mismatches	4 (1-6)
Cold ischemic time ^a (h)	18 (0-99)

^a) Median (range).

Figure 1 Distribution of donor BDdur in hours



Differences in BDdur between groups

Recipients who suffered from DGF had donors with a mean BDdur of 25.0h, while grafts transplanted into recipients with immediate graft function had sustained a mean BDdur of 25.7h ($P = 0.001$). No statistical difference in donor BDdur was found between recipients who needed treatment for rejection within one year after transplantation and rejection-free recipients. Recipients with functioning grafts at one year after transplantation (92.7%) had kidneys from donors with a mean BDdur of 25.7h, while recipients with graft failure at one year had donors with a mean BDdur of 24.2h ($P < 0.001$). Similarly, at three years after transplantation, mean BDdur of functioning grafts (90.6%) was 25.8h as compared to 23.7h for failed grafts ($P < 0.001$)

BDdur and risk of delayed graft function

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 risk of DGF, BDdur was not an independent risk factor for DGF ($P = 0.14$). Table 2 shows the covariates included in the multivariate analysis.

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)	0.111
Donor age (y)	1.013 (1.010-1.016)	<0.0005
Donor ethnicity: African-American	1.046 (0.945-1.156)	0.386
ECD donor vs. non-ECD donor	0.737 (0.658-0.826)	<0.0005
Donor cause of death: CVA	0.970 (0.875-1.076)	0.566
Donor cause of death: trauma	0.735 (0.665-0.813)	<0.0005
Donor history of hypertension	1.444 (1.321-1.579)	<0.0005
Donor history of diabetes mellitus	1.063 (0.931-1.213)	0.367
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 (y)	1.002 (1.000-1.005)	0.075
Total time spent on the wait list (y)	1.116 (1.096-1.136)	<0.0005
Number of previous kidney transplants	1.151 (1.048-1.264)	0.003

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 (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, $P = 0.008$).

Since Kunzendorf and colleagues (9) showed a difference in DGF and graft survival 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 posttransplant

In a multivariate 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 graft survival

Using Cox proportional hazards analysis, the influence of BDdur on one- and three-year graft survival was determined. In a univariate analysis, BDdur significantly lowered the risk of graft failure at one 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 one year ($P = 0.50$). 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 $BDdur < 470\text{min}$ and a 'long BDdur' group with $BDdur > 470\text{min}$ did not alter these outcomes; neither did a subgroup analysis including only donors ≤ 55 years.

For three-year graft survival, similar results were found. In a univariate Cox model, BDdur significantly lowered the risk of graft failure three years after transplantation with a HR of 0.996 ($P = 0.034$), but in the multivariate model BDdur was not an independent risk factor for graft failure ($P = 0.12$). Confounding factors were again donor age and recipient treatment for rejection in the first year. Also, in a subgroup analysis for donors ≤ 55 years, BDdur was no independent predictor of graft loss. Table 3 shows results for all covariates entered into the multivariate models.

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

Graft failure: variable ^a	Hazard ratio (95% CI)			
	1 year	P-value	3 years	P-value
Duration of donor brain death (h)	1.004 (0.993-1.016)	0.486	1.006 (0.998-1.014)	0.132
Donor age (y)	1.011 (0.999-1.024)	0.063	1.012 (1.004-1.020)	0.002
Donor ethnicity: African-American	1.233 (0.851-1.786)	0.269	1.541 (1.229-1.933)	<0.0005
Donor cause of death: CVA	1.246 (0.802-1.936)	0.328	1.085 (0.825-1.427)	0.558
Donor cause of death: trauma	1.142 (0.742-1.757)	0.547	0.978 (0.747-1.280)	0.869
Donor history of hypertension	1.137 (0.802-1.613)	0.471	1.111 (0.892-1.385)	0.348
Donor history of diabetes mellitus	1.599 (1.008-2.535)	0.046	1.707 (1.269-2.295)	<0.0005
Cold ischemic time (h)	1.001 (0.985-1.018)	0.868	0.996 (0.985-1.007)	0.476
Number of HLA mismatches	1.069 (0.985-1.160)	0.113	1.075 (1.020-1.133)	0.007
Recipient age (y)	0.996 (0.987-1.006)	0.449	0.999 (0.993-1.005)	0.727
Total time spent on the wait list (y)	0.918 (0.847-0.995)	0.037	0.958 (0.912-1.007)	0.092
Rejection treatment (<1 y post Tx)(%)	2.927 (2.185-3.919)	<0.0005	2.687 (2.225-3.246)	<0.0005
Number of previous kidney transplants	1.159 (0.812-1.653)	0.417	1.168 (0.925-1.475)	0.193
DGF in recipient	2.621 (1.980-3.469)	<0.0005	1.778 (1.479-2.138)	<0.0005

^a) Censored upon death with a functioning graft.

- 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 one- and three-year graft survival. In addition, we performed a multivariate analysis including several donor-, preservation-, graft- and recipient-related factors that have all been shown in 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. Also, 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. Likewise, the positive effect of BDdur on graft survival could be explained by donor age and chance of anti-rejection therapy in the first year after transplantation.

In the subgroup of donors ≤ 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 U.S. cohort was 23.8h. In Kunzendorf's European study, the median BDdur was 470 min, or 7.8h. 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 graft survival. 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. We therefore checked Kunzendorf's BDdur calculations by looking at donor BDdur times from kidneys allocated to our transplant center in Groningen, The Netherlands, which is part of the same organ sharing network as Kunzendorf's center (Eurotransplant), and we found a median BDdur of 10.5h. This value lies in the same order of magnitude as Kunzendorf's.

Personal communication with U.S. procurement coordinators learned that the difference can be explained by two factors. First, in the U.S. 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 to 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. On the other hand, early organ recovery as it is currently practised in Europe could lead both to a lower donor non-utilization rate and to a higher kidney discard rate, as accepting transplant centers are under high pressure to either accept or decline an organ offer.

To evaluate this, we compared American and German kidney donor non-utilization as well as kidney discard rates. Donor non-utilization 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 U.S., donor non-utilization 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 23.8h neither leads to more donor non-utilization, nor to a higher kidney discard rate. These data, also, seem to justify the American approach, where more time is taken to communicate with the donor family and standard hospital logistics are left relatively unaffected by a donor procedure due to the fact that organ retrieval is not performed with high urgency.

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). Due to 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 has been reported to result in superior graft survival in the recipient (26).

An interesting observation of our study is the negative correlation between BDdur and donor age. This can be explained by an increased hemodynamic instability in older donors, as older donors have been exposed to more concomitant morbidity than their younger counterparts (27). Organ retrieval should be initiated earlier in such unstable donors, to prevent organ discard due to unfavourable hemodynamic incidents during their ICU stay. Although it is not easy to test this theory in detail in a large database as used for this study, 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. An explanation might be that it takes less time for a procurement coordinator to evaluate older donors and allocate organs, as with increasing donor age the kidneys are more often the only organs offered for donation and transplantation. 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 one- and three-year graft survival 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, 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 patho-physiological mechanisms underlying this effect are currently unknown and will need further study. Longer BDdur, as seen in the U.S. when compared to Europe, does not lead to increased numbers

of donor non-utilization 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'.

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