Predictors Associated with Terminal Renal Function in Deceased Organ Donors in the Intensive Care Unit

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Background: Factors determining renal function at organ recovery in deceased kidney donors are not well established.

Methods: The authors studied the prevalence and risk factors associated with elevated prerecovery creatinine and calculated glomerular filtration rate in 458 deceased organ donors identified through the California Donor Transplant Network between January 2005 and December 2006. Data collected retrospectively included demographics, medical history, laboratory values, mechanism of death, and medical treatment in the intensive care unit. Factors were analyzed by both univariate and multivariate analysis.

Results: There were 260 men and 198 women in the study. The age was 43.2 ± 14.9 yr, and body mass index was 26.9 ± 6.0 (mean ± SD). In multivariate analysis, several factors were important determinants of both prerecovery creatinine and glomerular filtration rate. Admission creatinine or glomerular filtration rate were major determinants of respective prerecovery values (P < 0.0001). Higher body mass index was associated with worse renal function (P < 0.01). Higher average glucose values and greater variability in glucose (when included) were associated with worse prerecovery renal function (P < 0.01). Administration of desmopressin acetate was highly associated with preserved renal function (P < 0.001). Lower platelet count (P < 0.0001) and proteinuria (P = 0.005) were also associated with worse renal function.

Conclusion: The data identify several important factors that predict renal function at kidney recovery in deceased donors. In particular, tighter control of blood glucose may improve renal function in potential organ donors, but prospective studies are needed to confirm these findings.

KIDNEY transplantation is the most commonly performed transplant in the world. The overall number of kidney donors has increased annually over the past decade. However, kidney transplantation remains primarily limited by availability of transplantable organs. Donor quality is an ongoing concern as the success of transplantation is significantly affected by the prerecovery state of the donor organ. Although certain donor characteristics that may affect organ quality (i.e., gender, hypertension, and diabetes) are not modifiable, it is possible that aggressive medical management and pharmacological therapy during the period between the determination of brain death and graft recovery may help to maximize donor organ function. To avoid further organ function deterioration, every effort should be undertaken to avoid further damage. Reduction of warm and cold ischemia and optimal donor management are of significant importance in this context.

Deceased organ donors constitute a special intensive care unit (ICU) subpopulation. In the United States, once identified as a potential donor and after brain death is declared, medical management is directed by transplant coordinators from the local organ procurement organization (OPO). At this point, the primary ICU team is no longer involved in the care of the donor. Logistical reasons (organs are often allocated to 3–4 different transplant centers) and the large geographic area of the United States occasionally result in identified organ donors staying in the ICU for several days before organ recovery.

Critically ill patients in the ICU, even in the absence of diabetes type I or II, frequently develop hyperglycemia because of the development of insulin resistance (i.e., decreased glucose uptake in skeletal muscle), as well as accelerated blood glucose production and a relative insulin deficiency due to a lack of compensation by pancreatic β-cells. In the past, stress-induced hyperglycemia had been viewed as an essential metabolic defense mechanism and was interpreted as a beneficial adaptation. However, at the same time, hyperglycemia modulates several molecular pathways (inflammatory response, endothelial dysfunction, oxidative stress) that contribute to cellular injury. Van den Berghe et al. demonstrated that intensive insulin therapy (target blood glucose concentrations of 80–110 mg/dl) decreased inhospital morbidity by more than 50% in a mainly surgical patient population admitted to the ICU.2 A follow-up
study in medical ICU patients demonstrated a beneficial effect only in prolonged ICU stays of more than 3 days.\(^5\) Pooling data from both studies, Van den Berghe demonstrated in a large subanalysis that achieving normoglycemia with insulin therapy significantly protects renal function in critically ill patients.\(^4\) In a prospective cohort study, Quattara \textit{et al.} demonstrated that poor intraoperative glucose control in patients undergoing cardiac surgery resulted in worsened hospital outcome.\(^5\) In addition, Thomas \textit{et al.} showed in a meta-analysis that there is evidence that intensive insulin therapy is associated with a reduction in renal injury in critically ill patients.\(^5\) However, very strict normoglycemia may be required to gain any clinical benefits, and this is not universally accepted out of fear of inducing hypoglycemia. Furthermore, several recent studies were not able to demonstrate a beneficial effect or questioned the safety of tight glucose control.\(^7\) Despite this unresolved controversy, untreated hyperglycemia and glucose concentrations greater than 200 mg/dl are generally considered as unacceptable in critically ill patients.

Between declaration of brain death and organ recovery, the organ donor is under the care of a transplant coordinator from the local OPO. One of our goals was to review organ donor medical management in the ICU in a select OPO in Northern California and to evaluate whether predictors of renal function can be identified.

The main goal, however, was to investigate whether laboratory parameters such as glucose levels or medical therapy between declaration of brain death and organ recovery influence renal function in organ donors similarly to that observed in critically ill patients. For this purpose, we used creatinine values and calculated glomerular filtration rate (GFR) obtained immediately before organ recovery and determined the association with glucose concentrations collected between declaration of brain death and organ recovery.

**Materials and Methods**

All data for the current study were collected retrospectively after written approval from the California Donor Transplant Network (CTDN; Oakland, CA). Organ donor identities were coded.

A total of 536 organ donors were identified through the CTDN database during the time period of January 2005 through December 2006. After excluding pediatric donors (age < 18 yr) and donation after cardiac death, 458 deceased organ donors were enrolled in this study. Admission and terminal creatinine (final value before donation) values were used as continuous variables. Creatinine is clinically used as a surrogate for renal function. However, the term renal function, when used clinically, is often taken to mean GFR or the nearest approximation of GFR.

Prediction equations have been developed to obviate the need for timed urine collection, which is cumbersome and notoriously inaccurate. As creatinine excretion depends largely on muscle mass, these equations incorporate the major demographic predictors: age, sex, and race. We used the Modification of Diet in Renal Disease Study equation\(^*\) to calculate GFR based on obtained creatinine levels.

Furthermore, pertinent donor demographic information was recorded. The data included age, race, gender, body mass index, history of hypertension or diabetes mellitus as documented on the chart, mechanism of death, and time between declaration of brain death and organ retrieval. In addition, medical treatment (e.g., steroid administration, desmopressin acetate [dDAVP] administration, transfusion) after the declaration of brain death in the ICU were recorded. Relevant CTDN guidelines for evaluation and clinical management of adult organ donors are listed in table 1.

We made an effort to capture all documented glucose concentrations during the time period (declaration of brain death and organ recovery) when the donor was medically managed by the transplant coordinator.

Terminal laboratory values presented are the final values recorded in the ICU before donor transportation to the operating room.

**Statistical Analyses Were Performed As Follows**

For univariate analyses, the relationship of continuous variables to terminal creatinine or GFR was analyzed by Spearman rank sum correlation. For categorical variables, Mann–Whitney \(U\) test was used.

For multivariate analyses, all predictors were considered for entry into the model. Stepwise regression was used to identify the most significant predictors. After entering these variables into a multivariate model, all variables that could be reasonably considered in the model were entered and tested for statistical significance, whether they were significant in univariate analysis or not. The relationships among predictor variables were also analyzed (data not shown) to better understand the confounding relationships that might influence the various models tested. In this way, essentially all reasonable models were considered, which took repeated iterations.

The distribution of both terminal creatinine and GFR was skewed and made a simple linear model ineffective. Logarithmic transformation of both creatinine and GFR yielded an improved but not perfectly normal distribution. This led to a more robust multivariate model. A proportional hazard model was also tested and yielded essentially the same results as a linear multivariate model with the logarithmic transformation.

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Change in renal function was analyzed for both creatinine and GFR. No change was considered if terminal renal function was no more than 10% higher or lower than admission values. Differences in glucose in these groups were analyzed by the Kruskall-Wallis test.

Data are shown as mean ± SD for continuous variable or n (percentage) for categorical variables unless otherwise indicated. \( P < 0.05 \) was considered statistically significant. Data were analyzed with JMP 5.1 (SAS Institute, Cary, NC).

## Results

### Organ Donor Characteristics

The mean age of our 458-patient cohort was 43.2 ± 14.9 yr (table 2). Fifty-seven percent of the donors were male. The majority of donors were non-Hispanic white donors (n = 260, 57%) followed by Hispanic donors (n = 103, 22%), African-American donors (n = 48, 10%) and Asian-American donors (n = 47, 10%). The calculated body mass index was 26.9 ± 6, with 22% of donors with a body mass index ≥ 30 (obese).

Half of all deceased donors suffered from a cerebral vascular accident (n = 238, 52%), and the remaining experienced either head trauma or unspecified anoxia (table 2).

Thirty-six percent (n = 165) of the donors had a documented history of hypertension, while 9% (n = 43) and 3% (n = 12) patients suffered from type II diabetes mellitus or type I diabetes, respectively. The average time between declaration of brain death and cross-clamping of the aorta was almost 2 days (table 2).

The mean admission GFR was 87 ± 45 ml/min/1.73 m² (creatinine 1.1 ± 0.6 mg/dl). Data were missing or excluded on 2 donors for n = 456 data points.

### Univariate Analysis

#### Association of Donor Characteristics with Terminal Renal Function as Determined by Creatinine and Calculated GFR

Age was not related to terminal creatinine, but it was significantly related to terminal GFR (\( P < 0.001 \)). Male donors had significantly higher terminal creatinine (1.4 ± 0.9 vs. 1.1 ± 1.0 mg/dl) than female donors (\( P < 0.0001 \)). GFR, however, was not statistically different (male 81 ± 68 vs. female 79 ± 46 ml/min/1.73 m²). Terminal creatinine was significant lower for non-Hispanic white donors compared to all other donors (1.1 ± 0.6 vs. 1.4 ± 1.3 mg/dl; \( P = 0.0001 \)), but GFR was not statistically different. GFR was only statistically lower for Asian-American donors when compared to all other donors (67 ± 32 vs. 81 ± 58 ml/min/1.73 m²; \( P = 0.01 \)). Higher body mass index was
Comorbidities

Table 2. Univariate Analysis: Demographics and Comorbidities

<table>
<thead>
<tr>
<th>Outcome, P</th>
<th>Mean ± SD or n (%)</th>
<th>Median (IQ Range)</th>
<th>Terminal Cr</th>
<th>Terminal GFR</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>458 (100%)</td>
<td>1.0 (0.8–1.2)</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Admission Cr</td>
<td>1.1 ± 0.6 (456)</td>
<td>1.0 (0.8–1.2)</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Admission GFR</td>
<td>87 ± 4.5 (456)</td>
<td>79 (64–102)</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Age</td>
<td>43.2 ± 14.9</td>
<td>44 (30–54)</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>BMI</td>
<td>26.9 ± 6.0</td>
<td>26.0 (23.0–30.0)</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>BMI ≥ 30</td>
<td>129 (28%)</td>
<td></td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Comorbidities</td>
<td></td>
<td></td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Hypertension</td>
<td>165 (36%)</td>
<td>0.002</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>DM type I</td>
<td>19 (3%)</td>
<td></td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>DM type II</td>
<td>48 (9%)</td>
<td></td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Causes of brain death</td>
<td></td>
<td></td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Head trauma</td>
<td>162 (35%)</td>
<td></td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>CVA</td>
<td>190 (41%)</td>
<td></td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Anoxia</td>
<td>265 (57%)</td>
<td></td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Times</td>
<td>45.2 ± 17.8</td>
<td>42.0 (34.0–55.0)</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

Continuous variables analyzed by Spearman rank correlation; categorical variables analyzed by Mann-Whitney U test.
BMI = body mass index; Cr = creatinine; CVA = cerebral vascular accident; DM = diabetes mellitus; GFR = glomerular filtration rate; IQ range = interquartile range.

highly correlated with worse terminal renal function (P < 0.0001). Creatinine was higher (1.5 ± 1.1 vs. 1.2 ± 0.9 mg/dl; P = 0.0001) and GFR lower (65 ± 32 vs. 84 ± 61 ml/min/1.73 m²; P < 0.0001) in obese patients.

Creatinine was not different between these groups; however, GFR was higher for head trauma donors (93 ± 83 vs. 73 ± 32 ml/min/1.73 m² for all other donors; P < 0.0001) and lower for cerebral vascular accident donors (72 ± 32 vs. 88 ± 74 ml/min/1.73 m² for all other donors; P < 0.0001). The average time between declaration of brain death and cross-clamping of the aorta was almost 2 days (table 2).

Thirty-six percent (n = 165) of the donors had a documented history of hypertension. Hypertensive donors had significantly higher terminal creatinine (1.5 ± 1.4 vs. 1.1 ± 0.6 mg/dl; P < 0.002) and lower terminal GFR (68 ± 33 vs. 86 ± 65 ml/min/1.73 m²; P < 0.0001). Diabetes was not significantly related to either terminal creatinine or GFR (figs. 1 and 2); however, with the small numbers, this is likely due to type 2 error.

Association of Laboratory Values with Terminal Renal Function as Determined by Creatinine and Calculated GFR

Terminal GFR just before organ recovery was 80 ± 56 ml/min/1.73 m², and the terminal creatinine 1.3 ± 1.0 mg/dl. As expected, renal function on admission was strongly associated with terminal renal function. Ninety-six patients had no change in creatinine (within 10% up or down), and 120 had a decrease in creatinine. For GFR, 80 patients had no change (within 10%), and 136 had an increase. A total of 240 patients had a decrease in renal function (both by increase in creatinine and decrease in GFR).

Terminal platelet count was significantly associated with terminal GFR and creatinine, but hemoglobin was not (table 3). Albumin was significantly associated with both terminal GFR and creatinine. The presence of proteinuria was strongly associated with both terminal GFR and creatinine.

The first mean glucose serum concentration after admission to the ICU was 205 ± 81 mg/dl. The final mean glucose concentration before organ recovery was 241 ± 68 mg/dl. Final prerecovery glucose concentrations of 200 mg/dl or greater were observed in 72% organ donors and 39% of the donors experienced glucose concentrations 250 mg/dl or greater.

Between declaration of death and organ recovery, 4512 individual glucose determinations were performed in all organ donors. The average glucose concentration during this time period (mean, approximately 43 h) was 212 ± 42 mg/dl. Maximum glucose concentrations, prerecovery glucose concentrations, average glucose concentrations between declaration of brain death and organ recovery, and glucose concentration variability (as determined by SD) were all significantly associated with worsening terminal renal function. Laboratory results are listed in table 3.
Glucose was significantly higher in patients with a decrease in renal function and lowest in those with an improvement in renal function \((P < 0.0001)\).

**Association of Medical Treatment with Terminal Renal Function as Determined by Creatinine and Calculated GFR**

Approximately half of the deceased organ donors were transfused, and the majority required blood pressure support with vasoactive drugs (table 4). Transfusion was associated with improved terminal GFR \((81 \pm 31\) vs. \(78 \pm 76\) ml/min/1.73 m\(^2\); \(P = 0.001)\), but the use of vasopressors had no effect on terminal renal function.

dDAVP is frequently given to organ donors with clinical evidence of diabetes insipidus. Almost half of the patients \((n = 214; 47\%)\) received dDAVP. Sodium homeostasis is frequently disturbed in patients with diabetes insipidus. There was no association between dDAVP administration and terminal sodium levels (data not shown). The administration of dDAVP was significantly associated with better terminal renal function (Creatinine, \(1.1 \pm 0.5\) vs. \(1.4 \pm 1.2\) \([P = 0.0008]\); GFR, \(85 \pm 48\) vs. \(75 \pm 65\) ml/min/1.73 m\(^2\) \([P < 0.0001]\); table 4).

Thyroid hormone supplemenation was administered to only approximately 10% of the donors and did not demonstrate any effect of renal function (table 4). Varying doses of steroids were administered to all patients, except for one donor. The dose of steroid administration may influence glucose levels; therefore,
we determined the impact of the different steroid doses on terminal glucose levels. We found no association between administered steroid doses and terminal glucose levels (data not shown).

While some insulin treatment was initiated in approximately two-thirds of the donors, only approximately 20% received an insulin infusion. Use of insulin was associated with lower terminal GFR (77 ± 55 vs. 87 ± 59 ml/min/1.73 m²; P = 0.009).

Multivariate Analysis

Results of multivariate analysis for both terminal creatinine and GFR as markers of renal function are shown in table 5. Admission values of GFR and creatinine were significant determinants of terminal values in both univariate and multivariate analysis. Average glucose showed the strongest correlation with terminal GFR and creatinine and was included in the model. Average glucose correlated strongly with other glucose values; however, glucose variability (SD) was also statistically significant and was included in the model, although this reduced the P values for both parameters. Age was not a significant predictor of creatinine or GFR, although age is part of the calculation for GFR. Gender was significantly associated with both terminal creatinine and GFR, but more weakly associated with GFR. Hypertension was weakly associated with GFR, but not with creatinine.

Higher platelet count was associated with lower creatinine and higher GFR and remained statistically significant in the multivariate model. Platelet count was associated with several other variables, such as gender, obesity, ethnicity, and cause of brain death, which were already in the model.

Insulin use was not significant in the multivariate model, but this factor was highly correlated with higher average glucose. Transfusion was also not significant in the multivariate model, but it was highly associated with head trauma, which was significantly associated with better terminal GFR. Ethnicity was not a significant factor in the multivariate analysis, but it was related to several other important factors. Asian-American donors were older (P < 0.0001) and had a higher incidence of hypertension, whereas African-American donors had higher admission creatinine levels.

Discussion

Cessation of cerebral function will invariably result in a sequence of pathophysiologic changes8–17 leading to
Table 5. Multivariate Analysis

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Cr Parameter ± 95% CI</th>
<th>P</th>
<th>GFR Parameter ± 95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Admission Cr or GFR</td>
<td>0.63 ± 0.09</td>
<td>&lt; 0.0001</td>
<td>0.62 ± 0.089</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Gender</td>
<td>-0.086 ± 0.034 (F)</td>
<td>&lt; 0.0001</td>
<td>0.038 ± 0.038 (F)</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>BMI</td>
<td>0.0097 ± 0.0054</td>
<td>0.0006</td>
<td>-0.010 ± 0.0064</td>
<td>0.002</td>
</tr>
<tr>
<td>Cause of brain death</td>
<td>0.07 ± 0.05 (C)</td>
<td>0.006</td>
<td>-0.086 ± 0.055 (C)</td>
<td>0.007</td>
</tr>
<tr>
<td>Glucose average, mg/dL</td>
<td>0.012 ± 0.0091</td>
<td>0.01</td>
<td>-0.0014 ± 0.0010</td>
<td>0.006</td>
</tr>
<tr>
<td>Glucose standard deviation, mg/dL</td>
<td>0.017 ± 0.0012</td>
<td>0.008</td>
<td>-0.20 ± 0.0014</td>
<td>0.007</td>
</tr>
<tr>
<td>Platelets, 10^9/dL</td>
<td>6.97 ± 3.3 · 10^-7</td>
<td>&lt; 0.0001</td>
<td>7.79 ± 3.9 · 10^-7</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Proteinuria, Y/N</td>
<td>-0.046 ± 0.032 (N)</td>
<td>0.005</td>
<td>0.053 ± 0.037 (N)</td>
<td>0.005</td>
</tr>
<tr>
<td>Hypertension, Y/N</td>
<td>NS</td>
<td></td>
<td>0.042 ± 0.042 (N)</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>dDAVP, Y/N</td>
<td>0.062 ± 0.032 (N)</td>
<td>0.0002</td>
<td>-0.073 ± 0.037 (N)</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

Terminal Cr or GFR analyzed by multiple linear regression after logarithmic transformation.

BMI = body mass index; C = cerebral vascular accident; CI = confidence interval; Cr = creatinine; dDAVP = desmopressin acetate; F = female; GFR = glomerular filtration rate.

worsening of the donor’s organ function within hours unless appropriate intervention is undertaken. In part, these changes, combined with donor demographics and cold and warm ischemia times, may explain the increased delayed graft function rate when compared to grafts from living donors.

Organ donor management in the United States is dictated by the local OPOs, and there are currently no universally applied guidelines, albeit there is significant overlap and agreement for most of the endpoints. Interestingly, this is not the case for glucose control. Recommendations for glucose control range from tight glucose control (< 140 mg/dl) to no upper limit, depending on the respective OPO. In this study, all donors were managed according to the CDTN management guidelines (table 1).

Some of our findings are expected. An association of admission GFR (creatinine) with terminal prerecovery GFR (creatinine) is not surprising. Furthermore, men have higher serum creatinine levels for equal GFR compared with women. Our results are consistent with this. While gender was significantly associated with terminal creatinine, it was not with calculated GFR. Age reported for the entire cohort was not significantly associated with terminal GFR, which was not entirely surprising given the fairly homogenous age group. However, older age and hypertension was more prevalent in the Asian-American population and can therefore explain the observed decreased terminal renal function in this population. Diabetes type I or type II were not associated with decreased renal function, albeit the number of organ donors suffering from diabetes type I was very small; our data are not sufficiently powered to allow definite conclusion.

The majority of organ donors received vasoactive drugs, mostly phenylephrine and dopamine for blood pressure support. The impact of phenylephrine and dopamine on renal function in organ donors is not well studied, and evidence of beneficial effects is lacking. We cannot confirm findings from the study by Blasco et al. that epinephrine (albeit given to only 4% of the organ donors) is independently associated with decreased renal function, at least not when based on calculated GFR.

In this study, lower platelet count was highly associated with a decline in renal function in both univariate and multivariate analyses. We cannot rule out that this is simply a marker of disease severity as opposed to biologic cause and effect. Even if there is a biologic cause and effect, it does not necessarily mean that the benefit of treatment will outweigh the risk and cost. Platelets are very expensive and not without significant risk, and they represent an extremely limited resource. Platelet transfusion has been shown to be an independent factor for adverse outcomes in at least a subset of patients, and it is increasingly associated with inflammation, tissue repair, and ischemia reperfusion injury.

We confirm in a significantly larger cohort the findings from Blasco et al. that administration of dDAVP is associated with a significantly decreased risk of developing decreased prerecovery renal function. Administration of dDAVP was not associated with elevated sodium levels, implying that diabetes insipidus was either well controlled or did not appear to be a significant problem, at least just before organ retrieval. The use of dDAVP may improve terminal renal function indirectly by decreasing excessive urine output and maintaining normovolemia. Other than antidiuretic properties, dDAVP may have direct protective effects through induction of medullary proliferation and induction of nitric oxide. We do not have the data to determine whether the effect of dDAVP was solely through maintenance of euvolemia.

An important finding is the poor glucose control in this cohort between declaration of brain death and organ recovery and the strong association of average glucose concentrations and declining renal function (table 3).
Most intensive care units have adopted empiric protocols as at our institution (personal verbal communication with Michael Gropper, MD, PhD, Director Critical Care Medicine, Vice-Chair Department of Anesthesia and Perioperative Care, University of California, San Francisco, CA, June 17, 2008) with target glucose levels of less than 150 mg/dl. Furthermore, Egi et al. found that variability of glucose concentrations (as determined by calculation of SD of glucose concentrations in each patient) was a significant and independent predictor of ICU and hospital mortality and that it was a stronger predictor of ICU mortality than mean glucose concentration.27 Glucose variability, when included in the model, also demonstrated a significant association with decreased renal function, although there was a strong interaction with glucose average.

Overall, our observations in organ donors confirm that hyperglycemia and fluctuations in plasma glucose concentrations might also be important for renal injury during critical illness and that the highest benefit may be achieved by controlling glucose levels to some degree.4

Only 28% (n = 126) of the organ donors had documented prerecovery glucose levels less than 200 mg/dl. Thirty-nine percent (n = 179) of organ donors had prerecovery glucose levels of greater than 250 mg/dl. Even when applying less stringent target glucose levels, this study suggests that glucose control is very poor in deceased organ donors.

In humans, evidence that hyperglycemia is associated with renal injury is documented even in critically ill patients without diabetes.28 The possible mechanisms of increased renal injury during hyperglycemia are not well understood. Several suggested pathways include release of toxic substances (e.g., polyols, hexosamines) from several steps in the glycolytic pathway, impairment of normal autoregulated glomerular capillary pressure,29,30 enhanced production of nitric oxide,31 inflammatory molecules, and transforming growth factor beta 1.32

The study has several strengths and limitations. One of the strengths is that our cohort is quite large and is from a single OPO using a common protocol. Organ donors were in various hospitals in Northern California, and treatment was based on established ICU protocols in each respective hospital before determination of brain death. Once brain death was declared, a transplant coordinator nurse from the California Transplant Donor Network resumed care of the organ donor based on an established protocol.

One significant limitation is that the data were not randomized or prospective; as such, there were many confounding relationships, making it difficult to control for all interactions. More than one multivariate model was possible, and we have shown the model that fit the data best. The glucose values were all interrelated, although average glucose consistently showed the best predictive values. Glucose variability was also strongly related to creatinine. Because these predictors were so strongly related to each other, P values were lower when both were entered into the model. While only a prospective randomized study can demonstrate whether control of glucose will maintain renal function in donors, our multivariate analysis strongly suggests that the effect of glucose is not related to other more significant variables.

On the other hand, we have included platelet count in the model because of the strong association (P < 0.0001) with creatinine and GFR. Platelet count was related to several variables accounted for in the model and several variables not in the model, leaving a strong possibility of a complex confounding relationship, including possible relationships to other factors that were not measured. Such findings may prompt further observation and investigation that could elucidate something amenable to treatment and improvement of donor renal function.

In summary, we identified and confirmed several risk factors associated with decreased prerecovery renal function in organ donors. In view of the fact that identification of possible organ donors is a rather dynamic process and involves many health care providers, our data suggest that organ donor management after official declaration of brain death presents a unique opportunity for aggressive interventional therapy that may affect donor organ quality. In particular, a more aggressive management of hyperglycemia in organ donors seems to be warranted, albeit the beneficial effect needs to be validated in prospective studies.

The authors thank the California Transplant Donor Network for their collaboration. We are especially indebted to Sean Van Slyck, Associate Director of Donation Services, California Transplant Donor Network, Oakland, California.

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