Association of Brain-Dead Donors' Terminal Inflammation With Delayed Graft Function in Kidney Transplant Recipients

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ABSTRACT

Background. Systemic inflammation affects kidney function in a wide range of diseases. Even in kidney transplant recipients, higher levels of C-reactive protein (CRP) are invariably associated with both worse short- and long-term graft outcomes. However, little is known about systemic inflammation in kidney donors and, notably, brain death causes a strong systemic inflammatory response.

Objective. To analyze the role of systemic inflammation of brain-dead donors on short-term kidney graft outcomes (ie, delayed graft function [DGF], defined as the need of dialysis during the first week after transplantation).

Materials and methods. Retrospective analysis of clinical and biochemical characteristics of all brain-dead kidney donors generated in the Hospital Clínic of Barcelona in the 2006 to 2015 period (n = 194). Donors who were tested for CRP in the 24 hours before BD declaration were included (n = 97, 50% of initial population). Clinical and biochemical features of their respective recipients (n = 165) were analyzed, comparing recipients who developed DGF (n = 30) with recipients who did not (n = 135).

Results. Donors whose recipients later developed DGF had much higher CRP values (10.58 [5.1-18.21] vs 4.81 [1.42-12.2] mg/dL, $P = .025$). Other characteristics associated with the development of DGF were renal biopsy score and recipient dialysis vintage ($P = .025$ and $P = .002$, respectively). In logistic regression analysis, PCR maintained significance in the non–expanded criteria donor (ECD) group (odds ratio [OR], 1.102; $P = .027$), but it lost significance in the ECD group ($P = .67$).

Conclusions. Terminal donor CRP was associated with DGF in kidney transplant recipients and proved to be mostly significant in younger donors.

SYSTEMIC inflammation impairs kidney function through the activation of renal endothelium, the infiltration of inflammatory cells, the development of microcirculatory dysfunction, and a direct tubular injury [1]. The detrimental effects of systemic inflammation on kidney function have already been highlighted in many diseases, especially septic shock, independent of the hemodynamic status of the patient [2]. In renal transplantation, systemic inflammation of the recipient before and after graft implantation have been associated with worse short- and long-term outcomes [3–6], whereas little is known about the role of systemic inflammation in the kidney donor. Notably, brain-dead (BD) kidney donors experience an "explosive" systemic inflammatory response as soon as brain death develops [7]. Therefore, it is reasonable that in the meantime between BD development and organ

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0041-1345/17
https://doi.org/10.1016/j.transproceed.2017.10.003

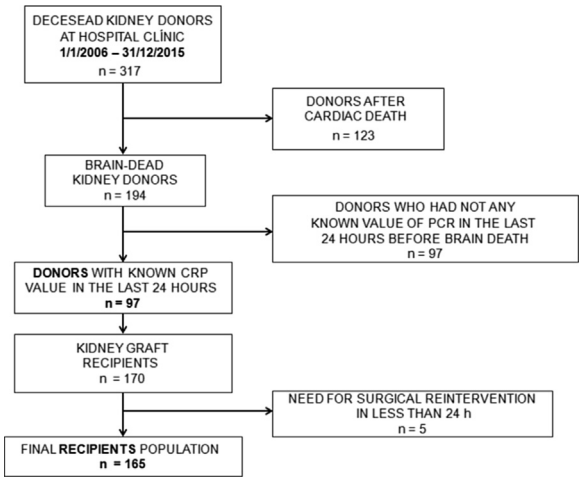

Fig 1. Study flowchart.

retrieval, donor systemic inflammation can start to affect kidney function even before ischemia-reperfusion injury. This has already widely demonstrated for liver and lungs transplantation [8–11]. Recently in kidney transplantation, the donor levels of resistin, as an inflammatory biomarker, were significantly associated with the development of delayed graft function (DGF) [12]. However, studies with more easily available and clinician-friendly biomarkers are currently lacking. Therefore, we aimed to investigate the effect of donor systemic inflammation on recipients' clinical short-term clinical outcomes (ie, DGF) through the study of the most widely used proinflammatory biomarker at clinical level, C-reactive protein (CRP).

MATERIALS AND METHODS

This is a retrospective monocentric study in which we analyzed the population of BD donors generated in our hospital in a 10-year period that had at least one measured value of CRP in the 24 hours before BD declaration (Fig 1). Data have been collected in an anonymous database according to the national legislation about privacy and after the local Ethical Committee evaluation and approval.

Briefly, all the BD donors generated in the Hospital Clinic of Barcelona in the 2006 to 2015 period have been included in the initial database (n = 194), and non-heart-beating donors were excluded (n = 123). The final database of kidney donors included only those patients who had at least 1 value of CRP measured in the 24 hours before BD declaration (n = 97, 50% of the initial BD donor population). All the respective recipients of these 97 donors were initially included (n = 170). The only exclusion criterion was the need of surgical reintervention in the first 24 hours after kidney transplantation (n = 5). Taking into account these inclusion and exclusion criteria, the final population of donors and recipients were 97 and 165 patients, respectively. The study flowchart is summarized in Fig 1. We chose DGF as the dependent variable, because it is the most important clinical outcome in the short-term after kidney transplantation; it prolongs hospital stay and patient's recovery, increases the risk of rejection, and affects graft survival in the long term. We defined DGF as the need of at least 1 dialysis session during the first week after renal transplantation [13].

In the literature there are no studies on the association of donor's CRP with DGF, thus it has not been possible to estimate the needed dimension of the sample before designing the study. Therefore, we set up a temporal window large enough (10 years) to reasonably guarantee a complete statistical analysis. Continuous variables have been described as mean or median values with standard deviation or interquartile range, as indicated by data distribution. Categorical variables have been described as absolute frequencies or percentages. Relations between variables of interest and clinical outcomes have later been explored with Student *t* test or Mann-Whitney test for continuous variables according to data distribution, and with χ^2 test for categorical variables. Those variables that proved to be significant in the univariate analysis were later analyzed in a multivariate logistic regression model. All statistical tests were conducted with a 95% confidence interval (CI), and a *P* value <.05 was considered significant. To carry out all the above-mentioned analysis, the software SPSS v 20 (SPSS Inc, Chicago, Ill, United States) was used.

RESULTS

Clinical features of recipients, donors, and donation process are summarized in Table 1. DGF occurred in 30 of the 165

Table 1. Recipient, Donor, and Donation Process Characteristics According to the Main Clinical Outcome

	No DGF (n = 135)	DGF (n = 30)	*P* Value
Recipient characteristics			
Age (y)	57 (46-64)	57.5 (46.75-70)	.7
Sex (% male)	90/135 (66.6%)	20/30 (66.6%)	>.99
History of diabetes (% yes)	35/135 (25.9%)	26.7%	>.99
HCV (% yes)	7/131 (5.3%)	(1/30) 3.3%	>.99
PRA >10%	11/135 (8.1%)	4/30 (13.3%)	.58
Previous transplant (yes/no)	28/135 (20.7%)	9/30 (30%)	.39
Dialysis vintage (months)	40 (25-63)	58 (46.5-84.75)	.002
Donor characteristics			
Age (y)	54.7 ± 1.41	58.47 ± 15.46	.18
Sex (% male)	70/135 (51.8%)	18/30 (60%)	.54
History of diabetes (% yes)	17/135 (12.8%)	2/30 (6.7%)	.53
HCV (% yes)	2/135 (1.5%)	0/30 (0%)	>.99
ICU stay (days)	2 (1-3)	1.5 (1-3.25)	.71
Terminal creatinine (mg/dL)	0.9 (0.67-1.1)	1 (0.7-1.2)	.11
ECD (% yes)	78/135 (57.7%)	20/30 (66.6%)	.48
CAR before BD (% yes)	20/135 (14.8%)	5/30 (16.7%)	>.99
CVA as cause of death	91/135 (67.4%)	19/30 (63.3%)	.83
CIT (h)	14 (11-18)	15.5 (9.5-20.5)	.8
Perfusion machine (% yes)	31/135 (23%)	6/30 (20%)	.91
Renal biopsy score	3 (2-4)	4 (2.25-4)	.021
CRP (mg/dL)	4.81 (1.42-12.2)	10.58 (5.1-18.21)	.025

Abbreviations: DGF, delayed graft function; HCV, hepatitis C virus; PRA, panel-reactive antibodies; ECD, expanded-criteria donors; CAR, cardiac arrest resuscitation; BD, brain death; CVA, cerebrovascular accident; CIT, cold ischemia time; ICU, intensive care unit; CRP, C-reactive protein.