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INVITED COMMENTARY

Prolonged brain death duration – does it improve graft quality?

Invited commentary on Nijboer *et al.*

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In this issue of *Transplantation International*, Nijboer and colleagues present a retrospective analysis of kidney transplantations within the US by investigating the impact of brain death duration (BDdur) on the outcome after transplantation. The study represents a very large review including 20 773 donor–recipient pairs during an 8-year span (1994–2007) and describes the effects of BDdur on delayed graft function (DGF), acute rejection and graft failure after 1 and 3 years post-transplantation. Notably, the authors report a decreased risk of DGF as well as better 1- and 3-year graft function with an increased BDdur of the donor after cerebral injury.

Brain death (BD) being a potential cause for inferior outcome after donor brain death (DBD) versus living donor transplantation was first described 13 years ago [1,2]. The difference between the two donor populations is mainly characterized by profound variations in certain physiologic phenomena. It appears, as if BD is more of a dynamic process than a static event leading to organ deterioration [3]. Haemodynamic stability is altered as a result of the 'catecholamine storm', resulting in global and regional malperfusion and consecutive tissue damage. Furthermore, cerebral injury is associated with a generalized inhibition of mitochondrial function because of a rapid loss of circulating thyroidal hormones (fT3) resulting from 'nonthyroidal illness' [4]. In addition, several anti- and pro-inflammatory cytokines are released within the context of BD and a significantly increased leukocyte infiltration into potential grafts leading to immune activation is apparent [5–8]. Ideally, early aggressive donor management protocols, namely optimal fluid substitution and hormonal replacement, are being employed to improve BD donor functional status and quality of the harvested organs.

The first study assuming a coherence between graft function and BDdur was published in 2001 by Muruve and associates [3]. The authors performed a retrospective analysis with 954 recipients of kidneys from brain dead donors within the US and described a significantly better kidney function at 1 and 5 years post-transplantation, when organs were procured between 24.6 and 59.3 h after declaration of BD. Similar findings were observed 1 year later by Kunzendorf and colleagues [9]. They studied the influence of BDdur on the incidence of primary kidney graft function, duration of DGF and graft survival within the EUROTRANSPLANT area, and identified a significantly protective effect of BDdur on the graft outcome longer than 470 min. Both in the US and in Europe, there appears to be a significant correlation between BDdur and graft quality after BD kidney transplantation. However, the tremendous discrepancy of time between the two studies

raises the question of whether BD duration itself or rather the act of 'taking one's time' is associated with a better graft function. According to the previous findings within the US, Nijboer and colleagues describe minimal, yet significant, differences in median BDdur between renal grafts with delayed function (23.2 h) and grafts with immediate function (23.8 h). However, the data on BDdur and graft survival remain conflicting, as other groups report BDdur longer than 24 h as an independent risk factor for impaired kidney function [10].

Nijboer and colleagues highlight the beneficial effects of a prolonged time of BD in favor of thorough ICU donor management before DBD organ retrieval and hint to the different policies of organ retrieval between Europe and the United States. Indeed, a prolonged time span between declaration of BD and organ harvesting in the US (24 h) compared with median BDdur in Europe (8 h) seems to have no impact on the number of organs donated and procured, as recently shown by a group from the University of Southern California [11]. Therefore, time-consuming donor management and elaborate organ allocation claim their validity and seem to have no negative effect on the persistent organ shortage. In addition, treatment of the potential organ donor has been a subject of extensive discussion lately. In this context, it has been recently shown that the treatment of BD organ donors with steroids [12,13] results in decreased expression of inflammatory cytokines and ameliorated ischemia/reperfusion injury in the post-transplant course accompanied by a decreased incidence of acute rejection in the setting of liver transplantation.

The question is, why prolonged BDdur should be beneficial for the graft quality, although shorter ischemia time is superior to longer ischemia time? If BD was a tissue-protective process, there would be no time limit for the evaluation of potential organ donors among the brain dead patients on intensive care units. Kusaka and colleagues [6] performed studies in deceased versus living donor kidney transplantation in a rat model, comparing cytokine production, cell infiltration and morphologic changes over 5 days post-transplant. The kinetics show that leukocyte infiltration and upregulation of pro-inflammatory cytokines in the graft increase with each day of BD. In humans, there is a high risk for instability when physiologic homeostatic mechanisms, that depend on a functioning nervous system, fail. There are clear data that both BD and prolonged BDdur result in graft damage, and successful organ retrieval after BD definitely relies on intensive donor management. However, there is yet a lack of information on the time course of deterioration of liver and kidney function after BD. Further experimental mechanistic studies clarifying the detailed kinetics of BD will be helpful to identify the crucial hours after BD. Ideally, the large time frame of BDdur could be narrowed down to a couple of hours that allow optimized donor management or even donor treatment, as well as keeping cold ischemia as short as possible.

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