

The Brain-Dead Organ Donor: A Missed Opportunity for Early Intervention

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We have witnessed significant advances in multiple areas of transplantation in the past two decades, ranging from improvements in surgical technique, organ preservation, immunosuppression and superior post-operative care. However, one area that has received insufficient attention is the appropriate management of the heartbeating brain-dead organ donor. Organ transplantation is a complex process that in most cases begins at the time of donation when a patient with severe central nervous system injury is declared brain-dead. Organs from deceased donors are outperformed by those transplanted from living donors in metrics such as patient survival, graft survival and in some studies the rate of rejection [1]. It seems to be clear that profound metabolic and hormonal changes triggered by brain-stem herniation play a significant role in the deterioration of organ quality and function. Furthermore, hemodynamic instability and autonomic dysregulation are hallmarks of brain-death induced ischemia/reperfusion injury to transplantable organs and we now know that ischemic tissue injury plays a role in the activation of innate immunity and tissue inflammation [2]. Using small and large animal models of brain-death, several groups have demonstrated up-regulation of pro-inflammatory mediators and graft infiltration by activated immunocytes (also termed passenger leukocytes), associated with poor graft quality and in some studies, disruption of tolerance in controlled transplant models [3]. More importantly, pre-clinical animal models of brain-death have shown that targeted therapy delivered at the time of brain-death protects kidneys, liver, heart and lungs improving organ function, graft survival and decreasing immunogenicity at the time of transplant [4,5].

Unfortunately, findings from therapy in animal models of brain-death have failed to translate into clinical practice. A recent review by Dikdan and colleagues effectively summarizes the results of available randomized clinical trials (RCT) focusing on donor management [6]. In their manuscript, they identified 32 studies relevant to donor treatment prior to tissue recovery and found that therapies aimed at improving perfusion and limiting ischemic damage provided a limited protective effect reducing levels of markers of organ injury and in one trial, the use of dopamine reduced the need for post-transplant dialysis [7]. In contrast, the use of immunosuppression targeting inflammation, passenger leukocytes and the peri-operative immune response remains controversial. Most clinical studies fail to provide evidence on the beneficial effects of pre-transplant steroid treatment in preventing delayed graft function and increasing graft survival. However, one trial conducted by Kotsch and colleagues investigated the routine use of Methylprednisolone on brain-dead donors and investigators found decreased pro-inflammatory mediator levels along with a decrease in the incidence of acute rejection after donor treatment [8]. Nevertheless, although the number of studies in this field is growing, the available data is insufficient to determine the effect of donor pre-treatment in the outcome of transplantation and well-designed RCT specifically targeting novel immune and non-immune mechanisms of organ injury are lacking.

The significant gap between organ supply and demand has led to the growing use of less than optimal organs for transplantation. In 2011, approximately 60% of organs destined for transplantation were recovered from deceased donors and the remaining fraction obtained from living donation. The use of organs from Expanded Criteria Donors (ECD) with respect to all donated organs grew from 21.4% in 2000

to 26.3% in 2009. In addition, the use of Donors after Cardiac Death (DCD) increased from 1.7% to 10% in the same period. This substantial increase in the use of suboptimal organs highlights the importance of finding alternative sources for organ donation and more importantly, the creation of standardized organ donor management practices with the potential to improve the quality of ECD and DCD organs. The ultimate goal of improving the quality of organs from deceased donors, especially extended criteria and cardiac death donors depends on advances in the following areas: 1) Appropriate funding of research aimed at understanding the immunobiology of ischemia/reperfusion injury in the context of deceased donation. 2) Increase in the number of prospective multi-center RCT addressing the impact of therapy at the donor level. 3) Standardization of management protocols among transplant centers across the country. 4) Development of sensitive and simple assays that predict graft quality prior to transplantation. 5) Development of novel immunomodulatory strategies targeting specific mechanisms involved in the activation of innate and acquired immunity in the context of brain-death or cardiac-death donation.

In summary, brain-dead donors are currently the main source of transplantable organs both in the U.S and world-wide. However, this condition substantially impacts organ quality and post-transplant survival resulting in significantly higher healthcare costs, need for more aggressive immunosuppression due to an increase in the incidence of acute rejection and ultimately, diminished quality of life for transplant recipients. Organ donation is the first step in the process of transplantation and constitutes an important opportunity to initiate timely intervention with the objective of protecting organs from imminent ischemia/reperfusion injury and allo-immunity.

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