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EDITORIAL

Management of the cadaveric donor of a renal transplant: More than optimizing renal perfusion?

Donor factors are important determinants of the short- and long-term outcomes of renal transplantation. This conclusion is supported by the similar fates of some paired kidneys removed from the same cadaver donor [1, 2], and the superior survival of transplants from living unrelated donors compared with cadaveric donors, despite the poorer donor-recipient HLA-matching of the former [3]. A complete understanding of these donor factors is elusive. Most studies have focused on the underlying structural integrity of the donor kidney by examining donor age, sex, nephron mass, etc., or by examining renal damage resulting from the hypotension and hypoperfusion associated with the acute injury or trauma that caused the brain death of the cadaver donor.

Although the structural integrity of the donor kidney is undeniably important, additional concepts are necessary to understand the report of Schnuelle et al in this issue of *Kidney International* [4]. These authors found that treating cadaver donors with catecholamines reduced the incidence of acute rejection and improved renal allograft survival. As the authors note, in other studies, administration of catecholamines to cadaveric donors has increased, decreased, or had no effect on initial allograft function and long-term outcomes. Poor outcomes may have occurred when high-dose catecholamines were employed in the setting of severe cardiovascular collapse, or when other detrimental factors such as advanced donor age or prolonged cold ischemia time were also present. A beneficial effect may result when catecholamines improve renal perfusion. A remarkable feature of the donors in the study by Schnuelle et al is that those which did, and those which did not, receive catecholamines had the same good blood pressure and urine output.

If the perfusion of the donor kidney is good, how would catecholamines reduce rejection? One possibility is that catecholamines mitigate the detrimental effect of acute traumatic brain death on the donor kidney. Explosive brain death in experimental rats is associated with cytokine production, adhesion molecule expression by renal endothelia, and renal inflammation [5]. After transplant, these cytokines and adhesion molecules could facilitate the entry of recipient leukocytes into the kidney and thus acute rejection. Supporting this concept is the observation that there is increased acute rejection in rodent models if the transplanted kidney is taken from a brain-dead, as opposed to a living, donor. Furthermore, human renal transplants from living donors have less adhesion molecule expression, less inflammation [6] and better outcomes [3] than those from cadavers. Acute brain death is also associated with profound neuroendocrine dysregulation. Initially, massive release of catechols may result in hypertension; then there may be insufficient catecholamines and thus hypotension [5, 7]. Consistent with the above hypothesis is the observation by Schnuelle et al that the salutary effect of catecholamines was most pronounced in donors that had suffered acute traumatic brain death.

Second, catecholamines may inhibit the inflammatory response of the kidney to injury, and thus decrease rejection. Matzinger has emphasized the importance of injury in initiating immune responses [8]. According to this hypothesis, the immune system ordinarily encounters a multitude of non-self antigens in the air we inhale, the food we eat, and the objects we touch. Yet, these non-self antigens are ignored. The immune system has evolved to be activated only after infections. Unlike innocuous non-self antigens, non-self antigens of infectious pathogens are associated with injury. It is the combination of injury and non-self antigens, ordinarily seen during infections, that activates an immune response. After transplantation, the non-self antigens are the alloantigens of the transplant, and the injury occurs during the transplantation process—hypoperfusion in the donor, cold ischemia during transport of the organ to the recipient, and warm ischemia during the surgical anastomoses (9). Catecholamines may diminish the injury by improving renal perfusion in hypotensive patients, and, as Schnuelle et al discuss, they may inhibit inflammation by inhibiting the expression of endothelial adhesion molecules.

Finally, any catecholamines transplanted with the kidney may have a direct local regulatory effect on the immune response. They may facilitate Th2 responses [10] that, in some studies, are associated with allograft tolerance.

In conclusion, the report by Schnuelle et al and other data [1, 2] indicate that donor factors influence the ulti-

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mate outcome of renal transplantation. Although the importance of choosing a cadaveric donor with a structurally intact kidney, and the importance of maintaining the structural integrity with appropriate cardiovascular management cannot be overemphasized, this report and other data reviewed in this editorial suggest that, in the future, optimal management of the cadaveric donor of a renal transplant may involve more than optimizing renal perfusion. Further research will determine how best to offset the detrimental effects of brain death, and how best to regulate the renal inflammatory response to injury.

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