Synergistic effects of prolonged warm ischemia and donor age on the immune response following donation after cardiac death kidney transplantation

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Background. *Organs from DCD (donation after cardiac death) donors are increasingly used for transplantation. The impact of advanced donor age and warm ischemia on the immune response of the recipient has not been studied. We developed a novel and clinically relevant model of DCD kidney transplantation and investigated the effects of donor age and prolonged warm ischemia on the recipient immune response after following DCD kidney transplantation.*
Methods. *DCD grafts from young and old F-344 donor rats were engrafted into LEW recipients who were nephrectomized bilaterally after a short (20 minutes) or prolonged (45 minutes) warm ischemia time.*
Results. *Analysis of the recipient's immune response early after transplantation showed an enhanced innate and adaptive immune response when old DCD kidneys were engrafted. Next, we studied DCD recipients with a supportive, contralateral native kidney in place, which allowed the recovery of the transplanted DCD kidney. Old DCD kidneys, demonstrated an impaired renal function associated with pronounced histomorphologic graft deterioration and an enhanced immune response by day 100 after transplantation. Interestingly, young DCD kidneys with a long warm ischemic time recovered from acute tubular necrosis and did not stimulate the long-term immune response.*
Conclusion. *Our observations emphasize that prolonged warm ischemic time and advanced donor age augment the immune response after transplantation of DCD grafts. These results provide an experimental model and a mechanistic framework of clinically relevant aspects in DCD donation. (Surgery 2013;153:249-61.)*

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THE NUMBER OF DCD (DONATION AFTER CARDIAC DEATH) organs that are used for transplantation is constantly increasing. Limitations and criteria in regard to donor age or duration of warm ischemia time are not yet clearly defined. It is well known that kidneys from DCD have greater rates of delayed and primary nonfunction as a result of extensive acute tubular necrosis (ATN).[1] Provided a careful donor selection is made, long-term outcome of DCD kidneys has been equivalent to kidneys from brain-dead donors.[1,2] Interestingly, DCD kidneys undergoing delayed graft function demonstrate a better long-term function than kidneys from brain-dead patients with delayed graft function, suggesting injury specific effects.[3] Explanations for this phenomenon may include adverse consequences of brain death and an improved recovery of DCD organs also potentially linked to age-specific repair mechanisms.

Nonetheless, the consequences of prolonged warm ischemia are closely associated with DCD donation.

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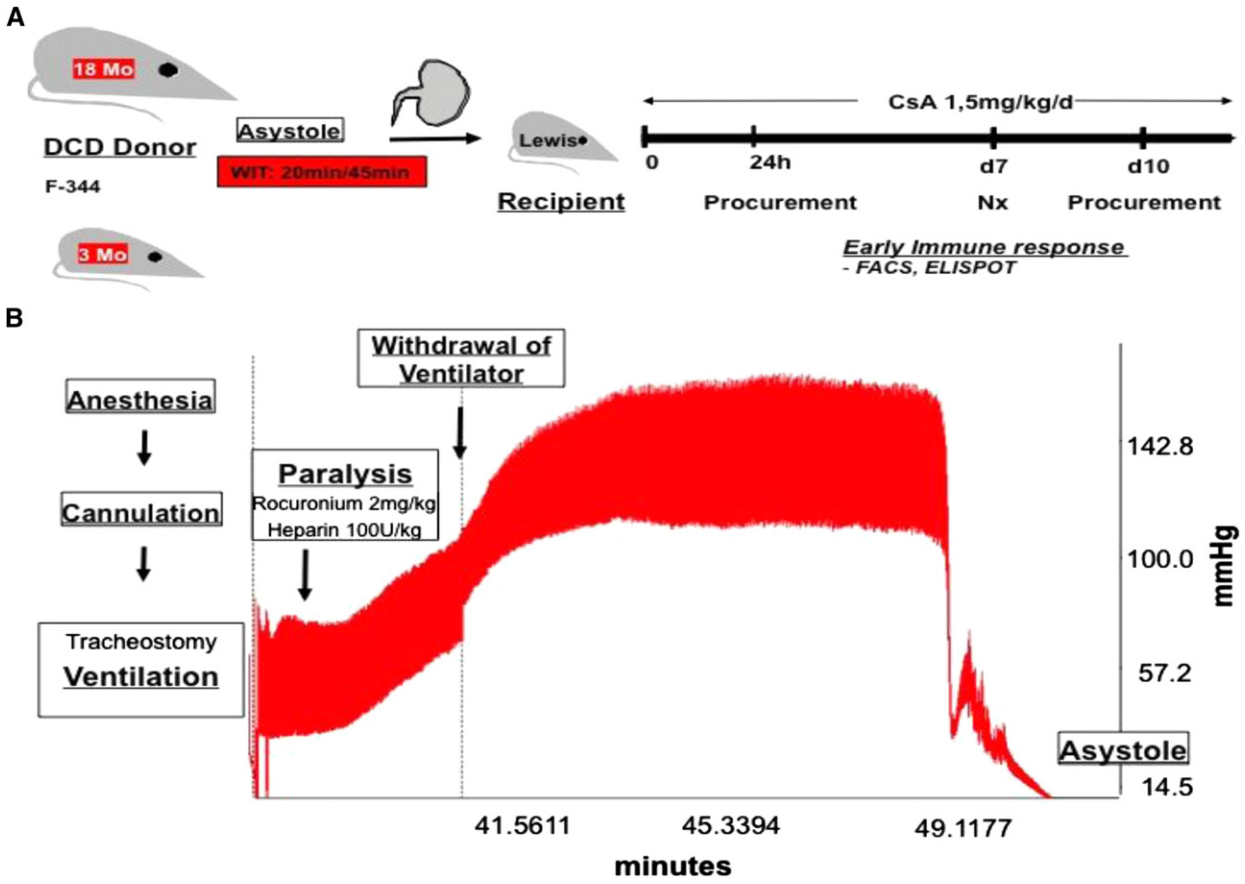

Fig 1. (*A*) The DCD model (I). After asystole, 3- or 18-month-old donor F-344 kidneys were exposed to a either short (20 minutes) or prolonged (45 minutes) warm ischemia time and subsequently transplanted into 3-month-old native Lewis recipients. Recipients received a short course of clcyosporine A (CsA; 1.5 mg/kg for 10 days). Although the right native kidney was removed during transplantation, the contralateral kidney was left in situ for 1 week to allow for recovery from acute tubular injury. Recipients were sacrificed after 24 hours and 10 days; graft, spleen, and draining lymph nodes were collected for further analysis ($n = 5$ per group). In additional groups, the native contralateral kidney was kept in place for 4 weeks to allow the recovery of ATN after warm ischemia ($n = 5$/group). Living donors (3-month-old F-344) served as controls ($n = 5$). (*B*) The DCD model (II). Depicted is a characteristic blood pressure curve during the different stages of the DCD procedure. See text for methodology. After the intravenous administration of heparin, donor rats were paralyzed with rocuronium and the ventilator was withdrawn 3 minutes after the cessation of any respiratory activity. Ischemic asystole occurred after an average of 8 minutes and was defined as the start of warm ischemia time in this model. (Color version of figure is available online.)

Their effects on the recipient's immune response remain to be elucidated. Brain death has been found to stimulate the early immune response in both, clinical and experimental studies.[4-6] Likewise, advanced donor age is known as a major risk factor for primary nonfunction, delayed graft function, and long-term allograft dysfunction in organs originating from brain-dead donors.[7-9] The correlation of these factors has not been investigated in DCD donors.

Experimental studies on the impact of advanced donor age on the recipient's immune response are inconsistent. Most but not all experimental studies suggested an increased immunogenicity of older donor kidneys, leading to an augmented adaptive immune response and more frequent acute rejection rates.[10-13] Prolonged warm ischemia is a unique feature of DCD organs linked to cellular damage—reflected by severe acute tubular necrosis—release of reactive oxygen species, up-regulation of cellular adhesion molecules, attraction of host leukocytes, and subsequent immunologic activation.[14]

On the basis of clinical experience, recommendations by the American Society of Transplant Surgeons suggest to limit warm ischemia times for liver grafts to 20 to 30 minutes and 45 to 60 minutes for kidney grafts.[15] However, the long-term immunologic consequences of prolonged warm ischemia time in DCD kidneys have not