

Editorial

Warming to Non-heart-beating Donors?

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Acute organ injury in the brain death, preservation, and implantation process is increasingly recognized as a mechanism of injury that has detrimental short- and long-term consequences in transplantation (1). A mainstay of organ preservation to prevent ischemia is cooling of the organ to between 1 and 4°C. Cooling slows adenosine triphosphate (ATP)-consuming metabolic processes and is typically well tolerated, for up to 48 h in kidney. The heart, on the other hand, tolerates cold ischemia poorly, with preservation times of 6 h or less. However, direct cytotoxic effects of cooling have long been appreciated, but are accepted as 'collateral damage' because of the other beneficial effects (2). Under conventional conditions, warm ischemia, whether prior to organ retrieval or during the transplant anastomosis, produces greater ischemic damage than a comparable duration of cold ischemia. Whatever the source of ischemia, much of the damage is believed to occur during reperfusion, with the production of free oxygen radicals leading to cell membrane destruction through lipid peroxidation. Transplantation from non-heart-beating donors is complicated by inevitable warm ischemia. This has resulted in very high rates of delayed graft function and higher rates of primary nonfunction, especially if uncontrolled non-heart-beating (NHB) donors are used. ('Uncontrolled' means the NHB donor is identified when already dead, as opposed to a 'controlled' donor whose heart is still beating when the organ retrieval team is present.) Nevertheless, this high rate of delayed graft function has not translated into poor long-term graft survival, especially if acute rejection is avoided (3). Cold machine perfusion has helped to reduce delayed graft function and improve graft survival in non-heart-beating kidneys. This may be due to reduced ischemic damage and/or the ability to discard suboptimal kidneys based on machine perfusion parameters (4).

In the study by Brasile et al. on page 316 of this issue, a novel approach is taken to improve renal function following significant warm ischemia. The Exsanguineous Metabolic Support (EMS) device perfuses an acellular solution at 32°C, which provides oxygen (bound to bovine hemoglobin), nutritional supplementation and free radical scavengers. There are three potential benefits to this technique: (i): leukocytes are not

present during reperfusion, which may prevent free-radical-mediated injury (5); (ii) injury from cooling is avoided; and (iii) active metabolism is apparently preserved in the kidney. Certainly, the idea of warm acellular perfusion has been used in other models, particularly in coronary bypass surgery requiring cardiac asystole (6). In the present series of experiments, all groups were subjected to 30 min of warm ischemia, followed by 18 h of cold storage or warm perfusion. Some kidneys with cold storage were then warm perfused and some with warm perfusion were then cold stored. In the first two groups, after initial warm ischemia, warm perfusion resulted in better renal function and structure when compared with cold storage. If warm ischemia was followed by cold storage, subsequent warm perfusion showed a time-dependent improvement in renal function. Conversely, cold storage after warm perfusion had a time-dependent deleterious effect.

This study represents an important extension of this group's proof of principle (7) that acellular oxygenated warm perfusion is superior to cold storage following warm ischemia in a canine autotransplant model. It is perhaps premature to conclude from the presented data that this study identifies 'cold ischemia as the major obstacle to expanding indications for organ donation with warm ischemically damaged kidneys'. Certainly, the isolated contribution of cold ischemia could only be determined by including a comparative group using cold perfusion rather than simple cold storage. There is little controversy that machine perfusion is superior to simple storage, whether warm or cold; the important question is whether this form of acellular warm perfusion is superior to the current standard. In addition, it would be interesting to see how long kidneys without warm ischemia can be safely stored on the EMS device. If metabolism is truly restored and reperfusion injury ameliorated, then storage times could be extended beyond the current barriers.

It will be exciting to see this work extended to an allograft model and finally to human kidneys, as not all therapies proven successful in animal auto-transplant models have translated to success in clinical transplantation. One should also determine the mechanism of the beneficial effects of warm perfusion. One can speculate on the mechanisms of the effect: for example, the benefits may derive from induction of heat-shock protein genes or protective genes such as hemoxygenase-1, or simply through the prevention of adhesion molecule up-regulation at the time of implantation. If such is the case, then the same beneficial effects could potentially be produced by pharmacologic (8) or gene therapy (9). Maintaining metabolism through this warm EMS device may give other biochemical benefits beyond the stan-

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standard inflammatory and apoptotic pathways that we commonly try to block. These early data show great promise for expanding the donor pool by reclaiming kidneys damaged by warm ischemia.

A more general point is the opportunity that exists for research in organ preservation in the post-genomic era. Too much of the practice is based on 1960s experiments or earlier. We may get major benefits from challenging the dogmas and exploring molecular mechanisms in this field, which lags far behind other fields such as immunology.

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