Wrong Endpoints

A one-year survival rate may have made sense 25 to 30 years ago, but is that the appropriate timeframe today? In an era of comprehensive care and payment models, perhaps patients would be better served by a more comprehensive quality assessment that also captures pre-transplant and factors impacting access to waitlist. Patient survival rates should have real life relevancy, which means factoring in dialysis and survival rates for patients who remain on a waitlist when evaluating performance.

References

2. Scientific Registry of Transplant Recipients https://www.srtr.org/

Novel Normothermic Perfusion Technique for Preserving Donor Organs

By Uday Nori

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t possible to turn unusable organs into transplantable organs? Ex vivo pulsatile machine perfusion of donor organs is a proven technique for superior organ preservation, reduced delayed graft function, and reduced ischemia-reperfusion injury. This has been the standard of care for over four decades in high-volume transplant centers.

The perfusate solutions used for kidneys are typically crystalloids with several additives, such as antioxidants, electrolytes, antibiotics, nutrients, vasodilators, and corticosteroids. The perfusion temperatures are typically kept at 4°C to 8°C to help minimize cell metabolism and hence, have a better preserved organ. However, the significant drawback of this hypothermic perfusion technique is its inherent inability to allow any cellular repair.

Marginal kidneys, designated as “high kidney donor profile index,” make up a substantial proportion of transplanted kidneys currently. The quality of deceased donor organs has declined significantly over the past three decades because of the cause of death: improved traffic safety led to fewer donors who died accidentally, and more organ donors died from natural causes or substance abuse. Therefore, in the current paradigm of organ shortage and high organ discard rates, perfusion techniques that allow organ repair in addition to the preservation are highly desired.

Figure 1. Schematic diagram of normothermic perfusion

The notion of organ perfusion at the usual body temperature has several advantages:

2. Aerobic metabolism allows the kidney to regain function and minimize or avoid the cold ischemic insult.

2. The kidney can be maintained in a stable state, allowing close observation and assessment of viability.

3. Organ perfusion provides the opportunity to add therapies to a functioning organ to directly manipulate and improve its condition.

Although the concept of normothermic machine perfusion (NMP) has existed for more than two decades, it was only in the past few years that significant progress has been made in terms of optimal perfusion solutions, equipment, and favorable outcomes in animal models (Figure 1). At present, most normothermic perfusate solutions include packed red blood cells for oxygen carriage and use highly specialized equipment. Many acellular solutions are being investigated to replace hemoglobin as the oxygen carrier. Although most of the studies using NMP involve the lung and liver transplantation fields, owing to their high organ discard rates and understaged marginal donors, the adaptation of NMP in kidney transplantation is seen as naturally feasible and practical.

There are several animal model studies that have shown the success of NMP, but some human trials were also recently reported. A study by Watson et al. (3) subjected 12 discarded livers to the NMP, with six of them under high perfusate oxygen tension and the other six under near-physiologic oxygen tension. All six in the latter category were perfused uneventfully, and 11 patients were alive at a median of 12 months. Vogel et al. reported a study of 13 discarded livers that were preserved with NMP for 24 hours, and they showed both biochemical and histologic evidence for suitability for organ transplantation (2). Similarly, Hosgood et al. reported that two kidneys from the same donor that were declined by all transplant centers and preserved with NMP for 60 minutes cleared up significant areas of ischemia (3). In the largest series so far, Nicholson and Hosgood compared 18 marginal kidneys that received 1 hour of preimplantation NMP with 47 matched hypothermic perfusion controls (4). Remarkably, low delayed graft function rates were seen with preimplantation NMP (5.6% versus 36.2%). The benefits of NMP are significant, because hypothetically, organ quality improves with time as opposed to a gradual decline with conventional hypothermic perfusion. Therefore, NMP offers improved organ utilization rate, minimized ischemia-reperfusion injury, reduced delayed graft function, and stabilized endothelial cells. However, the costs and labor of this modality are also exceedingly high at present, not to mention the logistic complexities.

NMP, which allows organs to undergo perfusion for extended periods of time, has also allowed for other novel therapies, such as targeted immunosuppression therapies using sirolimus-infused nanoparticles to “silence” endothelial cell signaling—an important mechanism for acute rejection.

Success in the NMP field is believed to be imminent by many investigators and can potentially change the practice of transplantation in many ways. The idea of a centralized organ preservation laboratory, where all of the marginal, unusable organs undergo NMP to improve their quality and then are distributed to the individual transplant centers, seems to be possible in the near future. A query of clinical trials.gov revealed 11 human clinical trials currently underway, with one in kidney transplantation. This is indeed a highly promising field to watch out for in organ transplantation.

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References


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