



## Improving Early Graft Function: Role of Preservation

J.H. Southard

**I**N ORGAN TRANSPLANTATION, the organ often does not immediately regain normal function. This delay in restoration of normal function (delayed graft function, DGF) is often blamed on "poor preservation" implying that, if preservation methods were better, DGF rates would be significantly improved. Certainly, injury caused by hypothermic preservation of organs contributes to the delay in restoration of normal graft function. But there are many additional factors that can cause DGF, either singly or when compounded with other potentially injurious conditions that are inherent in the donor and recipient condition. It is very difficult in clinical organ transplantation to separate the various factors (donor, recipient, preservation, immunologic) that can affect DGF. In this brief discussion, I will focus on the role of preservation injury in DGF and suggest some strategies for improving the preservation conditions of organs.

Preservation injury leading to DGF is a greater problem in clinical organ transplantation than in experimental organ transplantation. In the dog transplant model, the liver, kidney, and pancreas can be preserved substantially longer than in the clinical situation with little evidence of the development of delayed graft functions. For instance, the dog kidney can tolerate 72 hours of cold storage in UW solution with minimal injury.<sup>1</sup> Serum creatinine after transplantation rises only about three to fourfold normal (to 3 to 4 mg/dL) and quickly returns to normal (within 5 to 7 days). In this model there is no DGF. In the clinical situation DGF is common in 20% to 30% of transplants with preservation times of only 24 hours, on average.<sup>2</sup> In the laboratory, dog livers tolerate 48-hour preservation with 100% survival<sup>3</sup> and, although injured (elevated serum liver enzymes), correct this injury within 3 to 4 days, at which time the liver regains normal function. In the clinic, livers are generally thought to best tolerate only up to 20 hours of preservation and poor function rates increase to 10% or more if preservation is extended beyond 24 hours.<sup>4</sup> In the dog laboratory, the pancreas tolerates 72 hours of cold storage with rapid return of function,<sup>5</sup> but in the clinic the pancreas is routinely preserved for only about 17 hours, on average. These disparities between excellent laboratory research and poorer clinical results suggest that factors other than preservation/reperfusion injury. These other factors probably relate to the health of the donor organs and condition of the

recipient. In the laboratory, the dogs are healthy donors and recipients.

The better results obtained with kidneys from living unrelated donors (LURD) (ie, low incidence of delayed graft function and the reduction in chronic rejection) compared with cadaveric donor kidneys<sup>6</sup> is thought due to preservation. LURD kidneys are not exposed to significant periods of preservation but share comparable immunologic disparities with cadaveric kidneys. There are other significant differences between LURD kidneys and cadaveric kidneys. Cadaveric kidneys are from brain dead and seriously injured donors of various age, health background, size, and stabilization method used in the ICU. These factors could affect how the organ tolerates the period of preservation. However, the general consensus appears to be that the better results obtained with LURD kidneys are due to the absence of significant preservation injury.

Preservation injury as a major factor in DGF is also supported by the observation that greater DGF occurs in kidneys exposed to longer periods of preservation.<sup>7</sup> Although this is true, a closer look at the data suggests that additional factors, other than preservation injury, cause DGF. For instance, in the analysis of DGF in over 13,000 kidney transplants, it was shown that the DGF rate for kidneys preserved for only 6 hours or less, or from 6 to 12 hours (average DGF 20%), was similar to the DGF rate for kidneys exposed to longer periods (on average, about 25%). Thus, even short-term exposure to cold storage causes a significant number of human kidneys to show DGF, an event uncommon in the dog laboratory. This also suggests that factors other than preservation play a significant role in DGF.

If factors other than preservation play a major role in DGF, how then can preservation be expected to be improved so that early graft function can be improved? It seems scientifically tenable that improving upon the current results in organ preservation by simple cold storage is unlikely. The main reason for this supposition relates to the

---

From the Department of Surgery, University of Wisconsin, Madison, Wisconsin, USA.

Supported by NIH Grants DK18624 and DK35143.

Address reprint requests to Dr James H. Southard, Department of Surgery, University of Wisconsin, 600 Highland Avenue, Madison, WI 53792, USA.

conditions inherent in cold storage (ischemia) that set in motion the chain of events that leads to graft injury. With ischemia comes a rapid decline in the energy content of the organ, the onset of generation of a loss of homeostasis (biodegradation outpaces biosynthesis), and a time-dependent loss of structural competence of the vasculature–parenchymal cell interaction. These processes are greatly slowed by the cold, but do persist, at different rates in different organs, and in similar organs harvested from different donors. Some improvements in tolerance to the loss of energy can be obtained by the choice of preservation solution (UW appears superior to others at the current time), but it is unlikely that significant improvements in longevity or quality of preservation can be demonstrated clinically with new cold storage solutions. This is because new solutions do not address the central issue that limits preservation quality; that is, the lack of energy for the organ to maintain the integrity of structural elements necessary to reverse preservation injury.

Some might argue that a pharmacologic approach to organ preservation solution development might lead to significant improvements in initial graft function. However, the use of pharmacologic agents in a preservation solution is fraught with difficulties. For instance: (i) the agents are often inactive or insoluble at the temperatures required for preservation; (ii) the agents are often poorly permeable and do not get to the site of action; (iii) they may be rapidly washed out upon reperfusion when most needed; and (iv) injury involves multiple sites requiring multiple pharmacologic agents.

Therefore, it appears that improving organ cold storage solutions might not be the best approach to improve early graft function. Instead, one approach may need to concentrate upon preventing the reperfusion phase of the injury, which is an inevitable event in organ cold storage. Previous studies, however, suggest that reperfusion injury is also multifactorial, with opportunities to reverse injury limited to time-dependent “windows” of opportunity.<sup>8</sup> For instance, suppression of reperfusion-induced oxygen free radical injury may be limited to kidneys preserved for a limited amount of time (15 to 20 hours). Although oxygen free radical injury will occur in kidneys preserved longer, other types of injury (eicosanoid generated, activation of production of adhesion molecules, mitochondrial injury, etc) may also need to be simultaneously curtailed for improved early function. The use of a polypharmacologic approach to recipient treatment presents many potential complications and difficulties and it may be difficult to demonstrate clearly a superior outcome by this approach.

Despite the lack of evidence that improved early graft function can be obtained by improved cold storage, there is a potentially applicable method of preservation that could

improve early graft function for livers, kidneys, and the heart. Continuous perfusion has been shown in the laboratory to be a superior method to preserve these organs.<sup>9</sup> Not only is the quality of initial function greatly improved, but the longevity of preservation is extended significantly. The kidney tolerates 5 to 7 days of preservation, the liver 3 days, and the heart 1 to 2 days.<sup>9</sup> Clinical comparisons of DGF rates in kidneys preserved by cold storage or machine perfusion between different centers suggest that machine perfusion produces a significant reduction in DGF rates (about 10% or less vs 25% or more).<sup>10</sup> Reluctance to utilize this technology seems due to complications introduced by the necessity for organ sharing. Other potential problems often expressed include increased cost, labor intensity, and need for trained personnel. These are usually not major complications, especially when one considers the potential cost savings and decreased patient problems from the better results possible with machine perfusion.

In conclusion, improved early graft function may be achieved consistently if transplant centers perform machine perfusion of organs in an effective and careful manner. Improvement by the continued use of cold storage is probably unlikely, and the development of new preservation solutions significantly different from the UW solution has shown little promise in decreasing DGF. Future developments that will impact preservation technologies include a major effort to understand the fundamental mechanisms of preservation/reperfusion injury, the development of viability assays for organs that are machine perfused, and a clear understanding of the nature of the specific windows of opportunities to correct injury caused during the early phase of reperfusion.

## REFERENCES

1. Ploeg RJ, Goossens D, McAnulty JF, et al: *Transplantation* 46:101, 1988
2. Wahlberg JA, Love R, Landegaard L, et al: *Transplantation* 43:5, 1987
3. Jamieson NV, Sundberg, Lindell S, et al: *Transplantation* 46:517, 1988
4. Koyama I, Bulkley GB, Williams GM, et al: *Transplantation* 40:590, 1985
5. Barber WH, Hudson SL, Deierhoi MH, et al: *Transplant Proc* 22:446, 1990
6. Ploeg RJ, van Bockel JH, Langendijk P, et al: *Lancet* 340:129, 1992
7. Southard JH, Belzer FO: *Transplant Rev* 7:176, 1993
8. Koyama H, Cecka JM, Terasaki PI: *Clin Transplant* 7:199, (abstr)
9. Terasaki PI, Cecka JM, Gjertson DW, et al: *N Engl J Med* 333:333, 1995
10. Cecka JM, Terasaki PI (eds): *Clinical Transplants 1995*. Los Angeles, Calif: UCLA Tissue Typing Laboratory; 1995, p 1