Principles of Organ Preservation

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Organ preservation is the ability to maintain ex vivo organ viability in addition to the capacity to restore normal organ function at the time of restitution of physiological blood flow. It is currently the basis upon which clinical and research models of organ transplantation rely. Clinically, when the organ does not regain normal function rapidly after implantation surgery and reperfusion, there is either delayed graft function (DGF) or primary nonfunction (PNF). DGF by definition is impaired function that eventually returns to normal. On the other hand, graft PNF indicates complete failure of the organ to restore function or the inability to sustain life. In the clinical setting, DGF occurs in 10% to 15% of all liver grafts and 30% to 50% of cadaveric kidneys transplanted within 24 h of cold preservation. In heart, lung, or liver transplants, DGF can have devastating results in the individual patient, with prolonged ICU and hospital stays and possible long-term effects on organ function. PNF of vital organs results in death of the patient unless a retransplant is rapidly performed.

In the laboratory, organs can be preserved in the University of Wisconsin (UW) preservation solution for as long as 72 h with 100% immediate graft function in some animal models. Although the phenomenon of DGF is often blamed upon hypothermic preservation techniques that are currently used in clinical organ transplants, it is clear that other variables are critical, such as donor, recipient, and specific immunological conditions. To reduce the incidence of DGF and PNF, it is paramount to understand the mechanisms of graft injury during procurement, ex vivo transport, and subsequent reperfusion.

Mechanisms of Preservation Injury

To reduce the incidence of DGF and PNF, it is important to understand the types of injuries that occur at the cellular level. In the discussion of preservation and reperfusion injury, there are four different time periods that should be examined: prepreservation, cold preservation, rewarming, and reperfusion. While the prepreservation time period is distinct, the other three time periods are interrelated and codependent, making up the classic ischemia–reperfusion interval.

Prepreservation

Injury to solid organs can occur before the procurement process. Nonimmune-mediated processes may be very important to both short- and long-term patient and graft outcomes. On reviewing the current United Network of Organ Sharing (UNOS) database, immediate function and long-term graft survival are superior in grafts from living donors compared to those procured from classic cadaveric sources. Organ disease present in the donor either may be incompatible with graft survival after transplantation, such as severe hepatic steatosis, or may result in transmissible diseases, such as hepatitis C or B. Brain death triggers specific injuries in the cadaveric donor. Until recently, brain death in itself has not been considered a significant risk factor in the prepreservation period. The phenomena of brain death cause severe and profound derangements of the hemodynamic and endocrine systems as well as striking structural changes in the organs themselves. This chain of events may set the stage for the activation of various pathways at the cellular level, thereby triggering mechanisms of injury that may lead to increased immunogenicity and magnify preservation and reperfusion injuries.

Ischemic Injury

The current clinical methods used to preserve organs for ex vivo transport and later implantation in a suitable recipient are based on the suppression of metabolism by hypothermia at the time of removal from the donor. Organs are made tolerant to hypothermia by removing blood and replacing it with solutions designed to limit the physiological consequences of
hypothermic preservation. In addition to cellular injury sustained during hypothermia, there are also organ-specific homeostatic mechanisms that are perturbed in ways that prime them for augmentation of injury during reperfusion. Hypothermia decreases the cellular metabolic rate and the rate at which cellular enzyme systems function. When the temperature is decreased from normothermia, 37°C, to 0° to 4°C, there is a 12- to 13-fold decrease in metabolism. Cellular metabolism in the cold, however, does not cease completely.

Although hypothermia is essential to organ preservation, residual cellular energy requirements exceed the capacity of the cell to generate energy from anaerobic metabolism; this in turn leads to decreased intracellular energy, ATP, and adenosine diphosphate (ADP) levels as demonstrated in several laboratory models. In clinical transplantation, the period of warm ischemia during implantation may lead to further decrease in intragraft ATP, which is thought to be a marker of graft viability. Thus, one mechanism of ischemic hypothermic injury in all cells is the loss of mitochondrial homeostatic mechanisms that are perturbed in ways that prime them for augmentation of injury during reperfusion. Nonetheless, further decrease in intragraft ATP, which is thought to be a marker of graft viability. Thus, one mechanism of ischemic hypothermic injury in all cells is the loss of mitochondrial homeostatic mechanisms that are perturbed in ways that prime them for augmentation of injury during reperfusion.

As a consequence of the energy debt created during hypothermic conditions, several other intracellular events occur. Due to the use of anaerobic metabolism, there is an increase in intracellular acidosis secondary to lactate accumulation. The result of this acidosis, however, is unclear. After a critical period of ischemia, reperfusion precipitates irreversible injury. Reperfusion injury to several cell lines and experimental models was precipitated by a rapid return to physiological pH, the phenomenon described as a “pH paradox.” In this paradox, the cell injury and death are not from the acidosis caused by anaerobic metabolism but rather from the rapid return to normal pH during reperfusion.

Another mechanism of cell injury in the cold is cell swelling. This is caused by inhibition of Na+/K+-ATPase in hypothermic conditions, resulting in intracellular accumulation of Na+. This in turn leads to influx of Cl− while K+ exits the cell. With the decrease of the osmotic effect of the intracellular ions, there is an influx of water and resulting cell swelling.

Finally, based on theory and pharmacological intervention studies, it was initially hypothesized that reactive oxygen intermediates played a large role in the initial cellular injury that occurred at the time of reperfusion. Nonetheless, further and recent investigations into this phenomenon have failed to prove that reactive oxygen intermediates play a large role in cellular injury.

Preservation Solution

Successful ex vivo transport and reimplantation of graft organs is dependent upon the ability of the graft to survive hypothermic preservation. As such, preservation strategies have sought to optimize the components of the original cold storage Collins and Euro-Collins solutions. Based upon basic knowledge about hypothermic cellular injury, Belzer and Southard described the characteristics of the ideal preservation solution:

1. It must contain substrates to regenerate high-energy phosphate compounds;
2. It must have an alkaline pH to counteract acidosis;
3. It must contain materials to prevent injury from reactive oxygen intermediates; and
4. It must minimize cell swelling in hypothermic conditions.

As a consequence, University of Wisconsin (UW) solution contains several agents thought to facilitate storage of the liver, pancreas, and other organs such as heart and lung [Table 47.1]. It is also the only solution that is effective for prolonged preservation of isolated transplantable cells such as pancreatic islet cells.

Reperfusion Injury

During the ischemic phase of the injury, particularly in the liver, some cells are more sensitive to injury than others. The key to limiting the degree of preservation injury to cells is to restore normal physiological blood flow as soon as possible, that is, to limit the duration of hypothermic and normothermic ischemia (see Table 47.2 for optimal cold ischemia times for specific organs). The mechanism of reperfusion injury is multifactorial and not completely mechanistically defined, but it revolves around activation of specific cell types [e.g., neutrophils], expression of certain cell markers [especially cell adhesion molecules], increased production of specific cell mediators [such as TNF-α, IL-1, and interferon-γ], microvascular perfusion failure [both obstructive and regulatory], and programmed cell death [apoptosis]. Mechanisms of cell death are diagrammed in Figure 47.1.

<table>
<thead>
<tr>
<th>Organ</th>
<th>Cold ischemia time (in UW)</th>
<th>Evidence</th>
</tr>
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<tbody>
<tr>
<td>Kidney</td>
<td>&lt;24 h</td>
<td>II79</td>
</tr>
<tr>
<td>Kidney/pancreas</td>
<td>&lt;21 h</td>
<td>II80</td>
</tr>
<tr>
<td>Liver</td>
<td>&lt;12 h</td>
<td>II81</td>
</tr>
<tr>
<td>Lungs</td>
<td>4–6 h</td>
<td>I82,83</td>
</tr>
<tr>
<td>Heart</td>
<td>4 h</td>
<td>I4</td>
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