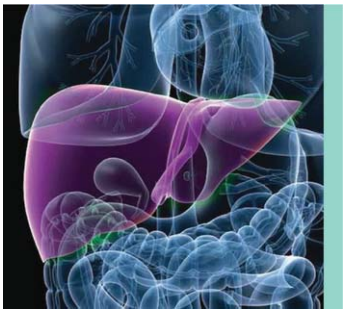

Normothermic Machine Perfusion of the Liver

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Static cold storage (SCS) has been the gold standard for organ preservation for more than four decades. This method of preservation works well for livers from young, healthy donors, achieving acceptable rates of early allograft dysfunction (EAD), primary nonfunction (PNF), and biliary complications, but it is limited by the effects of hypoxia during storage. Transplant teams have learned to avoid using livers that do not tolerate cold ischemia, such as steatotic livers and livers from older donors, but the progressive organ shortage has resulted in interest around superior methods of preservation.

Normothermic machine perfusion of the liver (NMP-L) is a technology that preserves the graft at near-physiological condition. The liver is quickly prepared by removing excess tissue and cannulating the blood vessels while the liver is in SCS; it is then connected to a heparinized circuit filled with warm, oxygenated blood and supplied with nutrients. NMP-L has many potential advantages over SCS. First, the period of SCS, known to be detrimental to the biliary epithelium and hepatocytes, is limited to only the time required for the donor liver explant and graft cannulation. This is expected to reduce the rate of both early (PNF and EAD) and late (biliary) posttransplant complications. Second, the near-physiological state of preservation allows a real-time graft function and ''viability'' assessment. In the case of a well-functioning liver preserved on the device, the risk for development of PNF is exceedingly low, even for high-risk organs. Without NMP-L, the test of organ viability occurs when the organ is transplanted in the recipient, and a poorly functioning organ results in EAD or PNF. Third, the ischemia-reperfusion injury in the liver and its resulting effects on the recipient, such as acute renal injury, are thought to be reduced by NMP-L. Finally, NMP-L can significantly extend preservation and could be a step toward organ allocation parity.

The conceptual benefits of NMP-L are easy to understand, and experiences gained by transplant teams with the technology are promising. Nevertheless, the efficacy of NMP-L has not been fully described by clinical trial

Abbreviations: AST, aspartate transaminase; COPE, Consortium for Organ Preservation in Europe; EAD, early allograft dysfunction; NMP-L, normothermic machine perfusion of the liver; PNF, primary nonfunction; SCS, static cold storage.

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data. Also, the complexity of NMP-L may introduce risk for an organ loss because of a technical error or device malfunction. Lastly, there is a potential for bacterial or fungal growth while the liver is on the device, although antibiotics are a standard component of the machine perfusion fluid.

REVIEW OF HUMAN DATA

The first-in-human NMP-L trial in 2013 confirmed the safety of the technology. In 20 patients transplanted with livers after NMP-L, there was 100% graft and patient survival at 6 months.[1] This safety study was not designed to evaluate other posttransplant outcomes, although a reduction in peak aspartate transaminase (AST) was noted. A similarly structured trial in Canada reported one graft loss and noted a prolonged length of stay.[2,3]

The efficacy of NMP-L was evaluated in a multicenter randomized COPE (Consortium for Organ Preservation in Europe) trial that completed patient enrollment in 2016. This seven-center European trial enrolled 272 donors using the OrganOx Metra device and was the first study to compare NMP-L with SCS. The trial endpoint was peak AST within the 7 days after transplantation, and the results are expected to be published this year. The preliminary data showed the livers randomized to NMP-L were about half as likely to be discarded compared with livers preserved by SCS, highlighting the potential for NMP-L to significantly increase organ utilization. Trials of similar design to the COPE trial are enrolling patients in North America, with primary endpoints of EAD and PNF.

VIABILITY TESTING TO IMPROVE LIVER UTILIZATION

Currently, many livers are discarded because they are perceived to be at high risk for PNF. NMP-L theoretically overcomes this risk by allowing functional liver assessment until the liver is implanted in the recipient.

Our current understanding of the liver viability testing is based on several experimental studies. Using discarded human donor livers, Sutton et al.[4] reported hourly bile production volume to be a marker of liver function, whereas Watson et al.[5] suggested sequential perfusate liver transaminases levels may predict the liver function. The most widely accepted method of viability tested was described by the Birmingham group in a pilot study in humans of five liver transplants performed using livers initially declined for transplantation that were subjected to NMP-L viability testing.[6] The organ function was assessed based on the perfusate lactate clearance after 2 hours of NMP-L. All five livers that were able to reduce lactate to levels less than 2.5 mmol/L were successfully transplanted, and none of the recipients had experienced EAD, PNF, or biliary complication 24 months later.

Designing an adequately powered clinical trial to demonstrate the benefit of NMP-L over SCS in high-risk organs has been difficult. Transplanting such livers after SCS for the sake of the trial would be unethical because the historical data suggest poor outcome of these grafts. A trial designed to push the envelope of utilization of the highest-risk livers has been started in Europe and enrolled its first patients. This VITTAL trial (Viability Testing and Transplantation of Discarded Donor Livers) includes only livers declined for transplantation by all the UK transplant centers if the liver meets predefined criteria objectively characterizing it as high risk. The organs are subjected to 4 hours of NMP-L to assess viability, and grafts meeting the perfusate lactate clearance requirement are transplanted. The study aims to validate the biochemical viability criteria and to identify biomarkers related to the long-term posttransplant outcomes, which might in the future shift the paradigm regarding which livers are usable for transplantation.

LOGISTICS

To date, clinical experience with NMP-L preservation is based on approximately 200 livers transplants, of which the great majority were put on the device in the donor hospital and subsequently transported to the transplant center in a state of normothermia. Such a strategy minimizes the preservation injury and could be the optimal strategy.[7] Although this approach is currently considered the standard for NMP-L, the technology could also be applied in a less logistically challenging strategy termed "end-ischemic liver reconditioning."[8] During end-ischemic reconditioning, the liver is brought to the recipient hospital in SCS and then put on NMP-L. Using this strategy, the device would not be transported to the donor hospital, dramatically easing the logistics and cost of NMP-L. In addition, this would allow the decision about the need for NMP-L to be driven by graft biopsy or challenges getting the recipient ready for transplant. Although the approach has been used in only a small

number of livers deemed too high risk for transplantation, it holds a great potential.[1,6,9]

DEVICES

In April 2017, three manufactured NMP-L devices were in clinical use. The available machines vary in portability, degree of automation, perfusate recirculation technique, and the way hepatic arterial flow is delivered.[10] The UK-developed Metra device (OrganOx Ltd., Oxford, United Kingdom) is a fully automated portable device, perfusing the liver at 37°C via a cannulated, closed perfusion circuit that provides continuous (nonpulsatile) arterial flow. The Organ Care System (OCS) Liver produced by TransMedics (Andover, MA) is a fully automated and portable device, perfusing livers at normothermic temperature. It delivers a pulsatile flow through the hepatic artery and recirculates perfusate via a reservoir into which the hepatic venous outflow empties. The Liver Assist (Organ Assist, Groningen, the Netherlands) is semiautomated with limited portability. It does allow liver perfusion at temperatures ranging from 8°C to 37°C, and the arterial and portal pressures can be set by the operator to control the vascular flow rates. It delivers pulsatile flow to the hepatic artery recirculates via an open reservoir. With its limited portability, the device is primarily designed for end-ischemic reconditioning. The optimal interplay between SCS and normothermic perfusion is not established, so more data are required before a device could be considered superior.

SUMMARY

The key points of this review are:

- SCS is the standard method of liver preservation. The detrimental effects of the concomitant cold ischemia are not suitable for high-risk livers. Therefore, some potentially transplantable livers are being discarded.
- Normothermic machine liver perfusion is an alternative method of preservation that may reduce ischemia-reperfusion injury, biliary complications, EAD, and PNF.
- The clinical benefits of the normothermic perfusion are currently being tested in numerous clinical trials.
- Normothermic perfusion allows functional assessment of the liver, termed ''viability testing.''
- The ability of the liver to reduce lactate in the perfusate is the most widely accepted marker of viability during normothermic machine perfusion, although clinical data are being generated.
- Normothermic machine perfusion can be intended to entirely replace SCS or be used for postischemic graft reconditioning, although the risks and benefits of these strategies are not currently well-defined.
- The potential of this technology to increase liver utilization is challenging to study in a clinical trial, but will be important to consider.

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