Real-Time Direct Measurement of Human Liver Allograft Temperature from Recovery to Transplantation

Rosa Villa,1 Constantino Fondevila,2 Ivan Erill,1 Anton Guimerà,1 Ernest Bombuy,2 Cristina Gómez-Suárez,3,4 Juan Carlos Sacristán,3 and Juan Carlos García-Valdecasas2

Temperature is a key parameter in organ preservation that has been consistently linked to primary nonfunction (PNF). In this communication, and for the first time anywhere, continued and direct measurements of human liver intraparenchymal temperatures are reported in six clinical cases of orthotopic liver transplantations (OLT). These measurements cover the entire transplantation procedure and include the full transport phase. In contrast with long-held beliefs, these data demonstrate that liver allograft temperatures reach and stabilize at near 0°C, instead of 4°C, during transport using standard protocols. Furthermore, these low temperatures do not appear to contribute to graft failure when negative factors such as long preservation, the presence of hepatic steatosis, or advanced donor age are present. The clinical and experimental implications of these findings, together with other relevant elements derived from the direct and continuous monitoring of human liver allograft intraparenchymal temperatures, are discussed.

Keywords: Liver, Monitoring, Temperature, Transport, Viability.

In the field of transplantation, hypothermia has long been considered the standard method for organ preservation. Even though graft cold-preservation has been around for more than three decades, the current protocol for graft transport was established with the introduction of University of Wisconsin (UW) preservation solution (ViaSpan Bristol Myers Squibb) (1, 2) and similar cold preservation solutions (Celsior, Eurocollins or Histidine-tryptophan-ketoglutarate). This protocol involves the placement of a sterile plastic-bag layer containing the organ immersed in UW solution in an ice slush-filled basin. Because the graft is perfused with chilled UW solution and hypothermia is maintained through indirect exposure to ice slush, conventional wisdom has held that the graft is maintained at a mean temperature of 4°C, which is also the temperature of standard refrigerators and hospital cold-rooms in which preservation of tissues is routinely carried out.

Even though temperature is important in graft preservation, most research has been carried out using indirect measures and/or in animal models because temperature monitoring of human organs in sterile conditions poses serious difficulties. In the case of the liver, early studies suggested that 4°C was an optimal temperature for liver graft preservation (3) and recommended monitoring of allograft storage and preparation temperatures (4). Ice slurries of salty solutions for ice-packing were discouraged, as they might lead to temperatures between −1°C and −3°C, resulting in cold injury and increased rates of primary nonfunction (PNF). Follow-up studies also suggested that inaccurate ice packing might lead to cold injury (5), but no correlation with adverse effects in liver function could be detected. In contrast, adverse effects were manifest when storage temperature was temporarily raised above 4°C.

Later work on storage temperature (6) suggested that liver-graft core temperature during preservation approached 0°C, although the measurement was by indirect means. Hertl et al. examined the effect of temperature variation (0°C to 5°C) on preservation outcome by measuring bile production and perfusate flow. The authors concluded that the optimal preservation temperature for the liver was near 0°C, and showed that small deviations (up to 5°C) caused a systematic deterioration of liver function. In a follow up study (7), core-temperature readings in human and pig livers were reported for the first time, demonstrating that pig liver grafts stabilized at 1°C during cold-storage and suggesting that this might also be the case for human liver grafts.

Surprisingly, little work has followed these findings. This is remarkable because storage temperature has been shown to be strongly related to PNF (4, 6, 8), may be a limiting factor in long-distance procurement (2), and is of interest to the development of sub-zero preservation methods (9–11). Some subsequent works have analyzed the effects of storage temperature in liver grafts (12, 13) but they are based on the premise that the optimal temperature for liver preservation is 4°C, a finding that they repeatedly and incorrectly attribute to Hertl et al. (6).

To assess the true value of storage temperatures using standard protocols, we have developed a miniaturized system for continuous monitoring of graft temperature during transplantation. The system consists of a 0.2°C-precision thermometer encapsulated at the end of a 15-mm-long needle and connected to a custom-developed wireless data acquisition system (Air Products Healthcare) that sends temperature

This work was supported by the CO3/03 grant from the Instituto de Salud Carlos III and by the Consorcio Superior de Investigaciones Científicas.

1 Biomedical Applications Group, Centro Nacional de Microelectrónica, Bellaterra, Spain.
2 Liver Transplant Unit, Digestive Disease Institute, Hospital Clínic, Universitat de Barcelona, Spain.
3 Center of Excellence Medical, Air Products Healthcare, Madrid, Spain.
4 Address correspondence to: Cristina Gómez-Suárez, Carburos Metálicos, S.A. Matapinónera 9, 28700 San Sebastián de los Reyes, Madrid, Spain.

E-mail: gomezsc@carburos.com

Received 18 August 2005. Revision requested 31 August 2005. Accepted 7 October 2005.

Copyright © 2006 by Lippincott Williams & Wilkins
ISSN 0041-1337/06/8103-483
DOI: 10.1097/01.tp.0000195903.12999.bc
measurements every 5 seconds to an external personal data assistant. Intraparenchymal probe readings at a depth of 15 mm have been correlated with invasive measurements using standard temperature probes (Keithley) at the liver core (4-cm depth), showing peak deviations of up to 1.5°C in periods of convection cooling/warming (e.g., insertion in the abdominal cavity) that subside after a 15 to 20 min time-lag, and no significant deviations (i.e., less than 0.5°C) during cooling/warming through perfusion. The developed system, currently under a CE marking process for its use in the clinical setting, is minimally invasive and sterilizable. Thus, it can be seamlessly integrated into the standard surgical and logistic procedures of human allograft transplantation, providing continuous temperature monitoring for the entire transplantation process.

Using this system, continuous intraparenchymal monitoring of human liver allograft temperature was carried out by inserting the needle to full depth in the liver dome prior to perfusion in the abdominal cavity. When necessary, the needle was fixed on the dome surface by stitching at two superficial suture points. For the first time anywhere, subsequent continuous monitoring provided complete coverage of the entire transplantation process in a genuine clinical setting.

The results in Figure 1 neatly outline the different stages of allograft preservation. In this series, a rapid perfusion technique was used for liver recovery (15, 16). Both the aorta and the portal vein are cannulated without preliminary dissection of the hepatic vasculature. After cross-clamping, arterial and portal perfusion with chilled UW solution is started with concomitant addition of ice slush in the abdominal cavity. As can be seen in Figure 1, these maneuvers rapidly lower graft temperature down to 16°C in 11 min, after two liters of chilled UW solution have perfused the liver. During the next phase (21 min), the liver is harvested and all of its vascular structures are identified in a bloodless field. At the end of this period, liver temperature descends to 10°C, and it is at this
temperature that the graft is placed on the back table, surrounded by ice-slush, where it eventually reaches and stabilizes at 4°C. Following packaging and insertion in the transport cool-box, the graft cools down to 0.1°C to 0.2°C, a temperature at which it remains stable for the next 6 hours.

Once the liver is extracted from the cool-box, graft temperature builds up very slowly from 0.1°C, taking 10 min to reach 1°C. In conjunction with the data obtained on the back table prior to transport (75 min, 7°C average temperature), this may constitute a significant finding with clinical implications, as it confirms previous findings on pig liver grafts (7) and corroborates their applicability in humans. Given that back table procedures may last over two hours in difficult cases, and that temperatures above 4°C have consistently been reported as sub-optimal for preservation (3–6), our results endorse previous suggestions (7) on graft cleansing and preparation, hinting that back table procedures might be preferably carried out after transportation, when temperatures under 4°C on the back table may be guaranteed for nearly 1 hour (data not shown).

Further on, four different warming rates can be observed after placement of the organ inside the abdominal cavity. Warm-ischemia time (WIT) comprises the period in which suprahepatic cava and portal vein anastomoses are performed, leading to a graft temperature of 12.5°C after 15 min. Prior to completion of portal vein anastomosis, a cannula is introduced through its right corner and the liver cavity. Warm-ischemia time (WIT) comprises the period in which suprahepatic cava and portal vein anastomoses are performed, leading to a graft temperature of 12.5°C after 15 min. Prior to completion of portal vein anastomosis, a cannula is introduced through its right corner and the liver...
the existence of complications that could be attributed to the methodology reported herein. Therefore, these observations suggest that near-zero preservation temperatures are not cumulative to negative factors, such as long preservation (17) the presence of hepatic steatosis (18) or advanced donor age (19). In fact, and taking into account that these results were obtained in a well-established European reference center for the treatment of hepatic diseases, and following a standard protocol (20), one may assume that near-zero temperatures are routinely reached in many transplantation centers abroad following similar protocols.

Finally, the results reported here may have implications in the methodology of animal and modeling studies of liver transplantation. Usually, these studies have assumed that liver-graft storage temperatures lie near 4°C and have used this temperature as reference for their analyses and experimental setups. Our data, backed up by previous animal studies (7), clearly establish that liver-graft storage temperatures following standard protocols are stable in the 0°C to 1°C range, and thus cast some doubts on experimental and modeling results using 4°C as a reference temperature.

ACKNOWLEDGMENTS

We are indebted to Enric Calderón and Luis Sánchez for their excellent technical assistance, and also to Chuck Simmons for his revision of this manuscript.

REFERENCES