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Hypothermic machine perfusion of liver grafts can safely extend cold ischemia for up to 20 hours in cases of necessity

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Authors' specific contribution:

R De Carlis wrote the article.

A Lauterio, F Ferla, S Di Sandro, and R Sguinzi gave substantial contributions to concept and design of the article.

L De Carlis (director) corrected and approved the article.

All authors were involved in surgical management and decision process of the 2 cases reported.

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Abbreviations:

ALT, alanine transaminase

CIT, cold ischemia time

HCC, hepatocellular carcinoma

HCV, hepatitis C virus

HMP, hypothermic machine perfusion

LT, liver transplant

POD, postoperative day

SCS, static cold storage

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While static cold storage (SCS) allows the safe preservation of liver grafts for the length of time needed with ordinary transplant logistics, hypothermic machine perfusion (HMP) provides superior outcomes (1,2). We report about 2 liver transplants (LTs) in which unexpected operative complications necessitated changes in recipients. In these 2 cases, cold ischemia time (CIT) was extended to 18 and 20 hours using HMP with excellent results.

In the first case, a 42-year-old woman was referred to our center for urgent LT due to acute hepatic failure and hepatic artery thrombosis following pancreaticoduodenectomy for ampullary adenoma. The donor was a 65-year-old brain-dead female who died from spontaneous brain hemorrhage. Laparotomy performed on the recipient revealed extensive intestinal necrosis, and complete hepatic artery and portal vein thrombosis, which made LT impractical and futile. Another recipient, a 66-year-old female with hepatocellular carcinoma (HCC) and hepatitis C virus (HCV) cirrhosis, was selected. The retrieved liver was connected to an HMP Liver Assist® (Organ Assist B.V., Groningen, The Netherlands) after 12:15 hours of SCS, which provided additional time to organize the recipient's transport and preparation for LT.

In the second case, a liver from an 18-year-old male donor, who was brain-dead due to traumatic brain injury, was initially offered to another center and retrieved for combined lung and liver transplantation. Because the recipient developed severe hemodynamic instability after lung implantation, the surgeons decided not to proceed with LT. Subsequently, the liver was offered to our center and connected to HMP after 12:10 hours of SCS, to provide time to prepare the recipient (a 61-year-old female with HCC and HCV-cirrhosis).

In both cases, the grafts were perfused with cooled (10°C) and oxygenated Belzer MPS® solution (Bridge to Life Ltd., Columbia, SC, USA) from the portal vein (4 mmHg) and the hepatic artery (25 mmHg), with continuous and pulsatile flow, respectively. Vascular resistances during

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perfusion are shown in **Figure 1A**. Specific informed consent was obtained before the procedure. Biliary production was observed immediately after portal reperfusion. Total CIT was 18:15 in the first case and 20:00 hours in the second case. In both cases, the postoperative course was normal (**Figure 1B**) and without complications during follow-up of 9 and 4 months, for the first and second cases, respectively.

Prolonged CIT has been associated with a high incidence of early graft dysfunction and primary nonfunction (3). More than 25 years ago, Pienaar demonstrated the benefits of HMP in long-term liver preservation, reporting successful LTs after 72 hours of perfusion in a dog series (1). However, clinical reports on the logistical advantage of HMP are surprisingly rare (4). In our experience, despite the extraordinarily prolonged CIT, we observed excellent functional recovery. Our results are likely multifactorial and obviously influenced by the good graft quality and the donor-recipient matching. Nevertheless, the surprisingly low transaminase peaks posttransplant were indicative of minimal graft preservation injury. We did not observe the time-dependent increase in vascular resistances reported by other authors during prolonged perfusion (5), which was likely because HMP was initiated after SCS and the time of perfusion was limited in both cases despite the prolonged total CIT.

In conclusion, our experience suggests that, in cases where unexpected problems delay the ordinary transplant process, HMP can be used to prolong CIT with high-quality preservation and allow utilization of grafts that otherwise would be discharged because of logistical problems.

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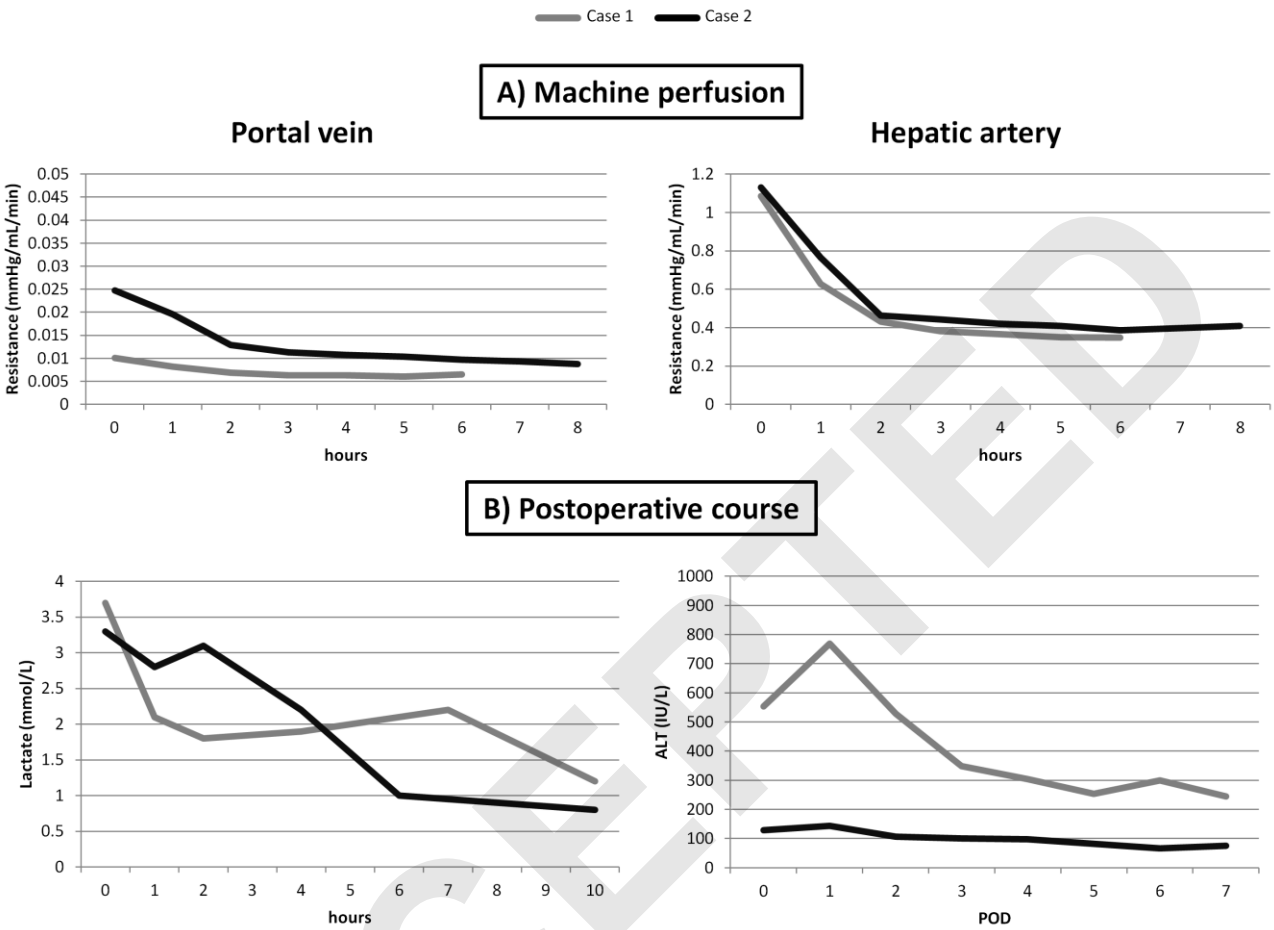
Figure Legends

Figure 1: A) Portal and hepatic arterial resistances during HMP. The grafts were perfused with cooled (10°C) and oxygenated (pO_2 = 60 kPa) Belzer solution, from the portal vein with continuous flow (P = 4 mmHg) and from the hepatic artery with pulsatile flow (P = 25 mmHg, 60 bpm). Perfusion lasted 6:00 in Case 1 and 7:50 hours in Case 2. We did not observe any increase in vascular resistances, probably because HMP was initiated sequentially after SCS, and perfusion time was limited in both cases, although the total CIT was exceptionally protracted. **B) Postoperative levels of serum lactate and alanine transaminase (ALT).** The postoperative course was normal and without complications. The surprisingly low peaks in the first postoperative days (POD) and the absence of early graft dysfunction indicated optimal preservation, despite the exceptionally protracted CIT. We noted similar results using HMP for organ donations after cardiac death liver transplants (6).

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Figure 1.



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