

One-week perfusion of human livers: how far can we go?

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Prolonged normothermic machine perfusion (NMP) already offers potential benefits in liver transplantation in three main areas: (i) Logistic – longer preservation times allow patients and donor organs to travel from further afield, for simultaneous donor offers to be accommodated by sequential transplants, and for operations to be conducted during daytime hours; (ii) Viability assessment – maintenance of liver function allows organs of marginal provenance to be tested and ‘de-risked’, thereby improving utilisation of otherwise high-risk organs; (iii) Repair – ex situ interventions may allow conventionally untransplantable organs to be rendered transplantable, particularly DCD and steatotic livers. A strategy allowing safe ex-situ liver NMP for several days before successful transplantation would constitute a further milestone in clinical practice.

The modern era of NMP in liver transplantation was heralded by the publication from Berlin of Schön et al in 2001¹, demonstrating in a porcine liver transplant model that four hours of NMP not only provided more effective preservation than static cold storage (measured by acute liver injury markers), but also enabled successful transplantation of DCD organs with a duration of hypoxic injury that was otherwise incompatible with post-transplant survival.

The Cambridge group, using a simplified circuit without the dialysis component used in the Berlin study, demonstrated that liver NMP for at least three days (without transplantation) could be achieved with preserved metabolic and synthetic functions². Reperfusion studies from Oxford³, followed by transplant studies⁴, confirmed the utility of NMP, in particular demonstrating successful porcine liver transplantation after 40 minutes of warm ischaemia and 20 hours of preservation. The same group later published successful porcine liver transplantation after 48 hours NMP preservation⁵.

Accumulating evidence from clinical studies now corroborates these animal data. A large multi-centre European trial confirmed that acute liver injury rates were reduced by NMP, despite longer preservation times and increased levels of utilisation, especially of DCD and steatotic organs⁶. Other investigators have shown the value of NMP as a means to test and select high-risk organs^{7,8}.

The recent publication by Eshmuminov et al from Zurich⁹ has extended the scope of NMP technology. Using a combination of porcine and discarded human livers, a number of circuit design questions have been addressed, with the objective of stable function for seven days. The inclusion of dialysis (as originally described by Schön) provides benefits in terms of electrolyte and haematocrit homeostasis. The mixing of venous with arterial blood in the portal inflow (as opposed to fully oxygenated blood in both arterial and portal inflows) is associated with improved arterial flow. The provision of pulsatile arterial flow is associated with reduced haemolysis. A more rigorous approach to glucose/glycogen metabolism, manipulating glucose, insulin and glucagon, suggests benefit with respect to carbohydrate metabolism. These studies corroborate the observations of others that perfusate markers of injury (e.g. transaminase levels) correlate with histological markers of organ viability. The use of radiolabelled glucose and PET scanning show homogeneous metabolism and fluorescein shows homogeneous perfusion. Conceptually as in the system used by Abouna¹⁰ in extra-corporeal liver support, a mechanical method to improve perfusion and avoid pressure necrosis seems effective and is innovative in a transplant setting.

The publication reinforces the need for further advance. More sensitive and specific perfusate viability markers are required (the currently used measures of perfusate and bile composition are imperfect). Including dialysis in the circuit, although beneficial for perfusate homeostasis, may

reduce the value of perfusate analysis as a viability marker. Recent studies show that not only are the levels of key metrics important (pO₂, temperature, flows, pressures) but also the transitions in these parameters. Experimental evidence has shown the benefits of 'controlled oxygenated rewarming'¹¹; this has recently been tested in a clinical setting¹².

The complexity of the device brings potential issues of usability and cost. It also renders the device non-transportable: much current debate centres on the need/desirability of initiating NMP immediately after organ retrieval, with increasing consensus that higher risk (DCD/steatotic) livers need to be managed with minimal exposure to cooling. Also, once undergoing NMP, logic suggests that the organ should remain perfused until transplanted. Increasing complexity comes at a price, both literally and metaphorically.

The data presented stop short of transplant survival-based studies. These are crucial before progressing to clinical implementation. Pre-clinical studies can test in ways that clinical studies cannot – pushing novel technology to establish its limits. Pre-clinical transplant studies are an essential proof of concept, and will inform the design of subsequent clinical trials, to ensure safety and to corroborate experimental data.

This Zurich paper points to future technological possibilities for NMP: it indicates where further gains might be made and some of the questions that should be addressed. Current methods of NMP viability testing are largely achievable within 24 hours or less. Newer more predictive tests (e.g. based on genomic, proteomic, metabolomic techniques) may need longer. The most obvious benefit of 7-day perfusion relates to organ repair. Current strategies for the removal of fat from severely steatotic livers may be more successful if it were possible to treat livers for longer¹³. The Toronto group has shown the feasibility of delivering gene therapy during NMP¹⁴. Other groups are testing the effects of NMP-based delivery of cell therapy (e.g. mesenchymal stem cells). A 7-day perfusion limit might transform the logistics of transplantation beyond what can be achieved with 24 hours – taking liver transplantation from a semi-urgent activity to a semi-elective activity. Health-economic analysis will be needed to quantify the benefit of such a change.

Like many high-impact papers, this article leaves more questions than answers. What is it that will determine whether this remains a technical tour-de-force, or leads to real clinical advance? For new technology to succeed, it has to solve a problem: what are the real-world challenges in liver transplantation and how will this development address these? Normothermic perfusion (of all organs) is transitioning from the realm of university-based research into the remit of commercial providers: what regulatory hurdles will such technology need to pass? What is the necessary price-point for commercial viability in a relatively small market, and will this pass the cost-benefit criteria used by healthcare funders?

(1004 words)

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