Editorial

A promising *ex vivo* liver protection strategy: machine perfusion and repair

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Liver transplantation is a lifesaving procedure for patients with end-stage liver diseases. With the development of surgical technique, imaging, and immunosuppressant agents, postoperative survival rate has increased steadily. However, organ shortage is still a major concern. To solve the organ shortage crisis, extended criteria donors are used which include aged donors, fatty donors, and cardiac death donors; these donors need more protection.

Machine perfusion (MP) is a promising alternative liver graft protection method for static cold storage (SCS), particularly for those organs of suboptimal quality. MP was first proposed by Belzer in the 1960s, and now can be divided into types which include hypothermic machine perfusion (HMP), hypothermic oxygenation machine perfusion (HOPE), end ischemia HOPE (EHOPE), dual HOPE (DHOPE), subnormothermic machine perfusion (SMP), controlled oxygenated rewarming (COR), and normothermic machine perfusion (NMP) (1).

There are numerous publications (2-5) indicating that MP is superior to SCS for improving graft quality and patient prognosis. The largest randomized clinical trial (n=220) published in *Nature* showed the enzyme of postoperative release in the NMP group was 50% lower than SCS and the rate of organ discard was also 50% lower (2). A recent clinical trial (3) found DHOPE decreased stroma necrosis and deep peribiliary glands injury, protecting donation after cardiac death (DCD) donors from reduced ischemia reperfusion injury. Furthermore, a pilot, open, randomized, prospective trial (4) for NMP evaluation in older donors (age over 70 years) showed NMP also protected aged grafts from ischemia reperfusion injury. A 5-year follow-up clinical trial showed overall graft survival rate of HOPE-treated DCD liver transplants (94%) was superior to the untreated DCD (78%) one, and was comparable with standard donation after brain death liver transplants (5). In other words, when compared to SCS, MP improved liver function and prognosis, while reducing billiard complications, especially for DCD donors.

MP provided a near-physiological condition, with oxygen and nutrients, allowing for therapeutic conditioning and function testing. Many markers like bile, perfusate enzyme release, and hemodynamic parameters are reported to be predictive of organ viability (6). However, the criteria for isolated liver graft viability assessment have not arrived at a consensus. A criteria based on NMP was advocated by Mergental *et al.* (7) in 2016 which consisted of perfusate lactate <2.5 mmol/L, bile production, and at least two out of the three following items: pH >7.3, hepatic artery flow >150 mL/min, and portal vein flow >500 mL/min, or homogenous graft perfusion with soft parenchymal consistency (the first 3 hours). Under these criteria 4 out of 5 declined livers were transplanted. Later, the same group simplified the criteria for high-risk livers into the following: achieving lactate clearance <2.5 mmol/L (the first 2 hours) during NMP without requiring any intervention to maintain extended perfusion (8). de Vries *et al.* (9) used pre-transplant sequential DHOPE and NMP perfusion for DCD grafts resulting in the following criteria: perfusate pH and lactate normalized, bile production ≥10 mL, and biliary pH >7.45 (the first 1.5 hours on NMP. With these criteria the 3-month graft survival was 100%.

Nowadays, there are several commercial devices for liver

preservation. The first HMP clinical trial was carried out by Organ Assist (Groningen, the Netherlands), which is a semi-automated device with limited portability and allows for temperatures ranging from 8 to 37 ℃ (10). The first NMP clinical trial was carried out by Metra device (OrganOx Ltd., USA); it is a fully automated, portable device with a temperature of 37 ℃ (11). The Organ Care System (OCS) Liver was developed by TransMedics (Andover, MA, USA); it is also a fully automated portable device. A clinical trial Revive Trial (NCT02449694) is currently ongoing. Life Perfusor 2000 (Hangzhou, China) is another fully automatic repair system for organ perfusion; preclinical trials showed it is safe and efficient in liver preservation (12).

There is a large deficit in the number of available donor organs when compared to the number of waiting list patients. The MP technique is undergoing rapid development and has entered clinical practice by improving organ preservation and acting as a platform for organ improvement. However, MP is still in its infancy. The efforts for optimizing perfusion settings (ideal perfusion solution, oxygenation, temperature control, pressures/flow velocity, perfusion route and protocols) should be made which aim to reduce discard rate and improve long-term outcomes of the highest-risk grafts. A combination of different modalities or even ischemia-free liver transplantation may be the optimal clinical application strategy.

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Footnote

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