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Machine perfusion and DCD

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Organ shortage and long waiting lists are not new challenge for the transplant society. Despite a consistent increase in the absolute number of annual liver allografts by expanding donor acceptance criteria, organ shortage and long waiting lists remain critical problems. There is a clear limit to expanding donor acceptance criteria to maintain justifiable patient and graft survival. Traditionally, static cold storage (SCS) has been the primary method for preserving organ function within a reasonable preservation timeframe. Cooling slows down metabolic processes and extends the period during which the organ can be deprived of oxygen without losing viability. This phenomenon, known as the Arrhenius Q10 effect, leads to a 97% reduction in metabolic rate at 4 °C. SCS is easy, simple and cost-effective. However, there are critical weaknesses in SCS as demonstrated well. The potential for direct cold damage to allograft cannot be underestimated, with well-documented direct deleterious effects on plasma membrane lipids, cytoskeleton, microtubules, mitochondria, and the disruption of ion-exchange pumps in the cell membrane leading to swelling and cell lysis, highlighting the risks of cold damage. More importantly, reperfusion injury poses a significant clinical risk to both the recipient and the allograft, occurring more frequently with expanded criteria donor (ECD) liver allografts. To overcome organ shortage, liver allografts from donation after circulatory death (DCD) are considered a good source, and their numbers are increasing. However, DCD liver allografts have been proven to have more primary non-function (PNF) and ischemic-type biliary lesion (ITBL), resulting in poor graft and patient survival compared to liver allografts from brain-dead donor. Therefore, each transplant center has established its own criteria to accept DCD liver allografts to maintain comparable clinical outcome. Donor age and donor warm ischemia time are universally accepted as the main risk factors for designating clinical outcomes. Based on each center's experience, they set limits on donor age and ischemia time. This practice is based on SCS, and there is not much opportunity to accept more DCD liver allografts. In fact, national data clearly show a discard rate of around 30% for DCD liver allografts after organ recovery, despite an increase in liver allograft offers from DCD donors. This opens up an opportunity to seek new organ preservation methods that overcome the weakness of SCS and result more transplants from ECD. A new method for organ preservation has become necessary to maximize the use of ECD organs in this era. When considering a new, different, and

improved preservation method, the primary goal should be to avoid cold damage, prolong preservation time, minimize ischemic-reperfusion injury, and ultimately achieve comparable clinical outcomes between ECD and brain dead-donor organs. In addition to this primary objective, if we can predict viability, address organ damage, and even provide treatment, it would be an ideal scenario. Any preservation method that differs from SCS is a candidate, such as flowing preservation solution instead of static, any temperature other than 4 °C, and different preservation solution compare to current commercialized ones. In fact, there were many experiments and clinical trials using different combinations of these conditions. In this lecture, we will focus on ex-situ normothermic (35-38 °C) machine perfusion (NMP) using blood as an oxygen delivery tool. NMP is currently the most popular organ preservation method among various new trials. There are few commercially available NMP systems. These machines exhibit distinct mechanical features and versatility. At present, no definitive conclusion has been reached regarding the superiority of one machine over the others. Furthermore, there are three distinct clinical scenario for the use of NMP: preservation NMP, post-SCS NMP, and pre-SCS NMP, depending on the intended application. General principle and effect, however, seems to be similar. Packed red blood cells (pRBC) is used as an oxygen carrier. In addition to oxygen supply, the energy source is important too since allograft will be metabolically active under normothermic conditions. Glucose and other additives are mixed with pRBC. Hepatic artery and portal vein are cannulated and perfused with normothermic solution that contains pRBC and glucose. Blood flow mimics normal physiology, controlled by pressure and volume. Critical benefit of NMP for DCD liver allograft is viability testing. Since liver allograft is metabolically active, there are many biochemical markers that we can test for viability. The most common and reliable biomarker currently used is the clearance of lactate. Producing bile is also an important marker to decide viability of the liver allograft. This characteristic of NMP gives an opportunity to sort out PNF and expand DCD liver allograft acceptance without fear of PNF. The clinical benefit to reduce ITBL by NMP, however, is not clear at this moment considering the etiology of ITBL. ITBL is believed to develop from irreversible biliary epithelium damage during warm ischemia and microthrombi on the biliary capillary system. This pathology happens during the DCD organ recovery process. There is no clear explanation if NMP is capable of resuscitating these pathologies. Single-center experience at Mount Sinai liver transplant center performed DCD liver transplantation with slowly expanding limits of donor age and warm ischemia along with good clinical outcome using NMP in DCD liver transplantation. Two additional clinical effort to reduce ITBL are infusing tissue plasminogen activator while the liver allograft is on NMP and a short time interval between portal vein and hepatic artery perfusion. At this moment, there is no ITBL using NMP in DCD liver transplantation under this protocol. More case and longer-term follow-up will be needed for a more definite conclusion. NMP is a new technique that needs more cases and longer-term follow-up to confirm its benefit. In the meantime, we should look at this new technique as a new paradigm for liver allograft preservation, and it has great potential to minimize liver allograft discard.