Pump-Priming Grant

Report – Syed Hussain Abbas

Title: Global assessment of liver function during normothermic machine perfusion in high-risk donor livers

Liver disease is the third leading cause of premature death in the UK, with liver transplantation as the only effective treatment for end-stage liver disease. However, the limited availability of suitable donor organs results in up to 20% of patients on the transplant waiting list dying before receiving a transplant.

A significant challenge is that a third of donated livers are unsuitable due to non-alcoholic fatty liver disease (NAFLD), which is prevalent in the UK due to rising obesity rates. Fatty livers are risky to transplant because they do not tolerate the cooling process used in traditional organ preservation (static cold storage, SCS).

Normothermic machine perfusion (NMP) is an alternative technology that preserves livers at body temperature, maintaining better organ function and allowing for testing before transplantation. Despite its benefits, NMP doesn't fully address fatty livers. We have tested a new method using existing drugs to remove fat during NMP, which improved liver function, potentially increasing the number of transplantable livers. The pharmacological interventions comprised of L-carnitine and Forskolin/NKH477 (to mobilise fat from liver cells), reduction in the rate of glucose and insulin infusion (to reduce de novo lipogenesis) and a lipoprotein apheresis filter to removed circulating fat.

Following our original research, we further tested this in an ex-situ model of liver transplant involving NMP for 12 hours followed by whole blood allogenic reperfusion for 6 hours to simulate liver transplantation in discarded human livers (declined for transplant), $n = 3$. In addition, we explored the potential of objective metabolic liver function assessment during normothermic machine perfusion (NMP) using the Maximum Liver Capacity (LiMAx) test, developed by Humedics GmbH. This test enabled real-time monitoring of CYP1A2 activity, an enzyme prevalent in functional liver cells but less so in damaged ones, through the metabolism of 13C-methacetin. The LiMAx technology has been employed to evaluate liver capacity in patients with liver tumours and those awaiting liver surgery or transplant, providing critical data to predict and monitor post-operative outcomes.

Hypothesis: The LiMAx test could deliver valuable point-of-care information during NMP. Unlike conventional liver function tests that mainly indicate liver injury or damage, the LiMAx test offers a more comprehensive and objective assessment of liver function across all liver segments during ex-situ perfusion.

Objective: The overarching aim of this study was to assess the utility of a CE marked LiMAx device in the setting of liver preservation

1. To establish the set-up of LiMAx and the NMP device

2. To investigate the ability of the LiMAx test to differentiate between livers that meet functional criteria for transplantation and those that do not.

Method & Results: LiMAx (Humedics GmbH) is a test developed for the quantitative measurement of the ratio of levels of $^{13}CO2$ to $^{12}CO2$. The portable LiMAx machine was connected to the OrganOx *metra* NMP circuit at the site of the oxygenator. The test is a based on metabolism of 13C-methacetin with a LiMAx test value of >100 ug/kg/h indicates favourable clinical outcome following liver resection or transplantation. As part of the functional testing at 6 hours of perfusion, we measured the point-of-care LiMAx reading, **see Figure 1**. The test was performed at 1h and 5h of perfusion and subsequently at 5h during whole blood reperfusion and the duration of each test was 60 min.

Figure 1: The LiMAx FLIP® 4.0 detection device connected to the CO2 outlet of the OrganOx *metra* oxygenator to allow quantification of the $^{13}CO2$:$^{12}CO2$ ratio.

Two out of the three discarded livers met functional criteria for transplantation at 6h of perfusion and with higher LiMAx values. One liver did not function during NMP characterised by a lack of lactate clearance, high ALT >10,000 and inability to metabolise glucose and these findings were supported by a lower LiMAx test result at all phases of perfusion and reperfusion, **see Figure 2.** It is important to note the non-functioning liver had severe steatosis, was from a donation after cardiac death donor and had a cold ischaemia time of >20 hours (which together contributed to ex-situ non-function).

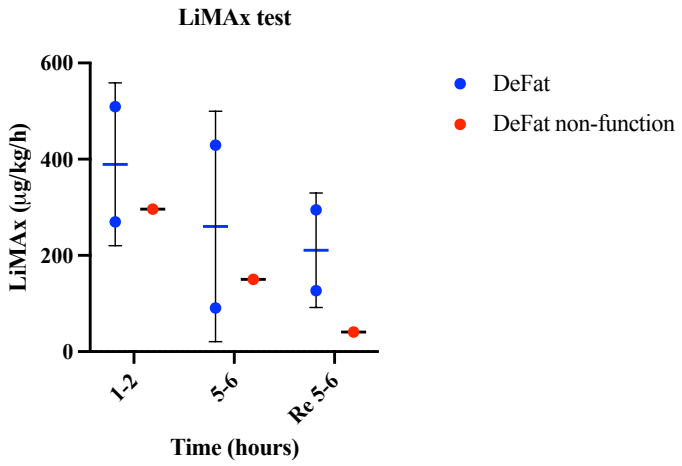

Figure 1: Non-functioning liver (red) demonstrating declining LiMAx test result during function during perfusion and reperfusion.

Outputs (publications/presentations)

Results to be presented as an abstract to The Transplant Society (TTS) Congress, Istanbul, 2024

Next Steps (what is it leading to)

In the future, the LiMAx test could become a standard component of NMP, potentially increasing the number of safe and successful liver transplants and we are aiming to validate our preliminary results in a setting of a clinical trial.