Human Liver Small-for-size graft (SFSG) Model to Study Mechanosensing in Liver Regeneration and Failure Pathophysiology

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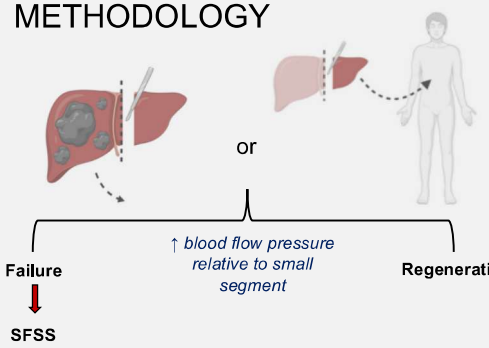
INTRODUCTION

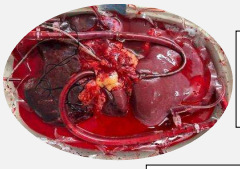
The liver regenerates after resection or transplantation, a process thought to be triggered by increased blood flow through the remnant liver or graft. Mechanosensitive pathways, including PIEZO1 ion channels, may detect these haemodynamic changes and initiate regenerative signaling. However, excessive portal inflow can cause injury and small-for-size syndrome (SFSS). As current evidence is largely derived from animal studies, human models are needed to investigate these mechanisms.

METHODOLOGY



12 Whole human livers

- Age < 18 years ✗
- Parenchymal disease ✗
- Extensive steatosis / fibrosis / cirrhosis ✗
- Age 18-75 ✓
- DBD or DCD ✓
- Absent Hepatitis B, Hepatitis C and HIV ✓



Whole liver NMP at physiological flow (4hr - Phase 1)

Split LLS:
Ligating inflow to right side
+
Microwave ablation

LLS NMP at flow >250 mL/min/100 g tissue [Yoda1/Yoda2, Dooku1 or L-NMMA at 45 min before the end of LLS perfusion] (6hr - Phase 2)

Measurements

- Blood flow and pressure (continuous)
- Biochemical/physiological liver functions (hourly)
- Bile production (hourly)
- Tissue for RNA seq/quant, histology and cell isolation PIEZO1 activity (0hr, 4hr, 7hr, 10hr)

Liver viability

Lactate < 2.5mmol/L + at least two of:

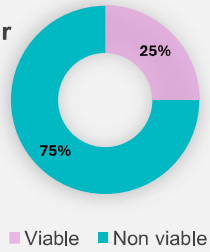
- Bile production
- pH ≥ 7.30
- Glucose metabolism
- HA flow >150 mL/min, PV flow > 500mL/min + homogenous graft perfusion

DBD: Donation after brain death
DCD: Donation after circulatory death
LLS: Left lateral segment
HA: Hepatic artery, PV: Portal vein
NMP: Normothermic machine perfusion
SFSS: Small-for-Size Syndrome

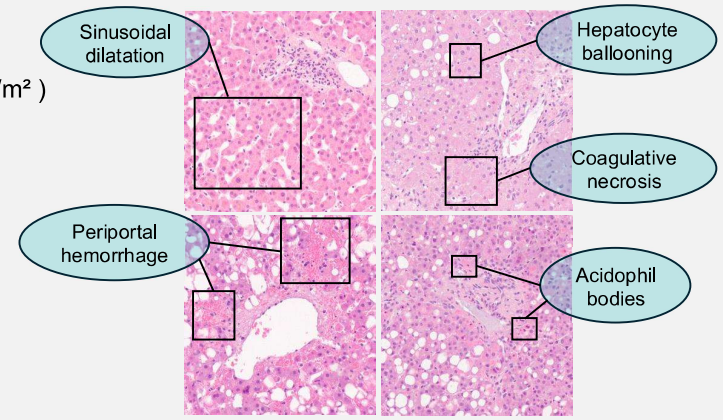
RESULTS

- Median donor age = 52.5 yrs (29-67 yrs)
- Median donor BMI = 31.7 kg/m² (25.8-42.7 kg/m²)
- Mean LLS weight = 336.3 ± 107.4 g

LLS at 10hr



Early changes of SFSS on histology at 10hr



CONCLUSION

Hyperperfusion of the LLS during NMP induced functional impairment and morphological changes characteristic of early SFSS, validating this model for studying vascular regulation and mechanosensitive pathways in human liver regeneration. Ongoing transcriptomic and proteomic analyses will compare whole livers and LLSs across treatment groups.

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