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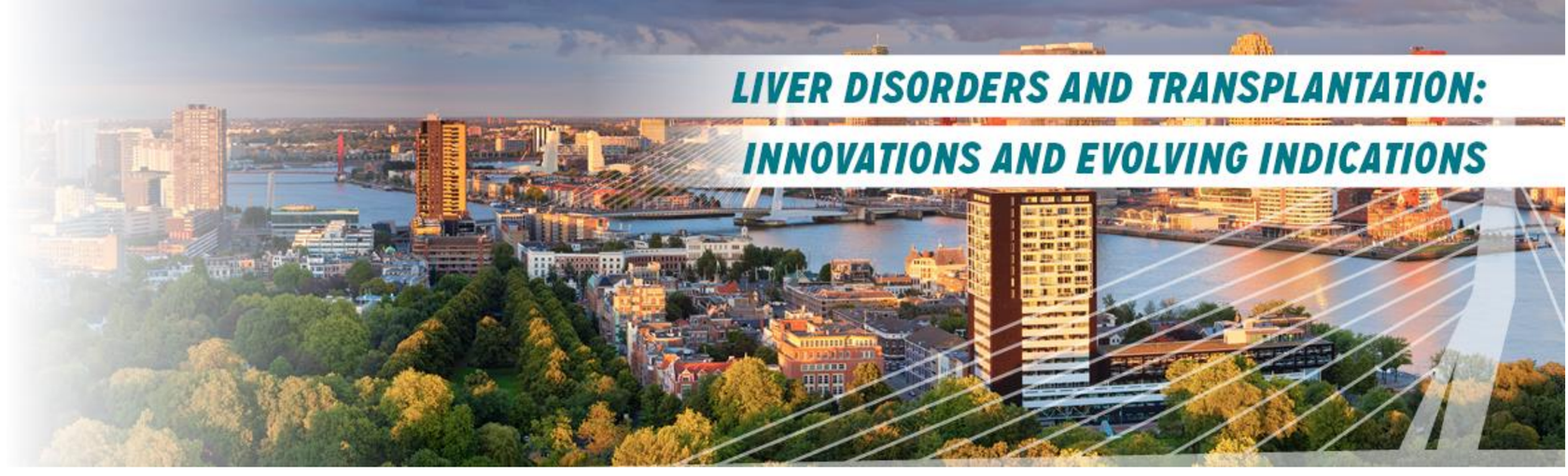

Optimization of ex vivo normothermic liver perfusion through the addition of (un)conjugated bile acids

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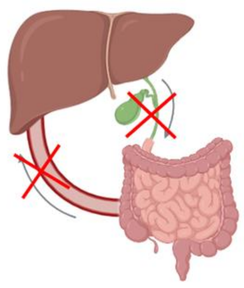
INTRODUCTION

- During normothermic machine perfusion (NMP) of the liver the enterohepatic circulation is missing
- In most protocols only taurocholate is infused [1,2]

‼ Physiologically seen, this can have major consequences for downstream feedback processes (e.g. gene expression, bile synthesis)



AIM

- **Study the effect of solely taurocholate infusion and**
- **We aimed to improve physiological resemblance of liver NMP through the addition of a representative bile acid enterohepatic circulation.**

METHOD

To study effect of <u>solely taurocholate</u>

1. Human (n=4) and porcine (n=5) livers underwent NMP for 360 min

To study effect of bile acid infusion on NMP:

2. Infusion of bile after 360 min in porcine livers (n=2)
3. Infusion of (un)conjugated bile acids in porcine livers (n=2) during 12 hours of NMP (40% gCDCA, 40% gCA, 10% CA, 10% CDCA)

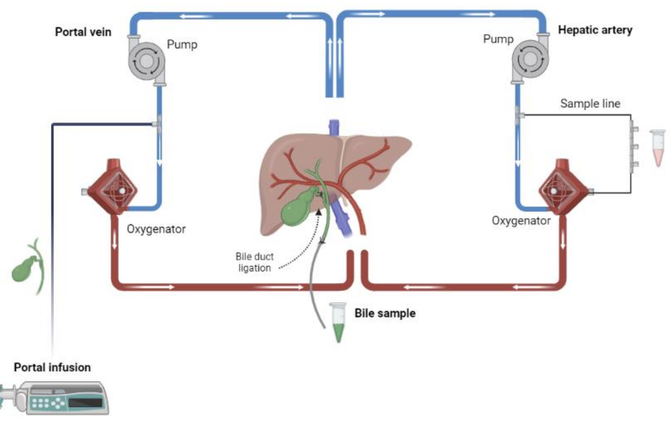


Figure 1. Schematic representation of ex vivo liver perfusion set up.

RESULTS

1. Lack of (un)conjugated bile acids during NMP affects gene expression

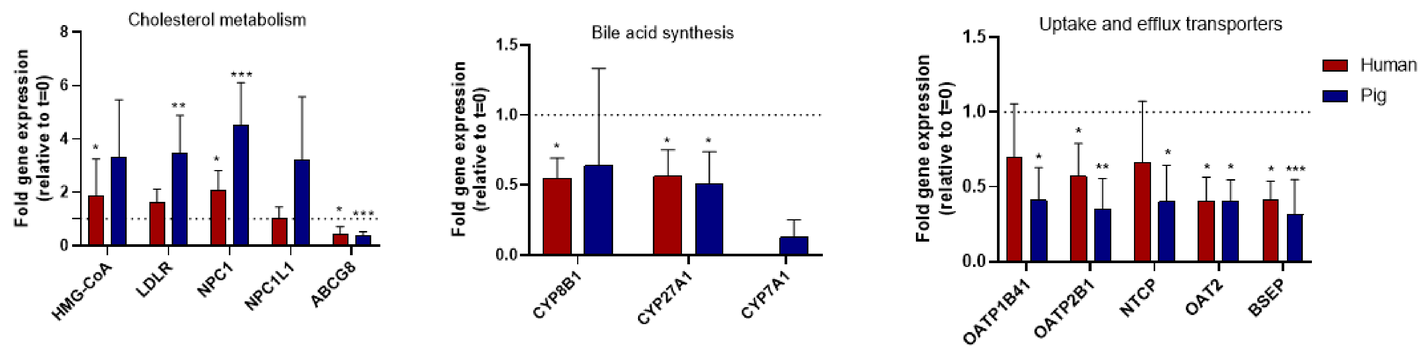


Figure 2. Changes in gene expression after hours of NMP in human (n=4) and porcine (n=5) livers. Genes related to (A) Cholesterol metabolism (B) Bile acid synthesis and (C) Uptake and efflux transporters. Fold changes was calculated as expression relative to t=0h. Significance was measured by paired t-test, *p<0.05, **p<0.01, ***p<0.001.

Bile composition shows de novo synthesis from cholesterol

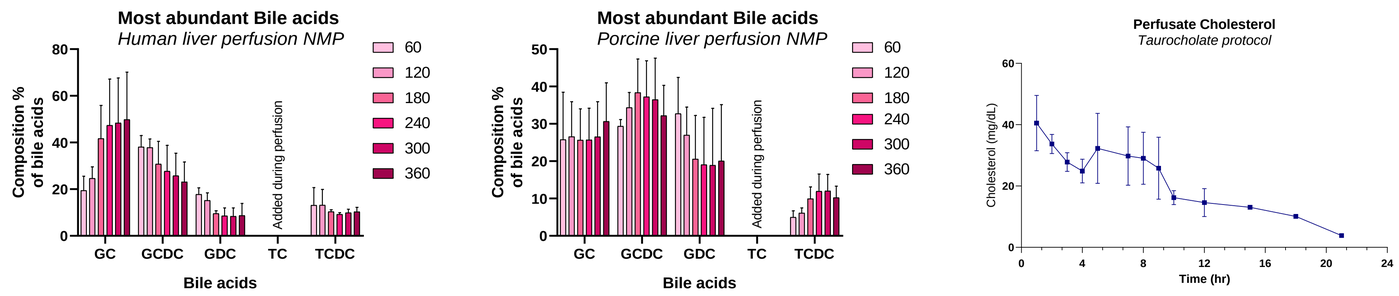


Figure 3. Bile acid composition during NMP of human (n=4) and porcine (n=5) livers. (A) Human bile acid composition of bile and (B) Porcine bile acid composition produced during 360 min of perfusion. (C) Porcine cholesterol concentrations during 21 hour perfusion

2. Gene expression returns to baseline after bile infusion during NMP

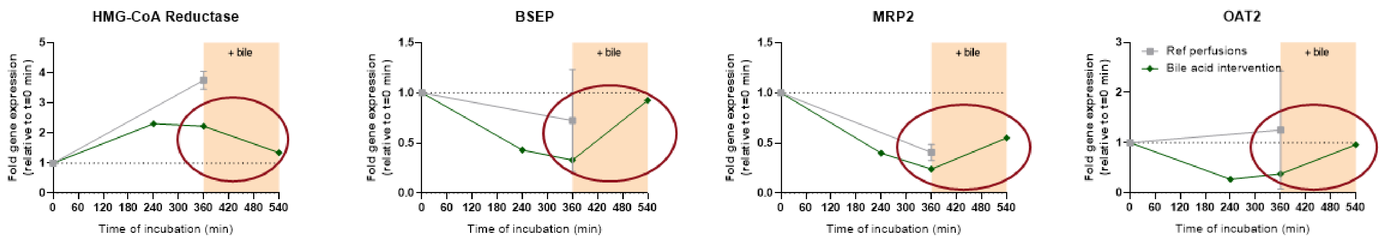


Figure 4. Effect of bile infusion on gene expression during 540 min of NMP porcine (n=2) livers. Expression of (A) HMG-CoA reductase (B) BSEP, (C) MRP2 and (D) OAT2 during 360 min of primary bile acid infusion and an additional 180 min of bile infusion

3. Infusion of (un)conjugated bile acids have a positive effect on liver viability

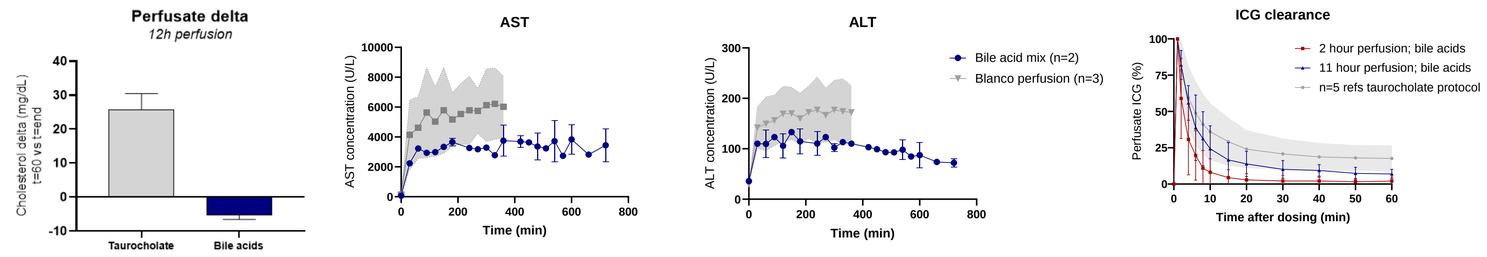


Figure 5. Effect of infusion of a (un)conjugated bile acid pool during 12 hours of NMP of porcine liver (n=3). (A) Perfusate cholesterol concentration in taurocholate (normal conditions) vs. Infusion of bile acids), (B) AST and (C) ALT perfusate concentrations during perfusion (D) ICG clearance from the perfusate

CONCLUSIONS

- 'Standard' perfusion protocols using taurocholate, affect gene expression
- Infusion of bile resulted in gene expression returning to baseline
- Portal infusion of (un)conjugated bile acids led to better liver function and improved cholesterol metabolism

REFERENCES

1. Eshmuminov, D., Leoni, F., Schneider, M. A., Becker, D., Muller, X., Onder, C., ... & Bautista Borrego, L. (2018). Perfusion settings and additives in liver normothermic machine perfusion with red blood cells as oxygen carrier. A systematic review of human and porcine perfusion protocols. *Transplant International*, *31*(9), 956-969.
2. Lascaris, B., Thorne, A. M., Lisman, T., Nijsten, M. W., Porte, R. J., & de Meijer, V. E. (2022). Long-term normothermic machine preservation of human livers: what is needed to succeed?. *American Journal of Physiology-Gastrointestinal and Liver Physiology*, *322*(2), G183-G200.

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