Assessing the behavior of steatotic livers under normothermic preservation with a porcine model

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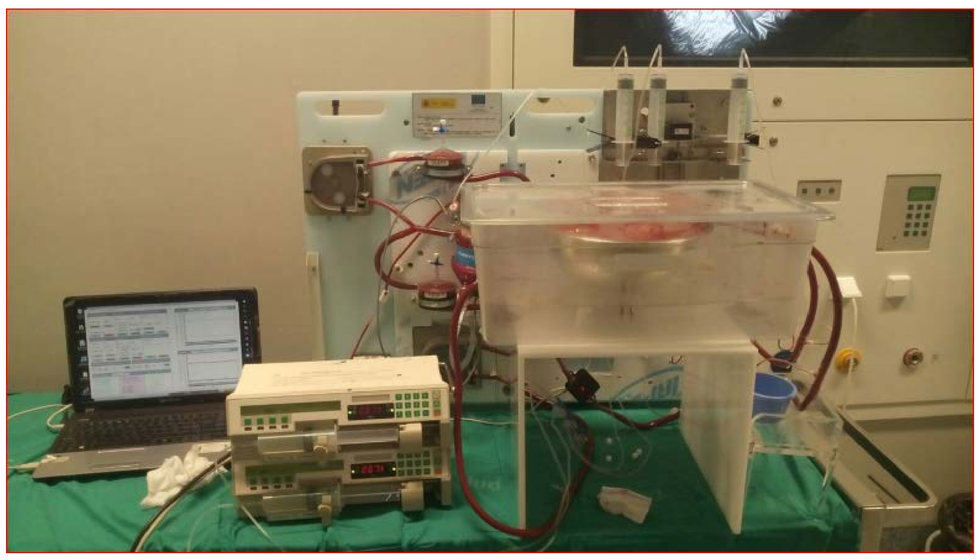
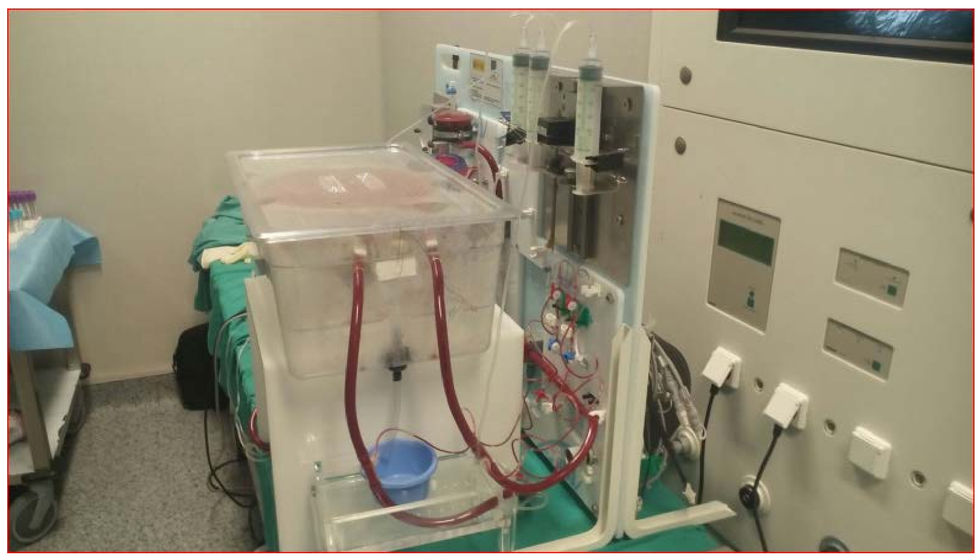
INTRODUCTION: Steatotic livers are more susceptible to ischemia-reperfusion injury than healthy livers, resulting in a higher rate of primary nonfunction, early allograft dysfunction and post-transplant vascular and biliary complications [1]. The goal of our study was to show that normothermic preservation (NP) can minimize preservation-related injury and maintain the organ function and viability.

METHODS: Experimental study with 10 Large-White pigs divided in a control group (healthy livers, n=5) and a steatotic group (animals were subjected to a steatotic diet for 5 weeks, n=5). The existence of pathologic steatosis was confirmed by biopsies performed in the first and second month after the introduction of steatotic diet. Following hepatectomy, livers were connected to the ARK ex vivo NP system developed by EBERS (Figures 1 and 2).

The ARK system is formed by a portable preservation unit, which features peristaltic and infusion pumps, heating and oxygenation systems, sensors and a control unit; and a disposable closed circuit, where the organ and the perfusate are contained in sterile conditions.





Figures 1 and 2. Normothermic perfusion circuit design for liver preservation with porcine model.

The organ was perfused through the portal vein (PV) and hepatic artery (HA) at physiological hemodynamic conditions with a perfusion solution composed by autologous blood of the donor animal, Ringer's Lactate solution, cefotaxime, methylprednisolone, heparin, insulin, a parenteral nutrition solution, epoprosterenol and sodium bicarbonate. Secreted bile was collected for analysis. 0h, 4h and 8h after connection of the organ to the NP system more than 30 variables of different types were monitored and compared:

- **Perfusion parameters:** PV and HA flow rate and pressure, pH, bile production.
- **Biochemistry:** AST, ALT, FA, GGT, urea, albumin, total bilirubin, Na+, K+, Cl-, glucose, lipemic/icteric/hemolytic index.
- **Histopathology:** macro/microsteatosis, fibrosis, portal inflammatory infiltrate, neutrophils infiltrate, isolated hepatic necrosis, central confluent necrosis, subcapsular necrosis, cholestasis.
- **Other parameters:** initial/final liver weight, warm ischemia time.

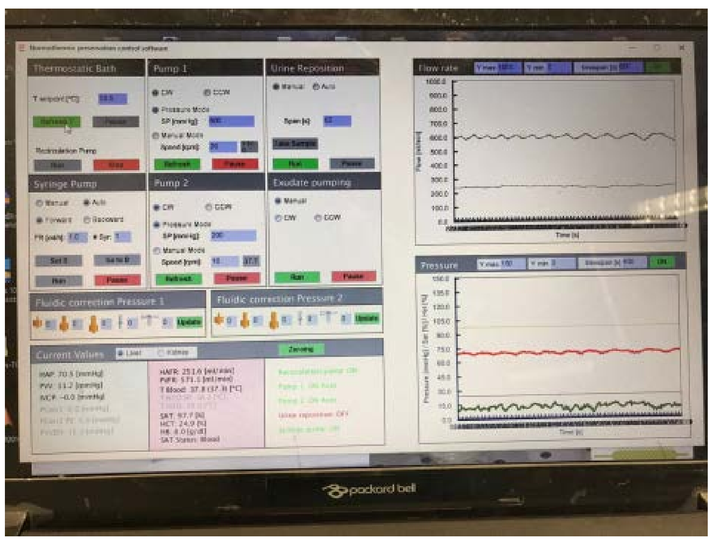


Figure 3. Software interface developed for system configuration and control while monitoring the adjustable and non-adjustable key variables for the normothermic perfusion process.

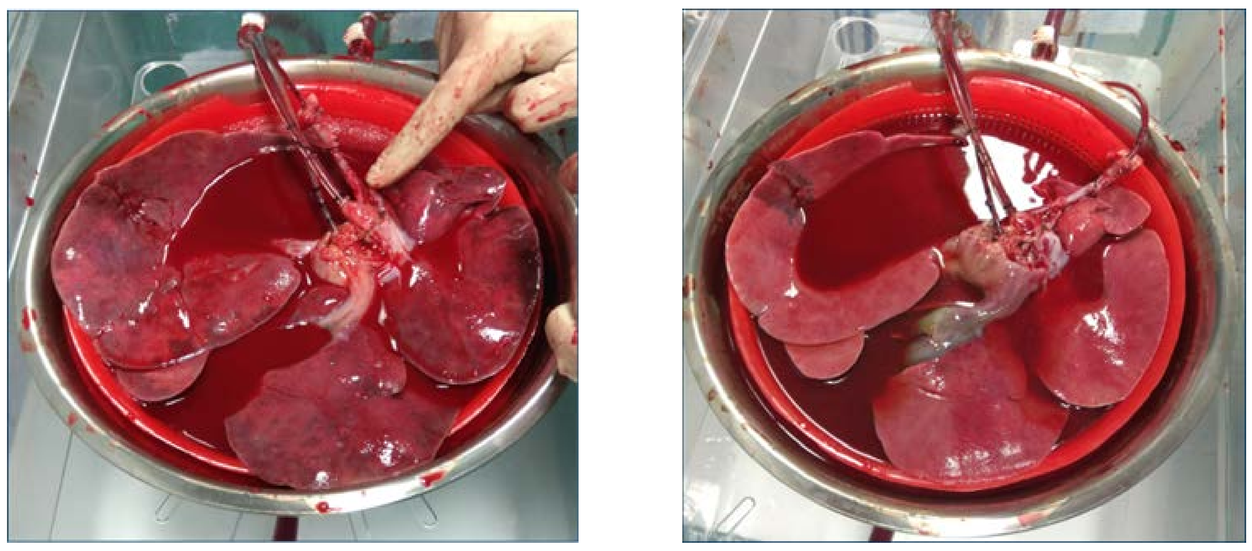


Figure 4. Example of tested liver recovery before the normothermic perfusion process and after a 6 hours perfusion.

RESULTS: Compared to healthy livers, steatotic livers were perfused in an equally satisfactory manner (Table 1), did not show worse values of hepatic damage (Table 2), had a larger production of bile (Table 2) and the histopathological parameters did not show any significant alteration concerning fibrosis, infiltrate, necrosis and cholestasis.

	HA Pressure (mmHg)	HA Flow Rate (ml/min/100 g)	PV Pressure (mmHg)	PV Flow Rate (ml/min/100 g)
Healthy Livers	86.6±9.3	14.9 ± 4.8	10.8 ± 6.1	50.9 ± 12.9
Steatotic Livers	95.3±18.8	15.9 ± 1.5	20.5 ± 5.2	54.3 ± 8.7

Table 1. Mean values of hemodynamic variables measured in the Hepatic Artery (HA) and the Portal Vein (PV) for healthy and steatotic livers throughout the 6-hour normothermic perfusion.

	AST (UI/l)	ALT (UI/l)	Bile production (g)
Healthy Livers	437.2 ± 299.8	32 ± 7.7	71.7 ± 60.8
Steatotic Livers	365.6 ± 165.1	21.4 ± 8.3	146.6 ± 77.7

Table 2. Mean values of AST and ALT concentrations and bile production measured for healthy and steatotic livers.

DISCUSSION AND CONCLUSIONS: These data illustrate the capacity of the ARK system to preserve healthy and steatotic livers in NP conditions. Steatotic livers maintained a viable hepatic function during NP and their behavior under NP was not inferior to healthy livers. NP can contribute to decrease the number of steatotic livers discarded for transplantation, thus increasing the donor pool.

[1] Linares I et al. Transplantation. 2019; 103(1): 78-90.

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