Different Timing of Cholangiocyte and Hepatocyte Damage in Liver Preservation: Time to Implement Donor Interventions and New Preservation Techniques to Prevent Ischemic-type Biliary Lesions

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We read with interest the article by Gilbo et al[1] assessing the impact of donor hepatectomy and implantation time on the incidence of early allograft dysfunction (EAD) and nonanastomotic strictures (NASs) in liver transplantation (LT). Donor hepatectomy and implantation time seem to have a linear negative impact on the incidence of NAS and EAD, respectively. A 10-min increase in either of these times is roughly as detrimental as a 1-h increase of cold ischemia time. This article expands our understanding of the importance of warm ischemia in LT, confirming findings from previous studies.[2]

We would like to provide further data and share our comments on this inspiring article.

In 2016–1017, we collected data about times and graft temperatures in 160 first adult LTs with grafts from brain-dead donors. Liver temperature was measured at different time points using an infrared thermometer. In our experience, we were unable to show a significant impact of donor hepatectomy and implantation time on LT outcome, likely because of limited sample size and different practices that led to very little variability of these parameters. Median (interquartile range) time of donor hepatectomy and portal vein anastomosis was 47 (40–55) and 24 (21–28) min, respectively, and correlated poorly with graft temperature at the end of donor hepatectomy ($R = 0.03$, $P = 0.61$) and before graft reperfusion into recipient ($R = 0.11$, $P = 0.16$). However, our data (Figure 1) clearly show that liver grafts do suffer from a period of warm ischemia during retrieval and implantation.

Analysis of EAD predictors in the study by Gilbo et al was somewhat hampered by the lack of inclusion of potentially important confounders, like macrosteatosis and severity of liver disease. Moreover, blood transfusions and early thrombotic events are also main determinants of EAD, as demonstrated by their incorporation in the recently developed early allograft failure simplified estimation score.[3]

Nonetheless, this study interestingly suggests that donor and recipient warm ischemia may impact differently on cholangiocytes and hepatocytes. Indeed, donor hepatectomy time had no effect on EAD (which is mainly determined by hepatocytes function), whereas implantation time was irrelevant with regard to NAS, which reflects cholangiocytes damage. Thus, cholangiocyte injury seems to happen at an earlier timing during graft retrieval and preservation, a finding in keeping with observations that histological damage to biliary epithelium and peribiliary glands is already apparent before graft reperfusion.

As a logical implication, interventions focused on the earlier phase of organ preservation are likely needed to tackle NAS, especially in donors after circulatory death, a setting in which normothermic regional perfusion and hypothermic oxygenated machine perfusion have been associated with a significant NAS reduction.[4,5]

Besides underscoring once more the importance of proper training and technique in LT, this study confirms the role of ischemia-reperfusion injury in determining NAS and highlights the need to implement donor and preservation strategies to reduce their incidence. Future studies will have to assess whether the detrimental role of donor hepatectomy and implantation time persists also when alternative retrieval or preservation modalities are used.

REFERENCES

1. Gilbo N, Fieuws S, Meurisse N, et al. Donor hepatectomy and implantation time are associated with early complications after liver transplantation: a single-center retrospective study. *Transplantation*. 2021;105:1030–1038.

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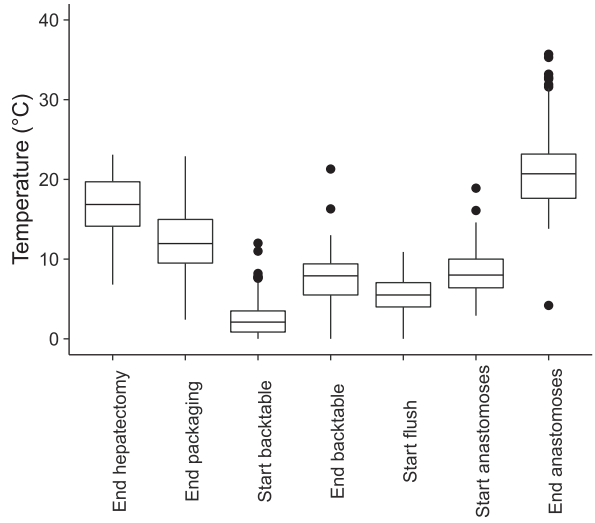

Timepoints	Median (IQR)
Retrieval	16.9 [14.1, 19.7]
Packaging	11.9 [9.5, 15.0]
Start backtable	2.1 [0.8, 3.5]
End backtable	7.9 [5.5, 9.4]
Start flush	5.5 [4.0, 7.0]
Start anastomoses	8.0 [6.4, 10.0]
End anastomoses	20.7 [17.6, 23.2]

FIGURE 1. Boxplot showing liver graft temperature at different time points during retrieval, back table preparation, and implantation. IQR, interquartile range.

2. Jochmans I, Fieuws S, Tieken I, et al. The impact of hepatectomy time of the liver graft on post-transplant outcome: a eurotransplant cohort study. *Ann Surg*. 2019;269:712–717.
3. Avolio AW, Franco A, Schlegel A, et al. Development and validation of a comprehensive model to estimate early allograft failure among patients requiring early liver retransplant. *JAMA Surg*. 2020;155:e204095.
4. Hessheimer AJ, Coll E, Torres F, et al. Normothermic regional perfusion vs. super-rapid recovery in controlled donation after circulatory death liver transplantation. *J Hepatol.* 2019;70:658–665.
5. Schlegel A, Muller X, Kalisvaart M, et al. Outcomes of DCD liver transplantation using organs treated by hypothermic oxygenated perfusion before implantation. *J Hepatol*. 2019;70:50–57.