venesection therapy [3]. They were taken back by the French Haute Autorité de Santé [4]. Then, all our patients received the same information about both initial and maintenance therapy for several decades.

- Delatycki *et al.* discuss about morbidity aspects. However we studied mortality and not morbidity. Fortunately a large proportion of patients with breast or colon cancer do not die from their malignancy. Thus it is not correct to compare mortality and morbidity data. This is likely also true for cardiovascular disease.

More importantly, iron stores in the body of patients who were not venesected because of normal SF at diagnosis were and remained higher than in those with moderately increased SF who were early enrolled in a phlebotomy program. Indeed, maintenance of SF below 50 μg/L results in lower than normal body iron stores. Therefore, assimilating two sub-groups that were absolutely not identical with respect to iron burden raises serious concerns.

For all these reasons we persist to hypothesize that the discrepancy in mortality data between patients with normal SF and those with moderately increased SF strongly supports a beneficial role of early management of hemochromatosis. However we agree that, as already stressed in our manuscript, we did not demonstrate that iron removal *per se* was responsible for decreasing mortality. Other factors must be discussed (lifestyle modifications, medical follow-up etc.). Nevertheless, the fact that patients had lower mortality when treated for mild hemochromatosis was well shown in this study, regardless of its precise cause.

Finally, in our view, a randomized study of venesection therapy in mild hemochromatosis is neither realistic nor ethical. Moreover, the AASLD guidelines endorsed by Powell *et al.* do not suggest to perform such a study and recommend that «... C282Y homozygotes who have an elevated ferritin (but <1000 μg/L) should proceed to phlebotomy ...» [5].

Conflict of interest

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References

[1] Bardou-Jacquet E, Morcet J, Manet G, Laine F, Perrin M, Jouanolle AM, et al. Decreased cardiovascular and extrahepatic cancer-related mortality in treated patients with mild HFE hemochromatosis. J Hepatol 2015;62:682–689.

[2] Zoller H, Finkenstedt A. Should C282Y homozygotes with mild iron overload be treated? J Hepatol 2015;62:510–511.

[3] Bircher J, Benhamou J, McIntyre N, Rizzetto M Rodés J. Oxford textbook of clinical hepatology. 2nd ed. Oxford University Press: New York, USA; 1999.

[4] Haute Autorité de Santé. Management of patients with HFE-related haemochromatosis; 2005 [cited 16/03/2015]; Available from: <http://www.has-sante.fr/portail/jcms/c_432802/en/management-of-patients-with-hfe-related-haemochromatosis-type-1-haemochromatosis>.

[5] Bacon BR, Adams PC, Kowdley KV, Powell LW, Tavill ASAmerican Association for the Study of Liver Diseases. Diagnosis and management of hemochromatosis: 2011 practice guideline by the American Association for the Study of Liver Diseases. Hepatology 2011;2011:328–343.

Edouard Bardou-Jacquet*
CHU Rennes, Service des maladies du foie, F-35033 Rennes, France
INSERM, U991, Hôpital Pontchaillou, F-35033 Rennes, France
Univ Rennes1, UFR médecine, F-35043 Rennes, France
*Corresponding author.
E-mail address: edouard.bardou-jacquet@chu-rennes.fr

Fabrice Lainé
CHU Rennes, Service des maladies du foie, F-35033 Rennes, France
INSERM, CIC 1414, Hôpital Pontchaillou, F-35033 Rennes, France

Yves Deugnier
CHU Rennes, Service des maladies du foie, F-35033 Rennes, France
INSERM, U991, Hôpital Pontchaillou, F-35033 Rennes, France
INSERM, CIC 1414, Hôpital Pontchaillou, F-35033 Rennes, France
Univ Rennes1, UFR médecine, F-35033 Rennes, France

Preservation injury of the distal extrahepatic bile duct of donor livers is representative for injury of the intrahepatic bile ducts

To the Editor:

We recently published an article in the *Journal of Hepatology* describing the histology of biopsies taken from the distal end of the extrahepatic bile duct of donor livers at the time of transplantation [1]. This study demonstrated the presence of severe biliary injury, characterized by loss of the lining biliary epithelium, mural stroma necrosis, as well as injury of the peribiliary glands (PBG) and peribiliary vasculature. Injury of deep PBG and peribiliary vasculature was identified as significant predictors of later development of non-anastomotic biliary strictures (NAS) after transplantation [1]. Severe injury and loss of the lining biliary epithelium is almost universally found in over 90% of donor extrahepatic bile duct biopsies taken at the time of transplantation [2,3]. The observation that the degree of injury of PBG and vascular plexus correlates strongly with the development of NAS after transplantation suggests that insufficient regeneration of biliary epithelial lining after liver transplantation, due to destruction of the progenitor cell niche (i.e. the PBGs) and insufficient blood supply to bile ducts, is a critical component in the pathogenesis of NAS [1,4]. In our previous study, as well as two other studies on bile duct histology of donor livers, biopsies could only be obtained from the distal end of the donor extrahepatic bile duct [2,3]. It is, however, unknown whether the degree of injury at this level is representative for the degree of injury in the rest of the biliary tree, including intrahepatic bile ducts.

To investigate whether histological injury detected in biopsies taken from the distal end of a donor liver bile duct is

Table 1. Donor characteristics and surgical variables.

Variable	Number (%) or median (IQR)
Age (years)	65 (52-68)
Gender (male)	7 (78%)
Body mass Index	26 (23-30)
Cause of death	
Cardiovascular	3 (34%)
Trauma	2 (22%)
Post-anoxia	2 (22%)
Brain tumor (benign)	1 (11%)
Subarachnoid hemorrhage	1 (11%)
Type of donor	
DCD, Maastricht type III	8 (89%)
DBD	1 (11%)
Reason livers were declined for transplantation	
DCD+ age >60 years	5 (56%)
DCD+ high body mass index	1 (11%)
DCD+ high serum transaminases	2 (22%)
DBD+ adenomatosis hepatis	1 (11%)
Preservation solution	
University of Wisconsin solution	9 (100%)
Type of graft	
Full size graft	9 (100%)
Donor warm ischemia time in DCD* (min)	17 (14-21)
Cold ischemia time (min)	433 (322-560)

*Donor warm ischemia was defined from the moment of cardiac arrest after planned withdrawal of life support until cold flush out. DCD, donation after circulatory death; DBD, donation after brain death.

representative for the degree of injury of more proximal and intrahepatic large bile ducts, we have performed a study in nine donor livers that were declined for transplantation for various reasons (Table 1). Livers were collected after informed consent for research was obtained from donor relatives. All livers were procured in a standard fashion and preserved by cold flush out and storage in University of Wisconsin solution. After a median static cold storage time of 6.7 h biopsies were taken from the distal end of the extrahepatic bile duct as well as intrahepatic bile ducts at two different levels of sectoral ducts and segmental ducts (Fig. 1A). Injury of the bile ducts was assessed using a systematic histological scoring system as described previously [1,2] and were compared as matched pairs.

Biliary epithelial loss of >50% of the bile duct lumen was observed in all different levels of the biliary tree (Fig. 1B). The degree of mural stroma necrosis was not different among extrahepatic and intrahepatic bile ducts (Fig. 1B and C). There was minimal injury of peribiliary vascular plexus (<50% vascular changes) in 92.5% of all the biopsies and there was no significant difference among extrahepatic and intrahepatic bile ducts (Fig. 1D and E). No signs of microthrombi were found in the peribiliary vascular plexus and only minimal intramural bleeding (<50% of the bile duct) was observed in 5% of all biopsies. The degree of injury detected in periluminal PBG as well as in deep PBG was not significantly different among the various levels of the biliary tree (Fig. 1F–I). Severe injury (>50% epithelial loss) of the periluminal PBG was found in 40% of the livers, while severe injury of deep PBG was observed in only 6.6% (p <0.0001; χ^2 test).

This is the first study describing the degree of histological injury of donor liver bile ducts at different levels of the biliary tree, including larger intrahepatic bile ducts. In accordance with previous studies [2,3], histological examination of bile ducts of donor livers after static cold preservation revealed signs of extensive injury. The current study adds important new information to the existing knowledge on biliary preservation injury obtained from studies describing the degree of injury in distal extrahepatic bile duct biopsies of donor livers [2,3].

A limitation of this study is that the donor liver grafts used were declined for transplantation by centers within Eurotransplant regions. However, the type and degree of bile duct injury observed at the level of distal extrahepatic bile duct was similar to that described before in our previous study including 128 liver grafts that were used for transplantation [2,3], as well as an experimental study using a porcine donation after circulatory death model [5]. Moreover, due to the nature of this study, which included collection of biopsies from larger intrahepatic bile ducts, there is no possibility to perform such a study in donor livers that are accepted for transplantation. Another limitation of this study is the small number of liver grafts used. Unfortunately, human livers are not available for research in large numbers.

In conclusion, the degree of histological injury detected at distal end of extrahepatic bile duct of a donor liver is also representative for the degree of injury in the proximal parts of the biliary tree, including larger intrahepatic bile ducts. This study indicates that the biopsies taken from the distal end of the donor extrahepatic bile ducts are a valuable tool in research focusing on preservation injury of donor bile ducts during liver transplantation.

Conflict of interest

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Authors' contribution

NK: Initiated the study, participated in the research design, performance of the research, data analysis and wrote the first draft of the paper. PDW: Participated in the performance of the research and writing of the paper. FB: Participated in the performance of the research and writing of the paper. ASHG: Participated in the performance of the research, histological analyses and writing of the paper. RJP: Initiated the study, participated in the research design, performance of the research, data analysis and writing of the paper.