Research Article

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Minimal portal vein stenosis is a promising preconditioning in living donor liver transplantation in porcine model

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Background & Aims: The main hindrance in promoting living donor liver transplantation remains the morbi-mortality risk for the donor. Considering the opposed remodeling influence of portal and hepatic artery flows, our working hypothesis was to identify a lobar portal vein stenosis capable of inducing a contralateral liver mass compensatory enlargement, without the downstream ipsilateral atrophic response.

Methods: Twenty-four pigs entered this study. Six of them were used to establish hemodynamic changes following a progressive left portal vein (LPV) stenosis, in blood flow, pressure and vessel diameter of the LPV, main portal vein and hepatic artery. Sixteen pigs were divided into 4 groups: sham operated animals, 20% LPV stenosis, 50% LPV stenosis, and 100% LPV stenosis. Daily liver biopsies were collected until post-operative day 5 to investigate liver regeneration and atrophy (Ki67, STAT3, LC3, and activated caspase 3) according to the degree of LPV stenosis. Finally, changes in liver volumetry after 20% LPVS were investigated.

Results: A 20% LPV stenosis led to dilatation of the hepatic artery and a subsequent four-fold increase in hepatic arterial flow. Concomitantly, liver regeneration was triggered in the non-ligated lobe and the cell proliferation peak, 5 days after surgery, was comparable to that obtained after total LPV ligation. Moreover, 20% LPV stenosis preconditioning did not induce left liver atrophy contrary to 50 and 100% LPV stenosis.

Conclusions: A 20% LPV stenosis seems to be the adequate preconditioning to get the remnant liver of living donor ready to take on graft harvesting without atrophy of the future graft.

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Abbreviations: HABR, hepatic artery buffer response; LPV, left portal vein; ALAT, alanine aminotransferase; ASAT, aspartate aminotransferase; GGT, Gamma-glutamyl transferase; ALP, Alkaline Phosphatase; TB, total Bilirubin; FFPE, formalin-fixed, paraffin-embedded; HA, hepatic artery; LLW, left liver weight; TLW, total liver weight; TLV, total liver volume; BW, body weight.

Introduction

The shortage of deceased donor organs compared to the number of patients on the waiting list for liver transplantation requires the use of other sources of grafts. The main hindrance in promoting living donor liver transplantation (LDLT) remains the morbi-mortality risk for the donor. This risk is correlated to the amount of resected parenchyma and to the volume of the donor remnant liver [1,2]. Unilateral portal vein ligation and percutaneous transhepatic portal vein embolization procedures can be performed prior to major hepatectomy. Both of these techniques occlude a lobar portal vein aiming to inducing the atrophy of the ipsilateral liver and thus the hypertrophy of the future remnant liver before hepatectomy. Nevertheless, the atrophic consequences of these techniques on the future liver graft preclude inclusion of these practices in the living donor preconditioning.

The rationale for this study is that the hepatic artery buffer response (HABR) maintains a constant hepatic blood flow-to-liver mass. Indeed, by this mechanism, reduced portal flow leads to accumulation of adenosine into the space of Mall and hepatic arterial dilatation, thereby serving to buffer the impact that changes in portal flow have on total hepatic blood flow [3–5]. Based upon passive, reflex, and active mechanisms, HABR highly contribute to the liver proliferative response following portal flow changes.

We also noted, from clinical and CT-scan personal observations in our patients, that a tumor-induced portal vein stenosis is frequently associated with substantial enlargement of the contralateral liver.

Moreover, Belghiti *et al.* recently published an interesting control matched study of consequences following a right hepatectomy for living donation and benign liver lesions [6]. They conclude that right hepatectomy in LDLT induces a more severe deprivation of liver volume that could represent "inherent limitation" in healthy donors that makes them more vulnerable for postoperative complications [6].

Our working hypothesis was to identify a lobar portal vein stenosis in the living donor liver capable of inducing the basic contralateral liver mass compensatory enlargement (i.e., to

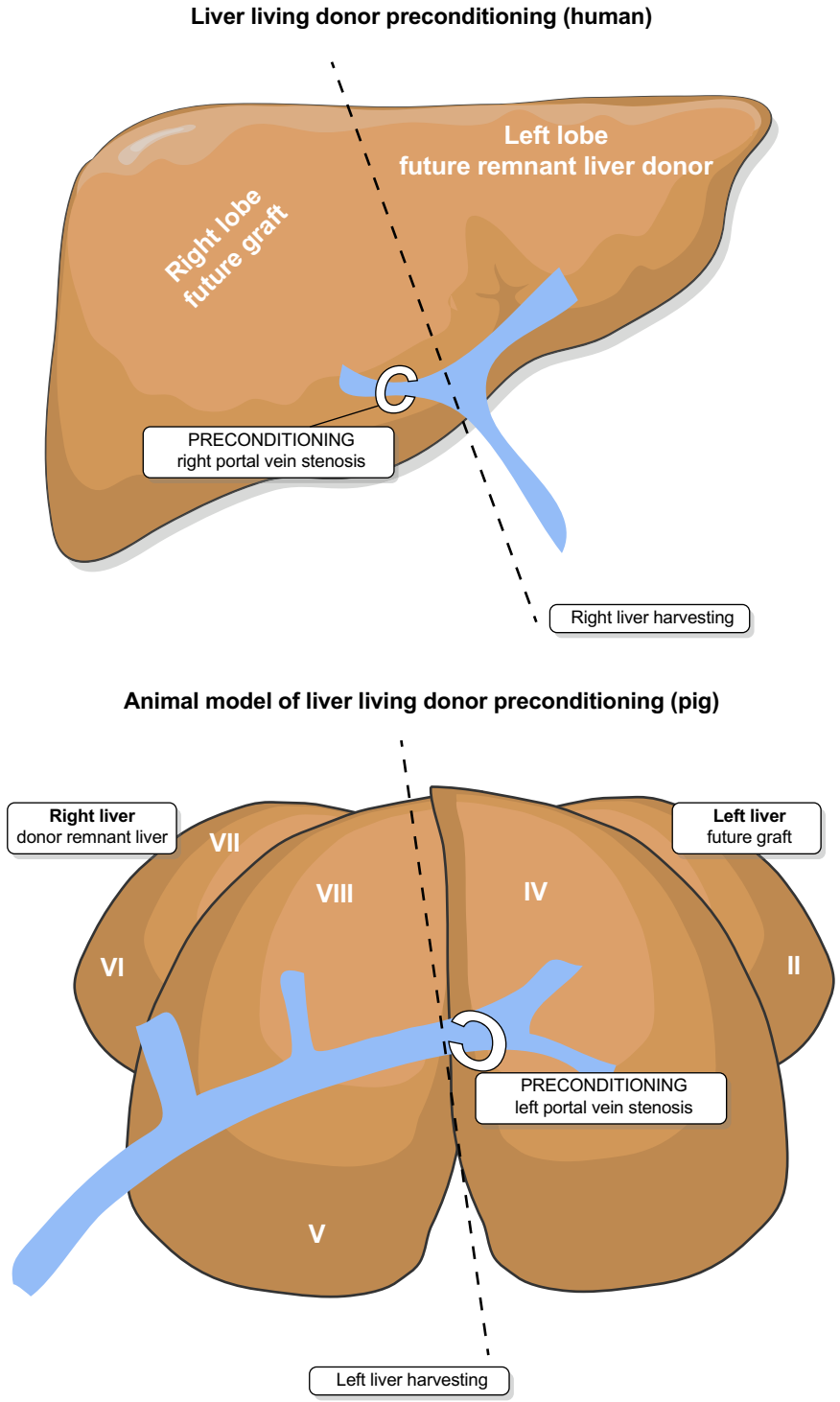

Fig. 1. The human and porcine model for living donor liver preconditioning. Our hypothesis: minimal left portal vein stenosis enhance regeneration in the right liver (donor remnant liver) without atrophy of the left liver (future graft). Animal model: the right liver represents the future remnant liver of the donor and the left liver represents the future graft in the porcine model. (This figure appears in colour on the web.)

prepare the future remnant liver of the donor), without the downstream atrophic response (i.e., protect the future liver graft) (Fig. 1).

We here report our results of a new liver preconditioning based on moderate changes in the portal venous flow in a porcine model, and their consequences on hepatic remodeling.