EASL EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER | JOURNAL OF HEPATOLOGY

Portal uptake function in veno-occlusive regions evaluated by real-time fluorescent imaging using indocyanine green

To the Editor:

We have read with great interest the article by Kawaguchi *et al.* [1]. The authors measured, in the operating room, the hepatic concentrations of indocyanine green (ICG) to evaluate the function of congestive hepatic segments. Three groups of patients were studied: partial hepatectomy, remnant liver of living donors, and hepatic grafts of recipients. Although preoperative three-dimensional computer tomography estimates the postoperative segment volumes, the function of congestive segments is not evaluated by the imaging technique. Interestingly, the authors showed that, following ICG injection, the dye concentrations were significantly lower in congestive than non-congestive segments. ICG hepatic uptake rates were also decreased in the congestive segments of the three groups of patients. However, the concentrations of ICG and ICG hepatic uptake rates greatly varied (between 10 and 80% of the values in non-congestive segments). Thus, some congestive segments conserve a near normal function while others have a poor hepatic ICG uptake rate. Even though peroperative ultrasonography detects anastomoses between hepatic veins, favouring blood drainage from congestive areas, the hepatic function of most congestive regions remain unknown. The congestive segments with poor function decrease the overall postoperative recovery, induce complications, and slow hepatic regeneration. These segments can be treated by hepatic venous reconstruction to better drain outflow. Interestingly, congestive segments V have higher ICG uptake than segments VIII and these latter segments benefit from hepatic vein reconstruction more than segments V do. Thus, the use of a camera with fluorescence imaging in the operating room can estimate the function of congestive segments and modify the surgical procedures.

The reason why ICG concentrations were lower in congestive segments was puzzling and the authors suggested that ICG flowing into sinusoids regurgitates back to portal veins without entering the extracellular space and without reaching hepatocytes. The transport of ICG through hepatocytes might also be involved. ICG enters human hepatocytes through the Organic Anion Transporting Polypeptides B3 (OATP1B3) and Na(+)/Taurocholate Cotransporting Polypeptide (NTCP) [2]. The dye is likely to exit without transformation through the multiple resistance-associated protein 2 (MRP2).

The expression of human transporters was never investigated in the congestive human hepatic segments described in the study. However, a decreased hepatic uptake through OATP1B1/

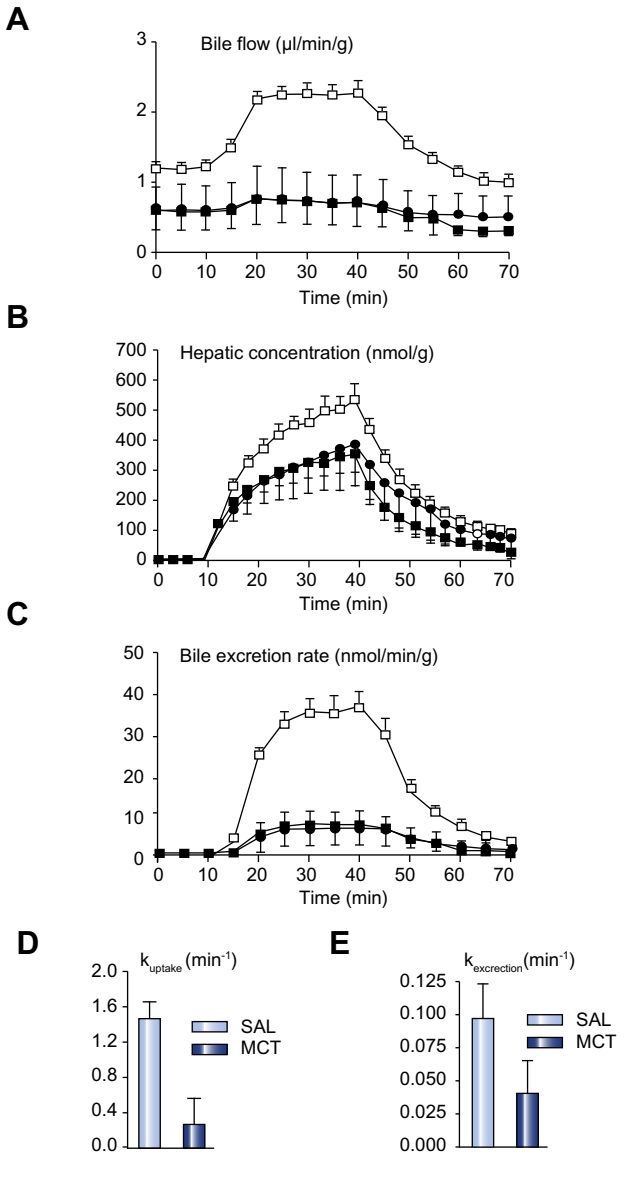

Fig. 1. Hepatobiliary transport of the magnetic resonance (MR) contrast agent Gd-BOPTA. Livers were isolated from rats treated with saline (SAL, white squares) or monocrotaline to induce a sinusoidal obstruction syndrome (MCT, black symbols). Rats (n = 14) were studied either 4 days (black squares) or 18 days (black circles) after MCT administration. Livers were perfused (non-recirculation system) with a Krebs-Henseleit bicarbonate solution (0–10 min), Gd-BOPTA (200 µM, 10–40 min), and a Krebs-Henseleit bicarbonate solution (40–70 min). In all experiments, the perfusate flow rate was 30 ml/min. Gd-BOPTA was labelled with 153Gd for measurements. (A) Bile flow [in µl/min/g of liver] over time. (B) Hepatic concentrations of Gd-BOPTA [in nmol/g of liver] measured by a gamma probe placed over the livers. (C) Bile excretion rate of Gd-BOPTA [in nmol/min/g of liver]. Pharmacokinetic analysis estimates Gd-BOPTA uptake into hepatocytes (D) and Gd-BOPTA bile excretion (E). Modified from [4]. MCT rats had a lower regeneration rates than normal rats after partial hepatectomy (70%).

B3 transporters has already been published in another chronic congestive pathology of the liver, the sinusoidal obstruction syndrome. Thus, sinusoidal obstruction syndrome following chemotherapy is associated with blood stasis inside sinusoids and patients with this syndrome have heterogenous hypointensities (decreased uptake) at magnetic resonance imaging (MRI) after injection of the hepatobiliary contrast agent Gd-EOB-DTPA [3]. In rats treated with monocrotaline (a toxic that induces sinusoidal obtruction syndrome), the hepatic concentrations and bile excretion of Gd-BOPTA are also lower than in control rats (Fig. 1) [4]. Gd-BOPTA is another hepatobiliary contrast agent close to Gd-EOB-DTPA that enters rat hepatocytes through rat Oatps and is excreted into bile through the canalicular transporter rat Mrp2 [5,6]. Interestingly, rats with sinusoidal obstruction syndrome have decreased regeneration rates following partial hepatectomy (70%).

The study by Kawaguchi *et al.* [1] reinforces the growing interest in hepatobiliary compounds that use the OATPs/MRP2 pathway through hepatocytes to evaluate the hepatic function of patients. Dyes (ICG), MR contrast agents (Gd-BOPTA and Gd-EOB-DTPA), and tracers (99mTc-mebrofenin) have been evaluated and the results of these studies are summarized in several recent reviews [7–9]. These articles describe how clearance tests and liver imaging with hepatobiliary compounds improve the scoring of hepatic function. Moreover, imaging the entire liver with dyes, contrast agents, or tracers offers an advantage over plasma biomakers since it studies all segments of the liver [10]. However, as pointed out by the authors, transport through this pathway does not represent all functions of hepatocytes.

Conflict of interest

The authors declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

References

[1] Kawaguchi Y, Ishizawa T, Miyata Y, Yamashita S, Masuda K, Satou S, et al. Portal uptake function in veno-occlusive regions evaluated by real-time fluorescent imaging using indocyanine green. J Hepatol 2013;58:247–253.

[2] de Graaf W, Häusler S, Heger M, van Ginhoven TM, van Cappellen G, Bennink RJ, et al. Transporters involved in the hepatic uptake of (99m)Tc-mebrofenin and indocyanine green. J Hepatol 2011;54:738–745.

[3] Shin NY, Kim MJ, Lim JS, Park MS, Chung YE, Choi JY, et al. Accuracy of gadoxetic acid-enhanced magnetic resonance imaging for the diagnosis of sinusoidal obstruction syndrome in patients with chemotherapy-treated colorectal liver metastases. Eur Radiol 2012;22:864–871.

[4] Schiffer E, Frossard JL, Rubbia-Brandt L, Mentha G, Pastor CM. Hepatic regeneration is decreased in a rat model of sinusoidal obstruction syndrome. J Surg Oncol 2009;99:439–446.

[5] Millet P, Moulin M, Stieger B, Daali Y, Pastor CM. How organic anions accumulate in hepatocytes lacking Mrp2: evidence in rat liver. J Pharmacol Exp Ther 2011;336:624–632.

[6] Planchamp C, Hadengue A, Stieger B, Bourquin J, Vonlaufen A, Frossard J-L, et al. Function of both sinusoidal and canalicular transporters controls the concentration of organic anions within hepatocytes. Mol Pharmacol 2007;71:1089–1097.

[7] Hoekstra LT, de Graaf W, Nibourg GA, Heger M, Bennink RJ, Stieger B, et al. Physiological and biochemical basis of clinical liver function tests: a review. Ann Surg 2013;257:27–36.

[8] Stieger B, Heger M, de Graaf W, Paumgartner G, van Gulik T. The emerging role of transport systems in liver function tests. Eur J Pharmacol 2012;675:1–5.

[9] Van Beers BE, Pastor CM, Hussain HK. Primovist, eovist: what to expect? J Hepatol 2012;57:421–429.

[10] Yamada A, Hara T, Li F, Fujinaga Y, Ueda K, Kadoya M, et al. Quantitative evaluation of liver function with use of gadoxetate disodium-enhanced MR imaging. Radiology 2011;260:727–733.

Sabine Schmidt
Alban Denys
Département de Radiology, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland

Catherine M. Pastor[1,*]
Laboratoire de Physiopathologie Hépatique et Imagerie Moléculaire, Hôpitaux Universitaires de Genève, Geneva, Switzerland
INSERM 773, département de Radiologie, CHU Beaujon, Clichy, France
*Corresponding author.
E-mail address: catherine.pastor@hcuge.ch

[1] The Swiss National Foundation No 310030-126030 funded the work.

Reply to: "Portal uptake function in veno-occlusive regions evaluated by real-time fluorescent imaging using indocyanine green"

To the Editor:

We have read with interest the comments made by Kobbe *et al.* to our recently published article, which demonstrated that portal uptake of indocyanine green (ICG) in veno-occlusive regions caused by dissection of the major hepatic veins decreased to approximately 40% of that in non-veno-occlusive regions (ranging from 10% to 80%) by using intraoperative fluorescence imaging [1]. In veno-occlusive hepatic regions, the portal veins can act as drainage of arterial blood flow, according to the severity of venous occlusion. Thus, we hypothesized that, in hepatic regions with severe venous occlusion, ICG flowed into the sinusoids from the hepatic arteries and portal veins following intravenous administration, but regurgitated and drained into the portal system before reaching the hepatocytes, leading to the decreased concentration of ICG in the hepatic parenchyma. This should be confirmed in further studies by using *in vivo* fluorescence microscopy [2], which may enable visualization of intrahepatic microvascular blood flow in the veno-occlusive regions.

Although the decreased portal uptake of ICG in the early phase of the hepatic venous occlusion would be caused by the