

## Per rectal thallium scintigraphy for the assessment of portosystemic shunt: an experimental study in the bile duct ligated rats

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**Abstract.** Bile duct ligated rats ( $n = 7$ ) have been investigated for 6 months. Two patterns of evolution have been observed: (i) progressive development of cirrhosis and portosystemic shunt (detected by <sup>201</sup>Tl per rectal scintigraphy) in three animals, (ii) repermeabilization of the biliary tract in four animals. Despite the small number of animals investigated, the <sup>201</sup>Tl per rectal scintigraphy seems to be a good indicator of portosystemic shunt secondary to biliary cirrhosis.

**Key words:** Biliary cirrhosis – Thallium scintigraphy – Cholestasis

It is well known that most infants with biliary atresia will develop clinical signs of cirrhosis and, even after surgical reconstruction of biliary drainage, about 75% of these patients will require a liver transplant (Alagille 1986). It is therefore important to detect as early as possible the presence of parenchymal impairment as well as the development of portal hypertension and collateral circulation between the portal vein and vena cava. To evaluate portosystemic shunting (PSS), radioisotopic techniques are attractive alternatives to the currently available methods which are often invasive or time consuming (Okuda et al. 1977; Syrota et al. 1981; MacLean et al. 1979). The <sup>201</sup>Tl per rectal scintigraphy proposed by Tonami et al. (1982) gives a quantitative estimation of the portal systemic circulation. In their study on alcoholic cirrhosis, Urbain et al. (1986) conclude that high values of a semi quantitative index, reflecting the degree of PSS are associated with an increased risk of mortality in patients with liver disease.

In order to test the accuracy of <sup>201</sup>Tl scintigraphy in biliary obstruction, we created an experimental model in the rat by ligating the common bile duct and comparing the scintigraphic parameters (<sup>201</sup>Tl portosystemic shunting) with the more classical biological parameters, the reference remaining the post mortem histological examination of the liver.

### Materials and methods

Seven 2-month-old Wistar rats were surgically ligated at the level of the common bile duct after nembutal anesthesia

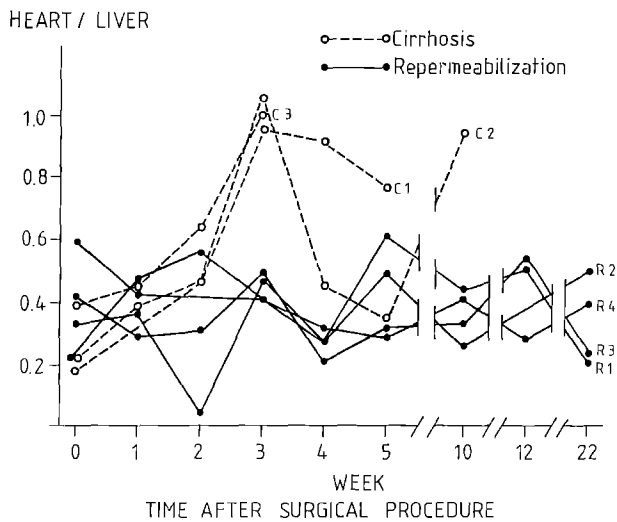
(sodium pentobarbital: 25 mg/kg) and followed up to 22 weeks.

The scintigraphic study was performed before, and regularly after the operation, with a gamma camera (Toshiba, Low Energy Gamma Camera GCA-10A) interfaced to a computer with zoom facilities. After anesthesia, the rats were immobilized in a supine position on the low-energy parallel-hole collimator of the gamma camera. Two radionuclide tests were successively performed. In the first, a polyethylene tube was inserted into the rectum and a dose of 7.4 MBq <sup>201</sup>Tl-chloride was administered. It is rapidly absorbed and, in normal patients, most of the absorbed <sup>201</sup>Tl is distributed, from the middle and inferior rectal veins, to the portal vein, and further retained by the liver cells. In the case of portosystemic shunting, significant amounts of the tracer will pass directly from the portal vein into the vena cava and will be trapped by the heart. <sup>201</sup>Tl trapped in an organ remains there for a couple of h. Twenty 1-min frames were recorded and the regions of interest in the heart and liver delineated. After correction for the number of pixels contained in these regions, the average heart:liver radioactivity ratio (H/L) was determined for the last 5 min. This ratio reflected the amount of shunting from the rectal veins to the systemic circulation (Tonami et al. 1982).

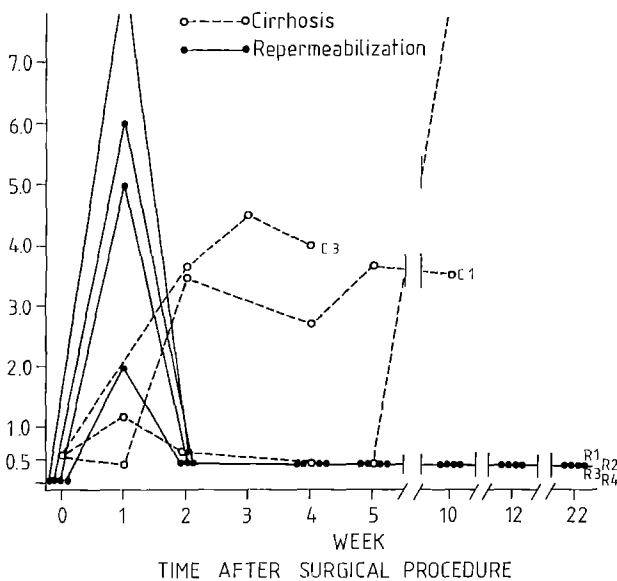
In order to evaluate the permeability of the biliary tract, a 2nd radionuclide test was performed: without moving the rats, 55.5 MBq <sup>99m</sup>Tc-HIDA (Solco-HIDA Basel) was injected. It is rapidly cleared from the blood stream by the liver hepatocytes. The excretion into the biliary tract follows rapidly and radioactivity appears in the intestines. Ten sequential 1-min frames were recorded and the results were expressed in terms of normal or no passage of the radioactivity in the intestines after 10 min. The difference of gamma energy between <sup>201</sup>Tl and <sup>99m</sup>Tc allowed this sequence of scintigraphy.

Two microtubes of blood were taken from the tail of the animals for microdosage of total bilirubin, gammaglutamyl transpeptidase (gamma GT), transaminases and alkaline phosphatases according to routine laboratory methods. The measurement was performed before the surgical ligation of the common bile duct then regularly afterwards.

Twenty two weeks after ligation the animals were killed. A histological study was performed on liver specimens from each rat. The biopsy sample was fixed in 10% formalin, embedded in paraffin and stained by hematoxylin eosin



**Fig. 1.**  $^{201}\text{Tl}$  scintigraphy results. Note the rise in the index value before death of the group C animals



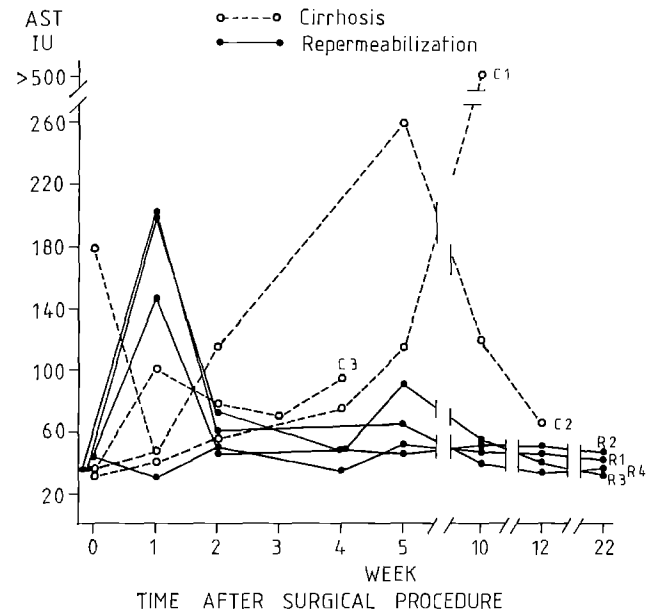
**Fig. 2.** Bilirubin serum concentration. Two different evolutive patterns: low immediate postligation value followed by progressive elevation (group C) and initial elevated value followed by a return to the normal range (group R)

safran, Mallory's trichroma, argentic impregnation and Perls' technique.

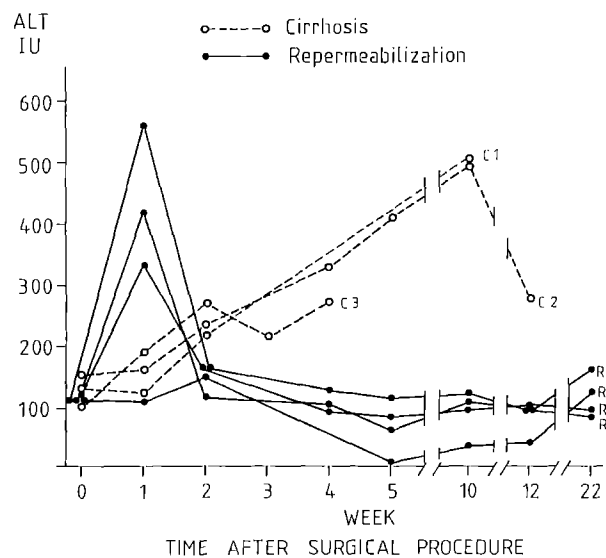
## Results

Preoperative H/L ratios gave normal values ranging from 0.2 to 0.6 (Fig. 1) and the intestines were visualized by cholescintigraphy for the duration of the test.

In the postoperative period, three rats had no intestinal leakage of radioactivity upon cholescintigraphy and were defined as the group C. One week after bile duct ligation, the values of the H/L ratio were comparable to those before ligation, although they were more clustered (Fig. 1). Beginning with the 3rd week, the ratio abruptly rose although



**Fig. 3.** AST: no clear cut difference between the two groups



**Fig. 4.** ALT: a regular elevation of this parameter three times above the initial value in group C and an acute elevation followed by a progressive return to normal in group R. The evolution is clearly distinct between the two groups

lower values were observed for rat C2 in the fourth and the fifth postoperative week. However, the premortem H/L values reached 0.8, 0.95 and 1.0 respectively, for rats C1, C2 and C3. High values of bilirubin, AST, ALT, GT and alkaline phosphatases (Figs. 2–6) were observed in the postoperative period which increased up to the death of the 3 rats on weeks 4, 10 and 12. The group C rats became apathetic on the 3rd week and an icterus of the conjunctiva appeared. In 2 of them, postmortem histology of the liver showed a marked portal fibrosis with severe ductal proliferation and lobular architecture disarray. In the 3rd rat, micronodular cirrhosis or portal fibrosis with preserved lobular architecture was observed in some areas of the liver as well as an important ductal proliferation, suggestive of

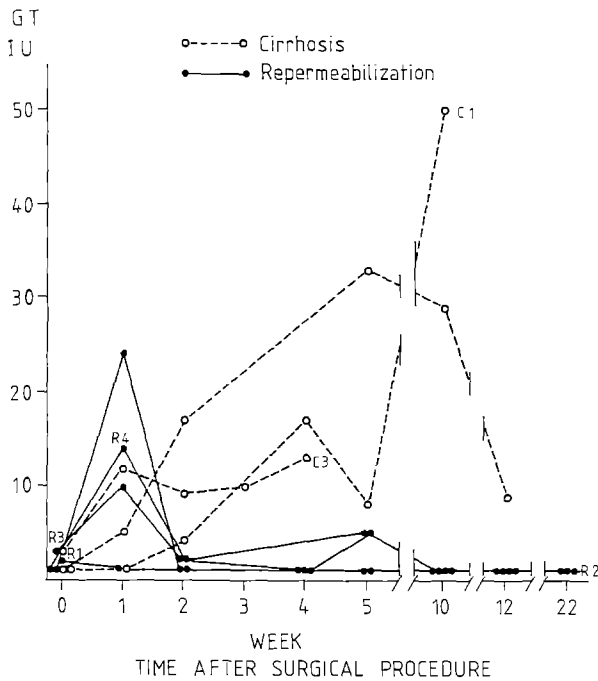


Fig. 5. Gamma glutamyl transpeptidase: in the R group, values are in the normal range up to the 2nd week

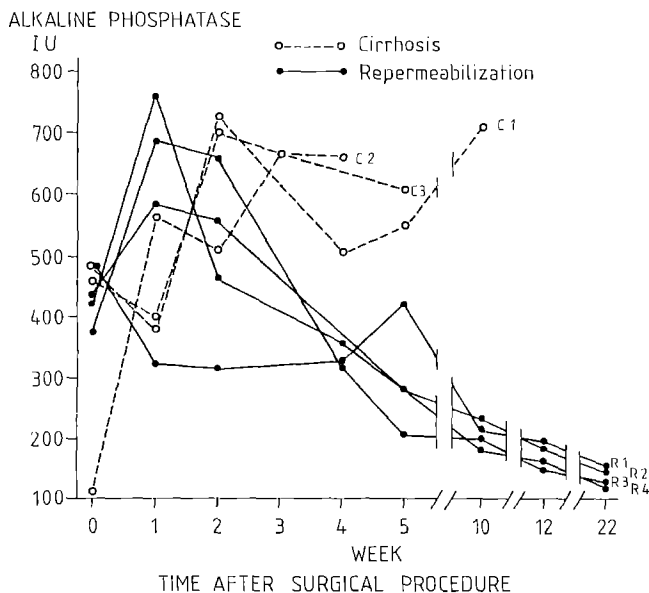


Fig. 6. Alkaline phosphatase evolution confirms at the cholestatic level the two patterns. The distinction appears later but is more pronounced

bile duct obstruction. However, no signs of inflammation could be detected.

Despite scintigraphic and biological evidence of acute cholestasis in the immediate postoperative period, injection of  $^{99m}\text{Tc}$ -HIDA in 4 rats 1 week after bile duct ligation allowed rapid visualization of the small intestine, thus showing spontaneous biliary repermeabilization. They were defined as group R. Hepatic enzyme activities were elevated in the immediate postoperative period; they were, however, within the normal range after 1 week. All the rats were

alive after 22 weeks and the histological postmortem examination of the liver was normal (Figs. 2–6).

## Discussion

Most, if not all, infants affected with biliary atresia will develop histological, and in some cases clinical, signs of biliary cirrhosis in the course of their illness. For those who have successfully undergone biliary drainage in the first months of life, it is mandatory to detect early signs indicative of cirrhotic aggravation, i.e. development of portosystemic shunting. In that way, liver orthotopic transplantation can take place as late as possible but before the occurrence of bleeding disorders, in order to optimize the success rate of surgery (Cuervas-Mons et al. 1986; Lilly and Hall 1987).

However, the measurements of hepatic enzyme activity is inadequate for diagnosis: a high percentage of patients with demonstrated cirrhotoses do not have significant changes in enzyme levels (Sherlock 1981). Liver echotomography provides images of periportal hyperechogenicity in some cases of cirrhosis with the possibility of a non invasive longitudinal follow up of these images. Unfortunately, small bowel interposition, as a result of the Kasai surgical procedure, sometimes renders the acoustic window unsatisfactory and decreases the accuracy of the echotomographic images. Moreover, hepatosplenic scintigraphy with  $^{99m}\text{Tc}$ -colloid, often used in adults as a marker of cirrhosis, is less sensitive in children (Ham et al. 1978).

The  $^{201}\text{Tl}$  scan introduced by Tonami et al. (1982) allows the detection and quantification of portosystemic shunts. Studies mainly centered on alcoholic cirrhosis, associated or not with evident oesophageal varices, proved the validity of the  $^{201}\text{Tl}$  scan (Urbain et al. 1986).

In order to evaluate the usefulness of this test for the detection of cirrhosis associated with bile duct atresia, we chose an experimental model where the causative agent of hepatic degeneration was uniquely mechanical. Although other origins (viral, toxic/chemical, vascular, immunological) have been proposed, a primary lesion is often suspected at the site of the bile duct epithelium (Schier and Schier 1987). In the present study, two clearly different evolutive patterns were observed: (i) group C was characterized by the progressive development of a postobstructive cirrhosis, (ii) group R corresponded to a spontaneous repermeabilization of the biliary tract.

Although a 10-min HIDA test cannot assess the diagnosis of obstruction, it was clear that, in the cirrhotic group, no radioactivity appeared in the intestines. This suggested an important stasis as a consequence of bile duct ligation. This is in contrast to the rapid visualization of the intestine in the group R.

Portosystemic shunting, as measured by the H/L ratio, showed normal values during acute postligation hepatitis (under a 0.6 ratio), which increased up until death for all 3 animals belonging to the Group C. Ratios were normal during the entire test period for the animals belonging to group R. This contrasted with the hepatic enzyme activities which reached a sharp peak in both groups 1 week after bile duct ligation, came back to normal values and later increased again in group C. Thus  $^{201}\text{Tl}$  per rectal scintigraphy appeared to be a specific indicator of a portosystemic shunt secondary to biliary cirrhosis and is independent of hepatocellular damage.

In conclusion, the H/L ratio might be a contributive test in the follow up of children with operated atresia. Preliminary clinical results in a small number of children have shown its validity. Normal H/L ratios were observed for some children in the weeks following a Kasai surgical procedure whereas very high ratios were observed in two cases of terminal cirrhosis. A longitudinal prospective study of children with operated bile duct atresia will be necessary to evaluate the usefulness of this technique.

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