Liver Regeneration and Restoration of Liver Function after Partial Hepatectomy in Patients with Liver Tumors

P. L. M. JANSEN, R. A. F. M. CHAMULEAU, D. J. VAN LEEUWEN,
H. G. SCHIPPER, E. BUSEMANN-SOKOLE & M. N. VAN DER HEYDE
Depts. of Gastrointestinal and Liver Diseases, Intensive Care, Nuclear Medicine, and Surgery, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands

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Liver regeneration and restoration of liver function were studied in six patients who underwent partial hepatectomy with removal of 30–70% of the liver. Liver volume and liver regeneration were studied by single-photon computed tomography (SPECT), using ^{99m}Tc-colloid as tracer. The method was assessed in 11 patients by comparing the pre- and post-operative volume measurements with the volume of the resected liver mass. The correlation coefficient between these methods was 0.899 ($P < 0.01$). Liver function was determined by measuring the galactose elimination capacity and the caffeine clearance. After a postoperative follow-up period of 50 days the liver had regenerated maximally to a volume of 75 ± 2% of the preoperative liver mass. Maximal restoration of liver function was achieved 120 days after operation and amounted to 75 ± 10% for the caffeine clearance and to 100 ± 25% for the galactose elimination capacity. This study shows that SPECT is a useful method for assessing liver regeneration in patients after partial hepatectomy. Our study furthermore shows that caffeine clearance correlates well with total liver volume, whereas the galactose elimination capacity overestimates total liver volume after partial hepatectomy.

Key words: Caffeine clearance; galactose elimination capacity; hepatic resection; liver regeneration; single-photon emission computed tomography

P. L. M. Jansen, M.D., Division of Gastrointestinal and Liver Diseases, Academic Medical Center, Meibergdreef 9, 1105 AZ Amsterdam, The Netherlands

Partial hepatectomy, with removal of a major part of the liver, is followed by a period of liver regeneration and restoration of liver function. Restoration of liver function depends on de novo synthesis of cytosolic and microsomal enzymes and on an increase of total liver mass.

Caffeine clearance is a test for microsomal liver function and depends on the total liver mass. Caffeine clearance is decreased in decompensated liver cirrhosis (1, 2). The galactose elimination capacity, as described by Tygstrup (3), is a test for cytosolic liver function, which is also decreased in decompensated liver cirrhosis (4). Partial hepatectomy and the postoperative phase of liver regeneration offer an opportunity to study the relation between liver function and liver mass. In rats a dissociation of microsomal and cytosolic liver function tests after partial hepatectomy has been reported: the microsomal function per unit remaining liver remained unaltered during liver regeneration, whereas cytosolic function increased (5, 6). This suggests that a microsomal function test, such as the caffeine clearance, closely correlates with the total functional liver mass, whereas a cytosolic function test, such as the galactose elimination capacity, has a functional reserve capacity, which is recruited when the liver volume is decreased. This was tested in a group of patients who underwent partial hepatectomy for various liver tumors. The total liver volume during liver regeneration was measured scintigraphically by single-photon emission computed tomography (SPECT).

SUBJECTS AND METHODS

Subjects

Only those patients who underwent a liver resection involving removal of 30–70% of the total liver mass were included in the study. The group consisted of six women and five men, aged 25 to 72 years. Surgery was performed for liver metastases (6), a cholangiocarcinoma (1), and a benign sclerosing lesion at the bile duct bifurcation (1), an empyema of the intrahepatic biliary tree in the right liver lobe (1), and a hemangioma within (1) or at the edge of the left liver lobe (1). Prolonged follow-up study (212 days) was achieved in only six patients because three patients died within a few weeks after operation, one patient refused repeated tests, and one lived abroad.

Methods

The volumes of the resected liver specimens were determined by immersion in a water bath. The total liver mass of each patient was determined scintigraphically by a SPECT technique. After intravenous injection of 120 MBq (3 mCi) of ^{99m}TC colloid, data acquisition was performed over 360°, using a rotating scintillation camera and a parallel-hole low-energy collimator. Transverse slices were reconstructed by means of filtered back-projection and a Butterworth filter. Attenuation correction was applied. Liver boundary in transaxial slices was delineated, using a count cutoff of 40% of the absolute maximum count value within the liver from the total transaxial slices. The number of pixels containing counts above this 40% threshold value was summed for all slices, and this total sum was converted to cubic centimeters by using the precalibrated pixel size.

The 40% threshold value was selected on the basis of phantom studies. Known simulated liver volume, in increments of 500 ml over a range of 500–2500 ml, was achieved by inserting a combination of one to five plastic bags filled with 500 ml of ^{99m}Tc solution (20 MBq, 0.5 mCi) into a tissue-equivalent torso that contained a cavity the size and shape of a liver (7, 8). The cavity shape assisted in moulding the bags to a realistic liver geometry and shape. SPECT was performed as described above for each simulated volume. The reconstructed SPECT images obtained for the simulated liver phantom mimicked those observed in patients. The volume was estimated from the simulated liver transaxial slices for different thresholds. The estimated volumes obtained for different thresholds were compared with the expected values. The 40% threshold gave the estimated values closest to those expected over the whole volume range investigated. The linear regression equation for the five volumes determined between 500 and 2500 ml was as follows:

$$\text{estimate} = 1.05\ (\pm 0.04) * \text{true} - 58\ (\pm 72)\ (\text{ml})$$

where constants are given with standard errors of the estimate between parentheses.

Liver function tests were performed after interruption of food intake for 12 h and refraining from caffeine-containing beverages for 24 h. The caffeine clearance was assessed by intravenous bolus injection of 1 ml containing 125 mg caffeine and 125 mg sodium benzoate. Blood samples were collected from the contralateral antecubital vein at 0, 30, 150, and 360 min. Caffeine was determined in serum by high-performance liquid chromatography as described by Scott et al. (9). The galactose elimination capacity was determined after intravenous injection of galactose in saline (0.5 g/kg body weight). Blood samples were obtained at 30, 40, 50, and 60 min and collected in sodium fluorate-containing tubes. In addition, the galactose concentration in urine was determined. Galactose was measured by enzymatic assay, using galactose dehydrogenase, and spectrophotometry (cat. no. 124273, Boehringer, Mannheim, FRG). All tests were performed 1 week before operation and were repeated within 10 days after operation and on postoperative days 45, 122, and 212.

Calculations

For pharmacokinetic analysis the caffeine data were fitted by computer to a monoexponential disappearance curve using a least-squares method. The clearance was calculated by using $Cl = k \times VD$, wherein $k = \ln2/t_{1/2}$ and VD (volume of distribution) = dose/Co.

The galactose elimination capacity was calculated by using only the linear phase of the disappearance curve (zero-order kinetics) and the equation proposed by Tygstrup (3).

All data are expressed as means ±SEM. Statistical analysis was done with Student's *t* test for paired analysis.

Informed consent

All patients gave their informed consent.

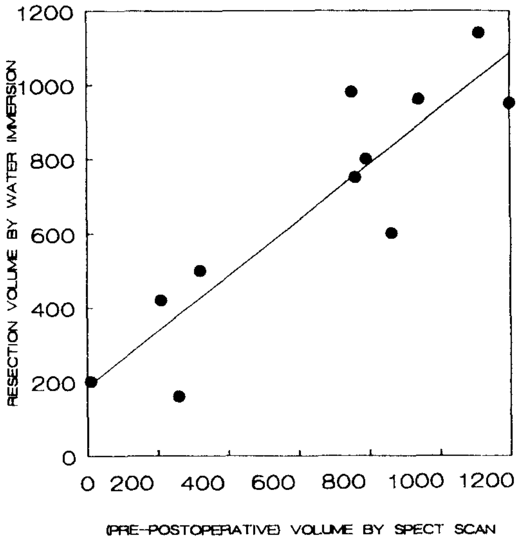

Fig. 1. The accuracy of SPECT scintigraphy for determination of liver volume. The liver volume was determined in situ before and after operation by SPECT scan, and the difference between these values, as depicted on the abscissa, was correlated with the size of the resected segment, as determined by water immersion (ordinate). The unit of measure in this figure is milliliters.

RESULTS

The SPECT technique, used to measure liver volume in situ in the patient, was clinically assessed by comparing the difference of the pre- and post-operative volume with the volume of the resected liver specimen as quantitated by water immersion. The results of the linear regression analysis are depicted in Fig. 1. The correlation between the two methods was highly significant (correlation coefficient, 0.899; $P < 0.01$). It is clear that the water immersion method gives somewhat higher values than the SPECT scan. An example of the images obtained is shown in Fig. 2. In this patient the left liver lobe was removed because of metastasis of a colon carcinoma. The volume was 2110 ml before operation, 1320 ml 1 week after operation, and 1670 ml 20 weeks after operation.

The average values for liver volume, caffeine clearance, and galactose elimination capacity, determined before and soon after operation, are depicted in Table I. Both caffeine clearance and galactose elimination capacity, when expressed per kilogram body weight, were decreased after operation. When expressed per 100 ml of liver, caffeine clearance and galactose elimination showed a tendency to be increased. This reached significance for galactose elimination capacity only. Forty days after operation the average total body weight of the patients was not significantly different from the preoperative body weight.

The relation between the restoration of liver function and liver regeneration is depicted in Fig. 3. Liver volume and caffeine clearance were both restored to maximally 75% of the original preoperative values, and these values were reached on the 45th and 120th day after operation, respectively. The galactose elimination capacity reached a maximal value of about 100% of the preoperative value on the 120th postoperative day.

DISCUSSION

After partial hepatectomy a period of liver regeneration starts that lasts 1 to 4 months. Our results clearly show that in humans liver regeneration

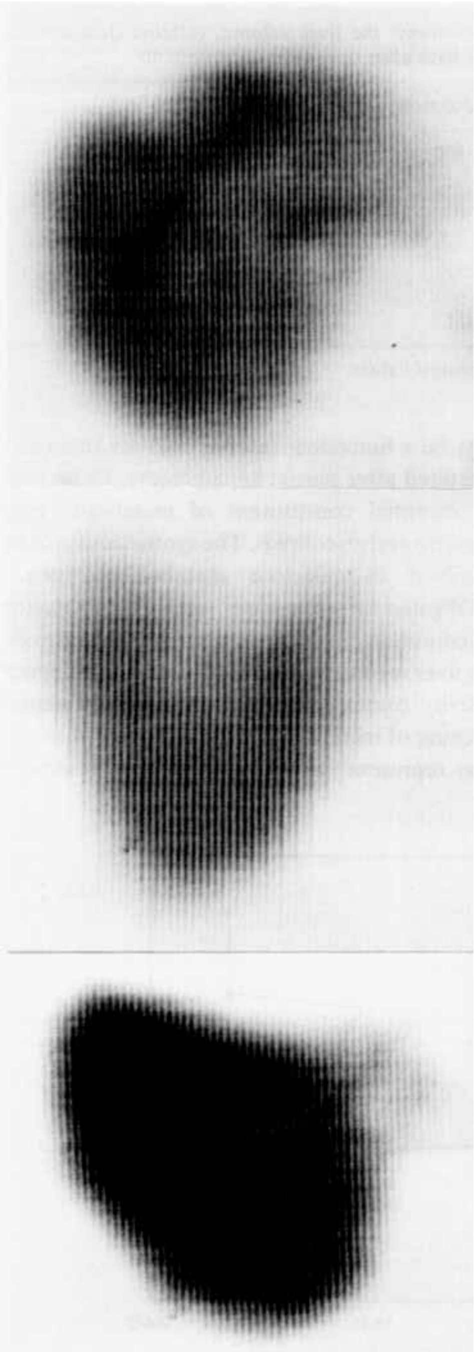

Fig. 2. SPECT images of the liver before and after partial left hemihepatectomy. In this patient a left hemihepatectomy was done because of a metastasis in the left liver lobe. Before operation the liver size by SPECT was 2110 ml (upper panel); after operation, 1320 ml (middle panel); and during the regeneration phase 20 weeks after operation, 1670 ml (lower panel).

does not lead to a complete restoration of preoperative liver volume within the present study period. Six weeks after operation liver regeneration appears complete at a maximally restored volume of 75% of the preoperative liver mass. This is in agreement with the data of Zoli et al. (10), who found, by ultrasonography, that 6 months after 50% hepatectomy the liver volume was restored to 85% of the preoperative liver mass.

In humans and animals there exists a fine tuning between the total liver mass and body weight. For example, liver transplantation studies in dogs showed that small transplants increase in size, whereas large transplants atrophy until a certain fixed ratio between liver size and body weight is reached (11). Apparently, in humans there exists a certain redundancy of liver mass, since the liver stops to regenerate when about 75% of the preoperative liver volume is reached.

Caffeine clearance is a liver function test that depends on microsomal cytochrome P450 activity (1, 2). Cimetidine inhibits cytochrome P450 activity (12), whereas barbiturates, many other drugs, and smoking increase the activity. The patients in our study were nonsmokers and received ranitidine in the immediate postoperative period. This drug does not affect drug metabolism to a significant degree (12). Our study shows that during liver regeneration the restoration of caffeine clearance was delayed. After 6 weeks the maximal liver volume was reached, whereas the restoration of caffeine clearance was only halfway. The reason for this is unclear. Four months after operation a good correlation between caffeine clearance and total liver mass was found.

Galactose elimination is characterized by a period of zero-order kinetics and a period of first-order kinetics commencing about 60 min after bolus injection. During the first phase the elimination depends on functioning liver mass, and during the second phase, when the bulk of the galactose has been eliminated, the elimination becomes mainly blood-flow-dependent (13, 14). In this study only the first elimination phase was considered. Our results show that the galactose elimination capacity is completely restored after

Table I. Liver volume and liver function after partial hepatectomy: the liver volume, caffeine clearance, and galactose elimination capacity were determined before and 9 days after operation in 11 patients

	Before resection	After resection
Liver volume (ml)	1900 ± 500	900 ± 300**
Caffeine clearance		
ml/min · kg body wt.	1.4 ± 0.4	0.7 ± 0.3**
ml/min · 100 ml liver	5.0 ± 1.9	6.2 ± 2.8
Galactose elimination capacity		
µmol/min · kg body wt.	32 ± 6	24 ± 7*
µmol/min · 100 ml liver	134 ± 51	215 ± 113***

* $P < 0.01$; ** $P < 0.001$; *** $P < 0.05$, Student's t test for paired values.

partial hepatectomy, whereas the liver volume only regenerates to 75% of the original liver mass. Thus, per volume unit the galactose elimination capacity increases such that the decreased liver size is fully compensated for by an increased galactose elimination capacity. This is in agreement with a liver regeneration study in rats wherein a dissociation was found between a microsomal liver function test and the galactose elimination capacity, a cytosolic liver function test (5). For the galactose elimination capacity there may be a functional reserve capacity that can be recruited after partial hepatectomy. Galactose is an essential constitutent of membrane glycoproteins and glycolipids. The synthesis of enzymes involved in galactose metabolism, such as UDPgalactose-epimerase and UDPgalactose-glycoprotein galactosyltransferase, increases during liver regeneration (15). This increased specific activity comes at a time of increased demand because of increased membrane biosynthesis and may represent part of the functional reserve ca-

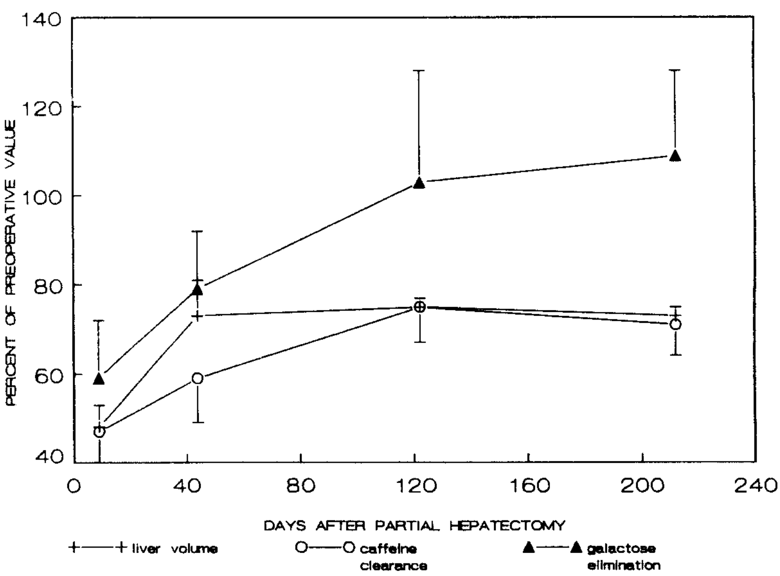

Fig. 3. Restoration of liver function and liver volume after partial hepatectomy. The liver volume, determined by SPECT scintigraphy, the caffeine clearance, and the galactose elimination capacity was measured 9, 44, 122, and 212 days after operation in six patients. The data are expressed as percentage of the preoperative value ± SEM.

pacity referred to above. However, the possibility cannot be ruled out that part of this functional reserve resides in extrahepatic tissues.

Several imaging techniques exist for assessment of liver volume in situ. In particular, ultrasonography has been applied for this purpose (16, 17). In this study the SPECT technique was used. The SPECT technique used is simple. Other authors have reported a similar SPECT measurement technique for assessing liver volume, but slightly different thresholds were found (18–22). The 40% threshold cutoff was appropriate for our measurements, but this value needs to be recalibrated for different SPECT systems and different organ shapes and sizes (20). For a large volume, such as the liver, the actual threshold used will affect the volume calculated less than for a small volume, for which border definitions become more critical (21).

The volumes obtained by SPECT before and after resection correlated well with the measured volumes of the pieces that were removed at surgery. SPECT depends on the uptake of technetium colloid by Kupffer cells. When tumors are surrounded by normal liver, the entire liver mass, including the tumor, is calculated as the total liver volume by SPECT. When a tumor is located at the edge of the liver, SPECT does not include the tumor in the calculation of the liver volume. In our study the tumors were in general small (10% or less of the total liver volume) and were located within the liver mass except for one hemangioma at the edge of the left liver lobe. With these limitations in mind, this appears to be a valid method for assessing the total liver mass in a noncirrhotic patient.

In conclusion, this study shows that after partial hepatectomy the human liver regenerates until a volume of about 75% of the initial liver mass is reached. Caffeine clearance correlates well with the total liver mass. For galactose elimination there appears to be a functional reserve capacity that is recruited after partial hepatectomy, part of which may be of extrahepatic origin.

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