Biopsy and Quantitative Hepatobiliary Scintigraphy in the Evaluation of Liver Transplantation

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Methods: Hepatobiliary scintigraphy with technetium-99m-mebrofenin including a first-pass study of 60 two-sec images and a functional phase of 40 one-min images was performed in 26 patients (42.5 ± 12.5 yr) in the early postoperative period (9.1 ± 4.3 days) after liver grafting. Needle biopsy was carried out within a mean of 0.5 ± 2.2 days of the scintigraphy study. Considering only rejection and cholestasis, biopsy results were used to classify the patients in three groups: control group I (11 patients) with minimal lesions, group II (9 patients) with moderate histologic modifications, and group III (6 patients) with severe dysfunction showing important structural changes. First-pass time-activity curves were used to calculate arterial (alpha-A) and portal (alpha-P) angles as well as a portal perfusion index. Functional time-activity curves were used to define two blood retention indices (BRI1 and BRI2) and two liver uptake indices (LUI1 and LUI2). Excretion was not quantified. **Results:** Simple linear regression analysis showed a significant correlation between portal perfusion index and BRI1 ($p < 0.05$, $r = -0.43$) and BRI2 ($p = 0.01$, $r = -0.53$). The validity of the histologic classification was assessed by the existence of significantly different ($p < 0.05$) mean values for alpha-P, portal perfusion index and LUI1 in the three groups. All other indices could distinguish significantly between groups I and II. Furthermore, arterial angle alpha-A allowed differentiation of group II from group III but not group I from group II; on the contrary, LUI2 and BRI1 distinguished group I from group II but not group II from group III. **Conclusion:** This study demonstrated a close correlation between early biopsy results and perfusion indices in patients with a liver graft as well as uptake parameters determined by hepatobiliary scintigraphy.

Key Words: liver; hepatobiliary scintigraphy; biopsy; transplantation

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Hepatobiliary scintigraphy with ^{99m}Tc-labeled iminodiacetic acid (IDA) derivatives is a useful technique for examining patients in the early period after liver grafting. This noninvasive method permits identification of structural complications such as infarcts, abscesses and bile leaks as well as functional complications related to hepatic perfusion, tracer uptake and excretion. Rejection and infection are the most common pathologic processes (*1*) that cause liver graft dysfunction. Both often occur before any significant clinical (*2,3*) or biochemical (*3–5*) changes are evident. Usually rejection does not develop before the fourth or fifth day after transplantation (*5*), but typically after 7 to 10 days. Biochemical tests lack sensitivity (*2–4*) and biopsy is currently considered to be the only definitive method for diagnosis.

Recently, Kuni et al. (*6*) and Engeler et al. (*4*) compared results of biopsies and scintigraphy with IDA derivatives in patients with a liver graft. These studies did not include first-pass examination and did not provide a quantitative analysis of scintigraphic data. Martin-Comin et al. (*7*) performed radionuclide first-pass studies with microcolloids in transplant recipients, and O'Connor et al. (*8*) demonstrated the validity of the radionuclide technique with ^{99m}Tc-diethylenediaminetetraacetic acid (DTPA) for measurement of arterial and portal contribution to hepatic blood flow in an animal model. In the same way, quantitative methods can be applied to assess the function of liver transplants (*9–11*).

The purpose of our study was first to establish a classification of biopsy findings based not only on the nature of the structural modifications, but also on the grade and on the extension of the lesions; second to determine whether quantified abnormalities in perfusion, blood pool clearance and hepatocellular extraction correlate with biopsy results; and finally, to test which scintigraphic perfusion and function parameters or which combination thereof could differentiate transplant recipients with the two main complications in the early postoperative period; namely, rejection and cholestasis.

MATERIALS AND METHODS

Patients

Out of a pool of 64 patients, 26 with suspected complications after liver transplantation were included in our study covering a 6-yr period. Two inclusion criteria were required: (1) early postoperative scintigraphic examination (i.e., performed within 20

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TABLE 1
Biopsy Findings and Group Classification

Class	Biopsy findings
0	Normal or subnormal
1A	Minimal intrahepatocellular cholestasis
2A	Moderate intrahepatocellular cholestasis
3A	Severe intrahepatocellular cholestasis
1B	Minimal rejection: minimal inflammatory infiltration of portal spaces and/or minimal endothelitis
2B	Moderate rejection: inflammatory infiltration of the portal spaces and/or endothelitis
3B	Severe rejection: inflammatory infiltration, endotheliitis, and destruction of the biliary ducts (classic triad)
1C	Minimal rejection and cholestasis
2C	Moderate rejection and cholestasis
3C	Severe rejection and cholestasis

Group I (n = 11) = 0 + 1A + 1B + 1C; group II (n = 9) = 2A + 2B + 2C; group III (n = 6) = 3A + 3B + 3C.

days after transplantation) and (2) biopsy done within 6 days of scintigraphy. There were 16 men and 10 women with a mean age of 42.5 ± 12.5 yr (range, 18.4–66.5 yr). The mean time between transplantation and scintigraphy was 9.1 ± 4.3 days (range, 1–18 days). The mean time between biopsy and scintigraphy was 0.5 ± 2.2 days (range, −4 to +6 days; the minus sign indicates that biopsy was performed before scintigraphy, which was the case for 8 (31%) patients).

Biopsy

Hepatic specimens were obtained by needle biopsy. They were routinely processed for light microscopy. Only 6 (23%) of 26 biopsies were performed with delays longer than ± 2 days between biopsy and scintigraphy. Biopsy specimens were classified according to the following code (Table 1) characterizing the histologic abnormalities: 0 = normal or subnormal; 1 = minimal; 2 = moderate; 3 = severe. Complementary distinction was made for cholestasis only (A), rejection only (B), and cholestasis and rejection simultaneously (C). Rejection was judged according to the classic triad of portal inflammation, bile duct damage and endotheliitis. The most important modifications of cellular structure in hepatocytes were also observed when severe histologic abnormalities were present. With these criteria, patients could be separated into three groups: group I (classes 0, 1A, 1B and 1C) or the control group with a well-functioning graft; group II (classes 2A, 2B and 2C) or the intermediate group with obviously impaired hepatobiliary function; and group III (classes 3A, 3B and 3C) with severe hepatobiliary dysfunction.

Biologic Parameters

Levels of bilirubin, gamma-glutamyltransferase (GT) aspartate aminotransferase (AST), alanine aminotransferase (ALT) and alkaline phosphatase were measured the same day the scintigraphic examination was performed.

Scintigraphy

Two-phase hepatobiliary scintigraphy was performed after intravenous bolus injection of 185 to 330 MBq of ^{99m}Tc-mebrofenin. A series of 100 abdominal sequential images were continuously acquired using a Philips rectangular gamma camera and the first phase was a series of 60 two-sec frames devoted to the study of the two components of liver perfusion: hepatic arterial flow and portal venous flow. The second phase was a series of 40 one-min frames registered in order to assess liver function. Data were obtained in byte mode using a 64 × 64 matrix (Paragon System, Medasys, Ann Arbor, Michigan). Patients were positioned supine under the gamma camera and the high-resolution collimator was centered over the upper abdomen including the whole heart region. The spectrometer was set at 140 keV with a 20% window.

Data Analysis

In each patient, a region of interest (ROI) over the whole liver was created to generate the liver perfusion time-activity curve (Figs. 1A, 2A and 3A). To assess liver function, we drew an adequate ROI over the left ventricle of the heart and another one over the right liver lobe as near to the external border as possible. This was necessary to minimize any bowel and renal as well as intrahepatic duct activity within the liver region. The time-activity curves were normalized per pixel for both perfusion and function phases. Liver perfusion curves were smoothed, but for the function study raw data were used. No background subtraction was performed and numerical results were introduced directly for index calculations.

Liver Perfusion: Arterioportal Perfusion Index Calculation

Figures 1B, 2B and 3B show three different perfusion time-activity curves obtained for the whole liver in one typical patient of each group. Temporal activity variation allows for distinguishing between the two perfusion components of the liver. The first rapidly rising part of the curves correspond to blood flow supplied by arteria hepatica. The second less rapidly increasing or sometimes decreasing part represents the portal venous contribution supplied by the vena porta. We used a computer program (MDS, Ann Arbor, Michigan) to calculate the arterial (alpha-A) and the portal (alpha-P) angles as represented diagrammatically in Figure 4. After curve smoothing, two cursors were placed to calculate separately the slopes and the corresponding angles of both arterial and portal components. Following the method described by Boyd

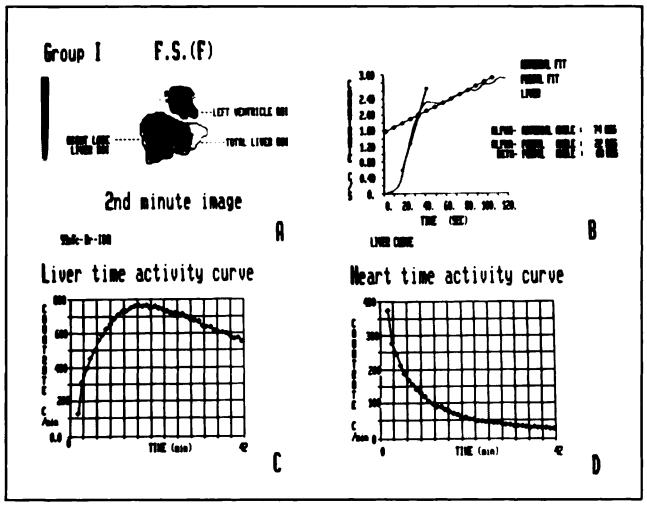

FIGURE 1. Group I. (A) Choice of liver and heart ROIs. (B) Typical first-pass time-activity curve for the whole liver. (C) Typical liver function time-activity curve. (D) Typical heart time-activity curve.

et al. (*12*), the portal time Tp was chosen at the inflexion point of the first-pass time-activity curve. A linear fit for the arterial component was using two cursors set at Tp and Tp − 4 sec. A linear fit for the portal component was obtained by placing the two cursors at Tp + 10 sec and Tp + 30 sec. Angles alpha-A and alpha-P corresponding respectively to the arterial and portal slopes were calculated in a standard coordinate reference system on the computer screen. To eliminate negative values of alpha-P, a complementary beta-P angle for the portal phase was calculated according to the following formula: beta-P = 90 − (alpha-P). A portal perfusion index (PPI) was defined by the following relationship: PPI = beta-P/(alpha-A + beta-P).

Function Study and Index Calculations

Heart (H) and liver (L) time-activity curves were used for calculations of indices. The following count rates were considered: NH1, NH5, NH20, NH42, NL5 and NL10; each number placed after L or H corresponds to a particular time (in minutes) after tracer injection for liver or heart curves, respectively. As demonstrated in Figures 1D, 2D and 3D, the heart time-activity curve shows continuously decreasing function for all examined liver grafts. At the beginning, the curve shows a more or less steep decrease. The second part of the curve decreases more slowly. Both components are simultaneously related to extravascular diffusion and to hepatic (and possibly to renal) clearance. In our study, two indices related to blood clearance were calculated: blood retention index-1 (BRI1) is the ratio of activity at 42 min to that at 1 min after tracer injection and for the left ventricle (BRI1 = NH42/NH1); and blood retention index-2 (BRI2) is the ratio of activity measured at 20 min to that at 5 min after tracer injection for the same ROI (BRI2 = NH20/NH5).

Figures 1C, 2C and 3C represent time-activity curves for liver function. Only the increasing part of these curves was analyzed to define uptake indices. Hepatocellular extraction potential was estimated using two liver uptake indices, LUI1 and LUI2. The first compares the count rates measured in the right liver lobe and in the left ventricle at 5 min after tracer injection (LUI1 = NL5/NH5). The latter is the ratio of the count rate difference between 5 and 10 min after tracer injection to the maximum count rate

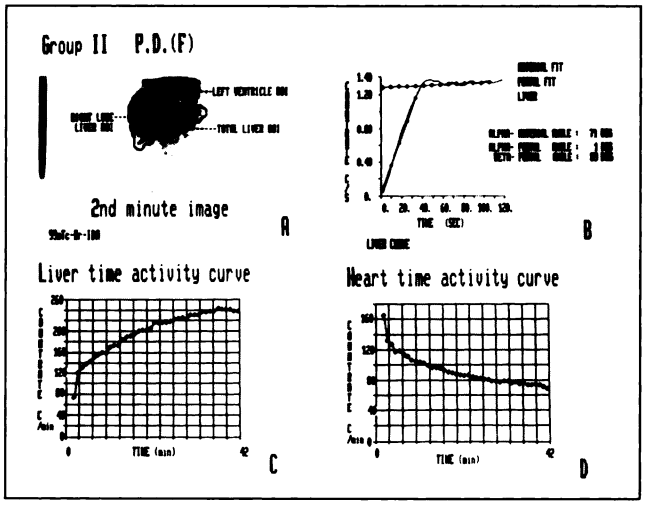

FIGURE 2. Group II. (A) Choice of liver and heart ROIs. (B) Typical first-pass time-activity curve for the whole liver. (C) Typical liver function time-activity curve. (D) Typical heart time-activity curve.

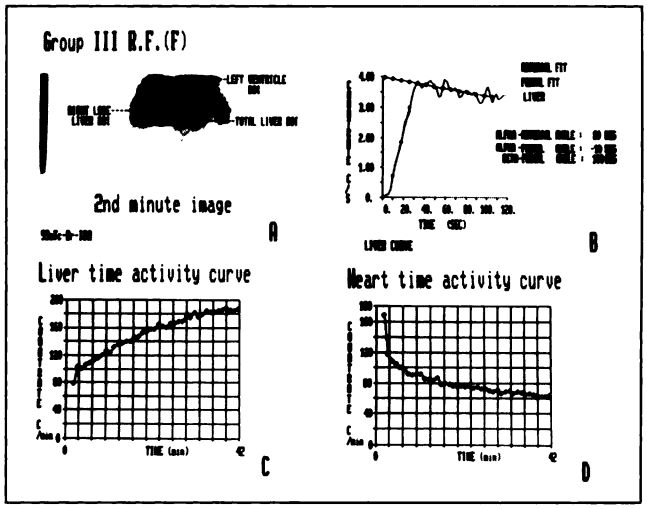

FIGURE 3. Group III. (A) Choice of liver and heart ROIs. (B) Typical first-pass time-activity curve for the whole liver. (C) Typical liver function time-activity curve. (D) Typical heart time-activity curve.

(NLmax) observed in the curve (LUI2 = (NL10 − NL5)/NLmax).

Statistics

Means and standard deviations were calculated for all quantitative parameters in this study. Variance analysis and the Kruskal-Wallis nonparametric H test were performed to compare the three patient groups. The Mann-Whitney *U* test was used to determine the significant differences between two groups. A multivariance test with two variables combining scintigraphic perfu-

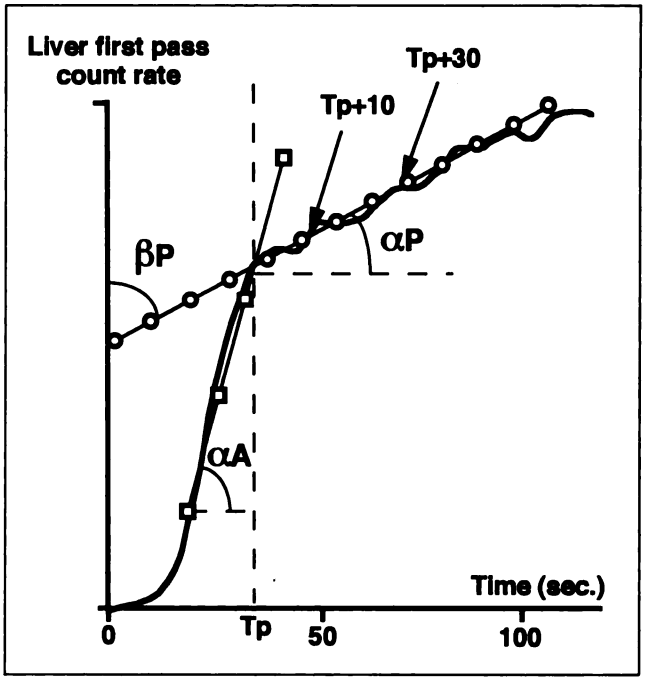

FIGURE 4. Decomposition of hepatic arterial and portal blood flow. The liver first-pass time-activity curve and the corresponding linear fits for calculation of arterial alpha-A and portal alpha-P and beta-P angles. See text for determination of the portal time Tp and following times Tp − 4, Tp + 10 and Tp + 30.

TABLE 2
Patient Identification, Liver Biopsy and Group Classification: Scintigraphic and Biological Data

Patient	Age (yr)	Liver biopsy				Liver perfusion indices			Liver function indices				Biology				
		Tx/Sc	B/Sc	Class	Group	Alpha-A	Alpha-P	PPI	BRI-1	BRI-2	LUI-1	LUI-2	Tot. Bil.	Gamma-GT	AST	ALT	Alk. Phosp.
MF(F)	35	8	0	0	I	79	11	0.5	0.55	0.19	1.30	0.19	43	122	42	293	84
WA(M)	41	7	1	1A	I	71	50	0.36	0.65	0.46	0.84	0.16	96	218	20	83	83
AJ(M)	60	9	−1	1A	I	77	32	0.43	0.35	0.08	3.62	0.23	63	181	28	103	113
HG(M)	40	10	0	1A	I	84	3	0.51	0.71	0.37	0.71	0.13	23	50	10	28	41
NJ(M)	53	6	2	1A	I	77	15	0.49	0.52	0.17	1.05	0.20	88	247	55	152	119
DN(M)	51	8	−1	1A	I	77	11	0.51	0.54	0.30	1.18	0.23	52	149	53	111	99
BM(F)	37	7	0	1B	I	69	23	0.49	0.30	0.06	3.62	0.19	48	63	12	47	42
SS(M)	66	12	−4	1B	I	#	#	#	#	#	1.72	0.17	51	130	33	218	69
FS(F)	49	7	0	1B	I	74	22	0.48	0.33	0.08	1.73	0.19	19	41	14	74	37
HN(F)	35	18	1	1B	I	77	22	0.47	0.16	0.56	#	0.19	25	116	48	126	250
LK(M)	57	17	1	1C	I	#	#	#	0.5	0.15	1.66	0.21	36	84	7	20	63
KC(M)	43	9	−2	2A	II	71	12	0.52	0.57	0.24	1.02	0.20	151	163	47	280	69
MP(M)	60	6	0	2B	II	73	15	0.51	0.55	0.22	1.17	0.20	56	96	84	137	86
DM(F)	31	8	4	2B	II	68	13	0.53	0.69	0.42	0.71	0.12	122	36	24	79	37
TO(M)	20	2	2	2C	II	76	12	0.51	0.76	0.47	0.92	0.10	44	#	1530	1630	779
HJ(M)	44	6	−1	2C	II	83	9	0.49	0.72	0.47	1.11	0.10	51	#	1300	1540	167
PD(F)	42	2	6	2C	II	71	1	0.56	0.69	0.29	0.66	0.09	80	#	2430	2223	290
KT(M)	25	15	3	2C	II	76	−1	0.54	0.74	0.44	0.93	0.10	183	175	22	44	356
MG(M)	41	9	1	2C	II	73	15	0.51	0.55	0.22	1.17	0.20	118	206	115	415	50
AC(F)	18	13	−3	2C	II	80	4	0.52	0.75	0.43	0.57	0.08	412	790	34	129	270
BD(M)	50	13	−3	3A	III	81	8	0.50	0.67	0.38	0.65	0.15	336	380	78	150	337
RD(F)	24	8	0	3A	III	83	0	0.52	0.69	0.36	0.66	0.06	340	201	96	353	52
VA(M)	56	12	2	3A	III	80	0	0.53	0.67	0.36	0.80	0.11	60	257	14	65	87
LJ(M)	45	8	3	3A	III	78	8	0.51	0.65	0.37	0.60	0.14	280	294	59	127	78
HS(F)	39	6	2	3B	III	80	−8	0.55	#	0.78	0.61	0.05	438	#	75	486	168
RF(F)	41	15	−1	3C	III	80	−10	0.56	0.78	0.49	0.85	0.08	321	687	54	108	512

Tx/Sc = delay in days between transplantation and scintigraphy; B/Sc = delay in days between biopsy and scintigraphy (minus sign indicates that scintigraphy was done before biopsy); Class = liver biopsy findings (see Table 1); Group = I, II, III according to liver biopsy classification (see Table 1); Alpha-A = arterial angle in degrees; Alpha-P = portal angle in degrees; PPI = portal perfusion index; BRI-1 = blood retention index-1; BRI-2 = blood retention index-2; LUI-1 = liver uptake index-1; LUI-2 = liver uptake index-2; Tot. Bil. = total bilirubin [μmole/liter]; Gamma-GT [IU/liter]; AST = aspartate amino transferase [IU/liter]; ALT = alanine amino transferase [IU/liter]; Alk. Phosp. = alkaline phosphatase [IU/liter]; # is missing data.

sion and function indices was also applied to assess the validity of our classification. As usual, significance was established at $p < 0.05$.

RESULTS

Detailed results of the 26 patients are presented in Table 2. In control group I (11 patients), only one patient had normal biopsy findings, five showed a minimal intrahepatic cholestasis, four had a minimal rejection with inflammatory portal infiltration and one simultaneously had minimal rejection and cholestasis. In group II (9 patients), one patient had moderate to intense intrahepatic cholestasis, two had moderate rejection and 6 simultaneously had moderate rejection and intrahepatic cholestasis. In group III (6 patients) four patients had cholestasis only, one patient had rejection only and one patient had both rejection and cholestasis.

Means and standard deviations for all scintigraphic parameters are summarized in Tables 3 (liver graft perfusion) and 4 (liver graft function). In the perfusion study, the arterial angle alpha-A was significantly different when group III was compared to groups I ($p = 0.02$) or II ($p = 0.04$), but no significant difference was found between groups I and II ($p = 0.56$). Portal angle alpha-P was significantly different for the three groups: I versus II ($p = 0.03$), I versus III ($p = 0.004$) and II versus III ($p = 0.04$). The PPI distinguished group I from II ($p = 0.01$) and group I from III ($p = 0.02$) but not group II from III ($p = 0.61$).

TABLE 3
Liver Perfusion Indices: Mean Values, Standard Deviation and Statistically Significant Differences between Groups ($p < 0.05$)

	Group I (n = 11)	Group II (n = 9)	Group III (n = 6)
Alpha-A [degrees]	76.1 ± 4.4*	74.7 ± 5.0	80.3 ± 1.6‡
Alpha-P [degrees]	21.0 ± 13.8*	8.1 ± 6.0†	−0.3 ± 7.6‡
PPI	0.47 ± 0.05*	0.52 ± 0.02†	0.53 ± 0.02

*Group I versus group III.
†Group I versus group II.
‡Group II versus group III.
Alpha-A = arterial angle in degrees; Alpha-P = portal angle in degrees (see text); PPI = portal perfusion index: PPI = [90 − (alpha-P)]/[(alpha-A) + 90 − (alpha-P)].

Index LUI1 was significantly different for the three groups. Index LUI2 was only significantly different for groups I and II. For LUI1 and LUI2, respectively, we found $p = 0.03$ and 0.001 for groups I and II, $p = 0.03$ and $p < 0.0001$ for groups I and III, and $p = 0.04$ and $p = 0.23$ for groups II and III. BRI1 could distinguish group I from III ($p = 0.01$) and group I from II ($p = 0.002$) but not group II from III ($p = 0.81$). BRI2 was significantly different between groups I and III ($p = 0.03$) but not between groups I and II ($p = 0.07$) or groups II and III ($p = 0.21$).

Discriminant analysis with two factors distinguished group II from III when alpha-A was tested simultaneously with alpha-P ($p = 0.03$) or with PPI ($p = 0.03$). In the same way, group I versus III and group I versus II could be distinguished when PPI was associated with one of the function indices LUI1, LUI2, BRI1 or BRI2.

Simple linear regression analysis showed a significant correlation between PPI and BRI1 ($p < 0.05$; $r = -0.43$) and BRI2 ($p = 0.01$; $r = -0.53$).

Means and standard deviations for bilirubin, gamma-GT, AST, ALT and alkaline phosphatase are presented in Table 5. All groups could be distinguished using bilirubin values: $p = 0.02$ for group I versus II, $p < 0.001$ for group I versus III and $p = 0.02$ for group II versus III. AST values could also distinguish between groups I and III ($p = 0.01$) and between groups I and II ($p = 0.04$) but not between groups II and III ($p = 0.15$). Other biologic parameters were not able to differentiate significantly more than two groups.

DISCUSSION

Histologic Results and Patient Classification

Comparative studies between biopsy results and scintigraphic data were recently published (*4,6*). In liver transplant recipients, the most frequently encountered functional complications in the early postoperative period are acute rejection and infection. About 40% to 60% of transplant recipients have one episode or more of such complications during the first 2 wk of the follow-up (*1*). Currently, only histologic results provide reliable arguments to assess liver graft dysfunction. Until now, attempts to classify transplant patients according to histologic results were based on pathologic entities without consideration of severity of hepatic damage. However, from the pathophysiologic point of view it is known that different pathologic processes can lead to the same hepatic dysfunction. Therefore, we proposed a classification that takes into account not only the type but also the grade of the histologic injury, based on both the nature of the structural abnormalities and their extension. Thus, considering hepatocyte lesions as accompanying phenomena, we distinguished only between rejection and cholestasis and categorized patients with minimal structural modifications (group I), those with moderate but clearly evident morphologic changes (group II), and finally those with severely impaired histologic structures (group III). This classification is well founded by the observed global hepatic function as assessed by clinical observations and biologic values. Also in this study, the fact that many scintigraphic parameters distinguished significantly the three groups of patients confirms quantitatively the validity of this classification. Although our population was limited, it is nevertheless a rather homogeneous one, especially regarding the time between biopsy and scintigraphy and between transplantation and scintigraphy.

TABLE 4
Liver Function Indices: Mean Values, Standard Deviations and Statistically Significant Differences Between Groups ($p < 0.05$)

	Group I (n = 11)	Group II (n = 9)	Group III (n = 6)
LUI1	1.74 ± 1.04*	0.93 ± 0.25†	0.69 ± 0.11‡
LUI2	0.19 ± 0.03*	0.13 ± 0.05†	0.10 ± 0.04
BRI-1	0.46 ± 0.17*	0.68 ± 0.07†	0.69 ± 0.05
BRI-2	0.24 ± 0.17*	0.36 ± 0.10	0.45 ± 0.17

*Group I versus group III.
†Group I versus group II.
‡Group II versus group III.
LUI-1 = Liver uptake index-1; LUI-2 = Liver uptake index-2; BRI-1 = Blood retention index-1; BRI-2 = Blood retention index-2.

TABLE 5
Mean Values and Standard Deviations of Biological Parameters and Significant Differences between Groups ($p < 0.05$)

	Group I (n = 11)	Group II (n = 9)	Group III (n = 6)
Total Bilirubin [μmole/liter]	49.5 ± 25*	135.2 ± 114.2†	295.9 ± 126.7‡
Gamma-GT [IU/liter]	127 ± 67*	244 ± 274	363 ± 192
AST [IU/liter]	29 ± 18*	620 ± 900†	63 ± 28
ALT [IU/liter]	114 ± 82*	719 ± 836†	214 ± 166
Alk. Phosp. [IU/liter]	91 ± 60*	234 ± 235	205 ± 182

*Group I versus group III.
†Group I versus group II.
‡Group II versus group III.

Hepatic Perfusion Study

Numerous articles have been devoted to the scintigraphic study of hepatic perfusion (*12–16*). Three methods have been proposed to analyze quantitatively the time-activity curves of first-pass studies. The first method is based on the calculation of slopes (*17,18*) or angles (*12,19*) corresponding, respectively, to the arterial and portal components of hepatic blood flow. The second determines the ratio of areas under each part of the time-activity curve (*13,20*) and the third uses deconvolution analysis (*8,15,21*). In the present study, we applied the first method because of its simplicity and availability. Generally, scintigraphic protocols that intend to evaluate the function of liver grafts do not include an angioscintigraphic phase. However, this first part of a complete protocol is able to provide important information and should not be neglected. Indeed, as shown by the results of this study, there exists a direct relationship between the arterial and portal angles (when portal flow decreases, arterial flow increases), and between perfusion values and functional capacity (when portal flow decreases, uptake parameters also decrease). This is

clearly demonstrated by the significant linear regression observed between PPI and BRI1 or LUI1.

The choice of alpha-A, alpha-B and PPI as quantitative indices for the assessment of hepatic perfusion is a first satisfactory approach. Indeed, with two exceptions, these parameters correctly differentiated the three histologic groups. They also allowed verification, in a limited population, of the existence of compensating mechanisms for hepatic blood flow even in transplanted livers. Obviously, arterial and portal angles are sensitive parameters. On the contrary, the PPI seems to be less sensitive in distinguishing the three groups.

Hepatobiliary Function Study

Beside the bicompartmental model (*5,22*), two methods can be applied to quantitatively analyze the function time-activity curves. The first is of an empiric nature and is based on index definition (*23,24*). The second corresponds to a more fundamental approach and uses a deconvolution technique (*10,25–27*). In this study we chose the first method because of its ease in application. Considering the frequent and sometimes important degradation of excretion function in patients with a liver graft, the index method seems inadequate to analyze quantitatively this functional aspect. Therefore, our study was restricted to the evaluation of uptake function in early postoperative liver grafts.

We defined two types of indices: first, LUI1 and LUI2, which assessed the uptake function itself; and second, BRI and BRI2, which characterized the vascular clearance of the tracer and thus gave complementary information on uptake function. The two indices LUI1 and LUI2 significantly distinguished between the three patient groups, except for groups II and III, when LUI2 was tested. Comparing BRI1 and BRI2, BRI2 appears to be more sensitive, but the rather high values obtained for the variation coefficients did not result in significant differences between each of the three groups. As emphasized before, it is important to remember the dependence of uptake capacity on hepatic perfusion. From the pathophysiologic point of view these results are consistent since structural lesions of portal spaces must be related to perfusion and function changes. Once again, this could be verified by discriminant analysis with two factors. Thus, the association of alpha-A or PPI with LUI1, LUI2, BRI1 and BRI2 significantly distinguished our groups except for some patients in groups II and III.

Discrimination Between Rejection and Cholestasis

As usual in organ transplantation, etiologic factors for dysfunction are numerous and varying. In liver graft recipients the two main causes of hepatic dysfunction are rejection and cholestasis. In addition to clinical symptomatology, an impaired function of the graft can be suspected if levels of biologic parameters such as bilirubin, gamma-GT, AST, ALT and alkaline phosphatase are increasing. However, variations of these parameters are in no way specific for an etiopathogenic entity. Furthermore, they are not able to distinguish between rejection and one of the other dysfunction factors (*2,4,28*). At the most, they characterize the severity of impaired function. The biologic parameters measured in this study confirm these facts since at least mean values for bilirubin and gamma-GT were clearly different in our three groups and increased from group I to group III. Bilirubin even significantly distinguished all three groups.

Engeler et al. (*4*) used scores to quantify uptake and excretion in patients with a liver graft but the uptake scores did not distinguish "normal" and "abnormal" cases. The same scores also did not significantly differentiate patients with rejection (36 cases in 76 patients, i.e., 47%) from those without rejection. On the contrary, excretion scores were significantly different for the two types of comparisons. According to our own classification, we observed the following rates of rejection in each histologic group: group I, 45% (5/11); group II, 89% (8/9); and group III, 33% (2/6). Except for group II, we encountered the same difficulty as Engeler et al. (*4*) in distinguishing between patients with rejection and those without rejection. But in our study, we did not consider any excretion parameters at all. Therefore, because quantitative analysis of excretion seems to characterize rejection, it is essential to complete this work with a deconvolution method to find new, more discriminant parameters. Combined with perfusion and uptake indices, these parameters could help to distinguish rejection from cholestasis.

In conclusion, the angioscintigraphic phase is an important part of the hepatobiliary scintigraphic examination, which should be systematically performed for liver graft assessment. Classification based on histologic data must take into account not only the nature of the damage but also the severity and extension of the lesions. Under these conditions, quantitative hepatobiliary scintigraphy can lead to more precise diagnosis in the early period after liver transplantation.

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