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HEPATIC FUNCTIONAL DETERIORATION AFTER PORTACAVAL SHUNT IN THE RAT

Effects on sulfobromophthalein transport-maximum, indocyanine green clearance and galactose elimination capacity

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The consequences of a portacaval shunt on liver function were studied in male Sprague-Dawley rats. Fourteen days after an end-to-side portacaval anastomosis the galactose elimination capacity and the plasma clearance of indocyanine green were reduced in proportion to the approximately 50% loss in liver mass. The biliary transport maximum for sulfobromophthalein, on the other hand, decreased by almost 70% from 153 to 52 nmoles per min per 100 g after portacaval anastomosis. This reduction of sulfobromophthalein excretion was accompanied by a significant decrease in the hepatic conjugation of the dye to glutathione. Our findings demonstrate that a quantitative and qualitative functional deterioration of previously normal livers results from portal blood deprivation.

Controlled clinical trials have shown that the portacaval shunt operation does not prolong survival in patients with cirrhosis of the liver.[1-3] Instead of dying from esophageal variceal hemorrhage, the shunted patients tend to succumb with the clinical picture of hepatic failure. Analysis of the reasons for the apparent postoperative hepatic decompensation, however, has been complicated by the unpredictable natural history of the cirrhotic process itself. To evaluate further the hepatic consequences of the end-to-side portacaval shunt operation, an experimental model was studied, which allowed elimination of the poorly controllable influences of hepatic disease. The portacaval anastomosis (PCA), carried out in the normal rat, may be viewed as a relatively well defined experimental situation.[4]

Because the liver is an extraordinarily complex organ, it is difficult to quantitate properly the functional consequences of a PCA on the liver in vivo. Such an undertaking would require measurement of the capacities of the many—in part poorly understood—partial functions of this organ. As an initial approach, we chose to assess the galactose elimination capacity (GEC) as an example of a "metabolic"[5, 6] function, and the biliary transport maximum (Tm) for sulfobromophthalein (BSP) as an index of an "excretory" function.[7] It must be remembered, however, that hepatic handling of BSP includes conjugation, a potentially complicating metabolic step.[8] In addition, clearance determinations were performed with submaximal doses of indocyanine green (ICG).[9] They may, therefore, be expected to reflect, to a large measure, changes in hepatic plasma flow and in efficiency of the hepatic uptake mechanism.

Taken together, the results of the study suggest that after PCA, quantitative as well as qualitative changes in liver function may occur.

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Materials and Methods

In all experiments male Sprague-Dawley rats (Süddeutsche Versuchstierfarm, Tuttlingen, Germany), who had free access to food (Altromin R, Altromin GmbH, Lage, Germany) and water were used. They were kept in groups of two to three in macrolon cages equipped with screens to reduce coprophagy. The experimental animals subjected to an end-to-side PCA as described previously, were all studied 12 to 16 days after the operation, because liver atrophy is well established and remains constant after the 10th postoperative day.[4] Because earlier investigations failed to reveal any difference between sham-operated and unoperated animals, the latter served as controls.[4] In a number of experiments, arterial blood pressures were measured with an electromagnetic transducer. All animals were autopsyed and shunt patency was verified in the operated rats.

Determination of Tm for BSP (BSP-TM). The rats (150 to 275 g) were anesthetized with pentobarbital sodium (Nembutal) intraperitoneally (5 mg per 100 g in controls, 3.5 mg per 100 g in shunted rats). Judged from clinical observation of the animals and the sleeping time, these doses seemed to result in a comparable degree of anesthesia. Rectal temperatures were maintained between 36.5 and 37.5°C with a warming lamp during the period of the experiment. A jugular vein and a carotid artery were cannulated with polyethylene catheters PE

50. The common bile duct was drained by PE 10 tubing, tied in just below the bifurcation of the two hepatic ducts. Bile was collected in 10-min periods using tared tubes. Bile volume was calculated from its weight, assuming a specific gravity of 1.0. In order to avoid clotting of the catheters the rats were given an anticoagulant intravenously, using 100 U of heparin (Liquemin). After the standardized control period of 20 min, BSP (Bromthalein) was infused intravenously at a rate of 130 to 260 nmoles per min per 100 g of body weight in normal animals, and 60 to 110 nmoles per min per 100 g in shunted animals. Pilot studies had shown that 30 to 60 min after onset of such infusion rates plasma levels of BSP rose linearly with time, and that above 35 nmoles per ml a constant BSP output without appreciable anticholeresis occurred.

Arterial BSP plasma concentrations were determined from 0.2-ml blood samples 30, 40, 50, and 60 min after the start of the infusion. Plasma 50 μl was diluted with 2.5 ml of phosphate buffer (pH 12.0) and read in a Unicam Spectrophotometer at 580 nm against a similarly prepared preinfusion plasma blank from the same rat. BSP concentration was also measured in every bile sample, the first two serving as blanks: 50 μl of bile were diluted with 5 ml of demineralized water. For determination of the extinction, this solution was further diluted 21-fold with phosphate buffer. Suitable dilutions of known amounts of BSP served as standards. At concentrations between 3 and 30 μmoles per ml the recovery of BSP added to rat bile was 98.9 ± 0.9% (n = 8).

The ratio of conjugated to free BSP in the bile was also determined spectrophotometrically after separation of BSP metabolites by thin layer chromatography on silica gel plates (Merck, Darmstadt, Germany), using a butanol-ethanol-acetic acid-water (60:10:0.5:20) mixture as solvent.

Determination of ICG clearance. After anesthesia, cannulation of blood vessels and heparinization as for BSP-Tm, ICG (Cardiogreen) was infused to rats weighing 195 to 358 g at rates of 3.2 to 11.8 nmoles per min per 100 g of body weight for normal rats, and of 2.7 to 5.2 nmoles per min per 100 g for shunted animals. The ICG was dissolved in a solution of 10% rat plasma in physiological saline and was administered at a rate of approximately 2.5 ml per 90 min. After an equilibration period of 60 min, four 0.2-ml arterial blood samples were drawn at 10-min intervals and added to 0.8 ml of a solution containing 0.6 g of human serum albumin in 100 ml of saline. After centrifugation the extinction of the supernatant (diluted plasma) was measured at 800 nm against a similarly prepared preinfusion blank.[9] Assuming steady state conditions, the ICG clearances were calculated as the ratios of the mean arterial plasma concentrations and the infusion rates.

Determination of GEC. A single injection method was used to measure GEC. To evaluate the possible disturbing influences of anesthesia on galactose metabolism, GEC was assessed in both anesthetized and unanesthetized control rats (121 to 356 g). No difference being found, the experiments with shunted rats (152 to 285 g) were all done with pentobarbital.

Anesthesia, cannulation of blood vessels, and maintenance of temperature were carried out as for BSP-Tm. To prevent renal excretion of galactose, all animals were nephrectomized bilaterally from a dorsal incision immediately before the cannulation of the blood vessels. After a recovery period of 1 hr, the rats were heparinized intravenously with 100 U of Liquemin, and 277 μmoles of galactose per 100 g of body weight were injected intravenously during a 1-min period. Pilot studies had shown that this dose yielded a linear plasma disappearance curve of galactose between 20 and 80 min after injection, with plasma galactose concentrations above 2.5 μmoles per ml throughout the entire test. Plasma galactose concentrations were determined enzymatically with a galactose-oxidase method[10] (source of supply of reagents: Kabi, Stockholm, Sweden) in 50-μl samples. The GEC was calculated as the ratio of the injected amount of galactose and the extrapolated time to zero concentration. No correction factor for uneven distribution of galactose within body compartments was applied. The principle of the procedure, therefore, is based on the single injection method used in man[5] and cannot be compared directly with the continuous infusion technique applied in rats by Keiding.[11]

Statistical procedures. All results are expressed as mean and SE. Statistical differences between experimental groups were estimated with the nonparametrical two-sample rank test.[12] Least squares fits were used for linear regressions. The nonparametrical Spearman's coefficients of rank correlation were calculated according to Diem,[12] where the data are not exhibited in detail.

Results

At the time of study, the body weight of shunted animals averaged 86% of the preoperative weight. Liver "atrophy" was prominent in all shunted rats, the liver weight being reduced to 2.27 ± 0.19 g per 100 g (n = 34), compared to the controls, 4.08 ± 0.16 g per 100 g (n = 53). Because of this dissociation between body weight and liver weight, it appeared important to consider the indices of hepatic function on the basis of both the body and the liver weight.[4, 13]

BSP-Tm. The BSP-Tm was assumed to be reached when BSP output remained practically constant over three 10-min sampling periods, whereas the plasma concentrations rose linearly with time. The fluctuations of the three values of BSP output taken as BSP-Tm around their mean averaged 5.2% in control rats and 9.8% in shunted rats.

The order of magnitude of the transport maxima obtained in control rats (table 1) is consistent with the data published from other laboratories.[14-16] In addition, the statistically significant correlations between BSP-Tm and initial bile flow, increment in bile flow during BSP infusion, and bile flow at Tm shown in table 2 agree with current concepts relating excretion of organic anions to bile flow.[14, 17-19] As expected, there was a highly significant correlation between BSP-Tm and body weight, as well as liver mass (table 2, fig. 1).

The results obtained in rats with a PCA have to take into account that the procedure is known to affect bile flow.[20, 21] Whereas the bile salt-dependent bile formation remains unchanged, the bile salt-independent fraction is reduced in proportion to the liver mass, resulting in a relative increase in bile flow if expressed per grams of liver weight. The data of the present study agree with the above concept: an initial bile flow of 2.4 ± 0.1 μl per min per g of liver in shunted rats compares with 1.8 ± 0.1 μl per min per g in control rats. This difference, however, appears insufficient to account for the magnitude of the decrease in biliary BSP concentration found after PCA (table 1). Consequently, the BSP-Tm was also reduced out of proportion to the loss in liver mass. In rats with a PCA the BSP-Tm appeared to be significantly correlated with the initial bile flow, with the bile flow at the Tm, with the body weight, and with the liver weight (table 2, fig. 1). Even though operative at a different

TABLE 1. *Biliary transport maximum for sulfobromophthalein (BSP-Tm), bile flow, and concentrations of BSP in plasma and bile during BSP infusion above the Tm in rats with portacaval anastomosis (PCA) and in controls*

Rats	Body weight	Liver weight	BSP-Tm		Initial bile flow	Bile flow at Tm	Bile BSP concentration at Tm
	g	*g/100 g*	*nmole/min/100 g*[a]	*nmole/min/g of liver*	*μl/min/100 g*		*μmole/ml*[b]
With PCA (n = 12)	214 ± 11[c]	2.2 ± 0.1[d]	52.1 ± 2.8[d]	24.4 ± 1.7[d]	5.1 ± 0.3[d]	5.2 ± 0.3[d]	10.2 ± 0.3[d]
Controls (n = 13)	222 ± 9	4.2 ± 0.1	153 ± 8.1	36.9 ± 1.9	7.5 ± 0.6	9.8 ± 0.7	16.3 ± 0.6

Values are means ± SE.

[a] The equations for the regression lines of BSP-Tm on body weight are for the shunted rats: BSP-Tm (nmole per min) = −45.2 + 0.74 × g of body weight (r = 0.75), and for the control rats: BSP-Tm (nmole per min) = −150.2 + 2.2 × g of body weight (r = 0.72).

[b] Average of the three sampling periods used to calculate Tm.

[c] Not significantly different from the controls.

[d] Significantly different from the controls ($P < 0.01$).

TABLE 2. *Matrix of the nonparametrical Spearman's coefficients of rank correlation between the variables measured for biliary transport maximum for sulfobromophthalein (BSP-Tm) determination*[a]

	Body weight	Liver weight	Initial bile flow	Increment in bile flow during BSP infusion	Bile flow at Tm
	g	*g*	*μl/min*	*μl/min*	*μl/min*
Liver weight (g)					
PCA[b]	0.71[c]				
Controls	0.74				
Initial bile flow (μl/min)					
PCA	0.46	0.64			
Controls	0.51	0.38			
Increment in bile flow during BSP infusion (μl/min)					
PCA	0.19	−0.11	−0.31		
Controls	0.42	0.75	0.28		
Bile flow at Tm (μl/min)					
PCA	0.67	0.69	0.72	0.33	
Controls	0.57	0.52	0.95	0.50	
BSP-Tm (nmole/min)					
PCA	0.68	0.50	0.58	0.35	0.86
Controls	0.73	0.74	0.75	0.72	0.84

[a] For practical purpose, the values in the table can be interpreted similar to correlation coefficients (r) in least squares regression calculations, their applicability, however, does not require normal distributions.

[b] PCA, portacaval anastomosis.

[c] The quantiles of the test statistics are for the 12 shunted rats, 0.50 for $P < 0.05$, and 0.67 for $P < 0.01$; for the 13 controls, 0.48 for $P < 0.05$, and 0.64 for $P < 0.01$.

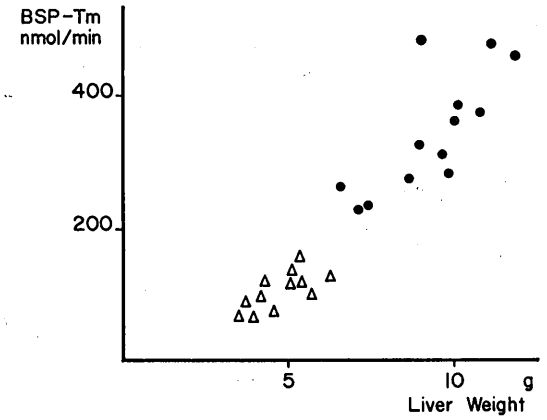

FIG. 1. Biliary transport maximum for sulfobromophthalein (*BSP-Tm*) as a function of liver weight in 13 control rats (●), and 12 rats with a portacaval anastomosis (PCA) (△). In the control rats the equation for the regression line is BSP-Tm = −62.8 + 43.8 × liver weight (r = 0.74). In shunted rats the linear correlation between liver weight and BSP-Tm does not reach statistical significance, possibly due to the small range of liver weights.

TABLE 3. *Biliary output of conjugated and free BSP during BSP-Tm determination in shunted and control rats of table 1. For each animal the mean of three collection periods starting 60 min after onset of the infusion was taken*[a]

Rats	Conjugated BSP in bile	Output of conjugated BSP at Tm	Output of free BSP at Tm
	% of total BSP	*nmole/min/g of liver*	
With PCA (n = 4)	78.8 ± 1.1[b]	22.7 ± 2.1[b]	6.1 ± 0.6[c]
Controls (n = 4)	86.0 ± 1.5	36.5 ± 3.6	6.1 ± 1.3

Values are means ± SE.

[a] BSP, sulfobromophthalein; Tm, biliary transport maximum; PCA, portacaval anastomosis.

[b] Significantly different from the controls ($P < 0.01$).

[c] Not significantly different from the controls.

level, these relationships appeared to be maintained after the shunt operation. It must be pointed out, however, that in animals with a PCA, bile flow did not increase during the infusion of BSP (table 1). In view of the depressive effect of unconjugated BSP on bile formation,[22] it appears interesting that shunted rats excreted a larger proportion of the dye in an unconjugated form (table 3). Because both experimental groups showed the same amounts of free BSP in bile, the reduced output of conjugates wholly accounted for the excessive decrease in BSP-Tm.

The decrease in BSP-Tm does not appear to be related to the lower plasma BSP concentrations in the operated animals, because the infusion rates exceeded the BSP output in every experiment; on the average they were 1.4 times higher in the control rats, and 1.5 times in the rats with a PCA.

ICG clearance. To validate clearance calculations on the basis of infusion rates and plasma concentrations, steady state conditions had to be verified. In each of our experiments the concentrations of ICG practically stayed on a plateau, increasing or decreasing less than 1% per min. To exclude possible differences in clearance values between the two experimental groups due to saturation phenomena, the infusion rates were varied between 2.7 and 11.8 nmoles per min per 100 g. Thus, no uniform ICG plasma levels were attained. The mean arterial plasma concentrations ranged from 4.7 to 13.6 nmoles per ml in the control animals, and from 6.7 to 11.6 nmoles per ml in the shunted animals. A plot of the mean arterial concentrations against the infusion rates (fig. 2) yielded linear relationships, indicating that the given doses were well below the transport maximum for the dye and that no saturation phenomena influenced the clearance values. The resulting average ICG clearance of 0.42 ml per min per 100 g after shunt, and 0.84 ml per min per 100 g in control rats appeared to reflect an alteration due to the experimental procedure roughly in proportion to the loss in liver weight (table 4).

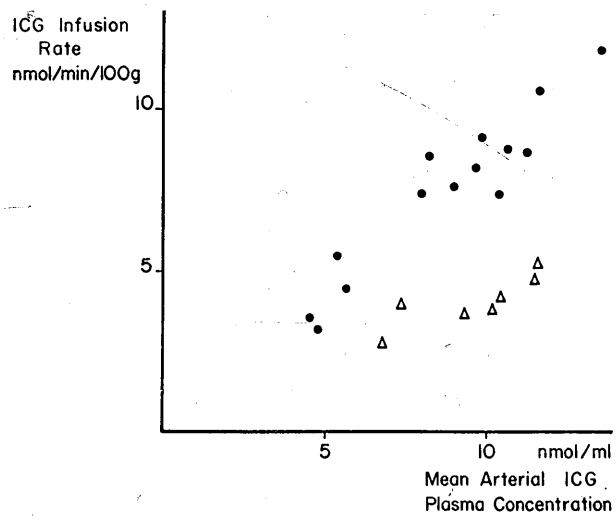

FIG. 2. Correlation between indocyanine green (*ICG*) *infusion rate* and mean arterial plasma concentration of ICG at equilibrium for 7 shunted (Δ) and 14 control (●) rats. The equations of the regression lines of ICG infusion on plasma concentration are for the shunted rats: ICG infusion = 0.66 + 0.35 × plasma concentration (r = 0.80), and for the control rats: ICG infusion = 0.27 + 0.82 × plasma concentration (r = 0.93). The slopes of the regression lines correspond to the plasma clearance of ICG. Even though the intercepts of the regression lines are not significantly different from zero, they explain the fact that the numerical values of the slopes are not identical with the clearance values given in table 4.

GEC. Under the chosen experimental conditions, the disappearance of galactose from arterial plasma was of zero order in each study. As expected from published enzyme studies,[23] and from experiments in man,[5, 6] galactose concentrations above 2.5 μmoles per ml seemed to saturate the galactose-metabolizing system also in our experimental system.

Even though Salaspuro and Salaspuro[24] had suggested an effect of pentobarbital anesthesia, no significant difference in average GEC between the two control groups could be observed (table 5). Based on our results in male Sprague-Dawley rats, the GEC determined after pentobarbital administration may therefore be considered as representative also for unanesthetized animals.

The significant correlation between GEC and body weight as well as liver weight, confirms findings of the infusion experiments carried out by Keiding,[11] even though our absolute values are about 2 times higher. Because Keiding used female and we used male rats only, the sex difference in galactokinase activity[23] is the most likely explanation of this discrepancy. The volume of distribution of galactose calculated from the given dose and the extrapolated concentration at the time of injection was similar in all three groups and averaged 33 ml per 100 g. It is in the same order of magnitude as the 41 ml per 100 g and 30 ml per 100 g calculated by Keiding and Waterman, respectively.[11, 25]

In the animals subjected to a PCA the GEC was also correlated to the body and to the liver weight. Figure 3 shows that livers of similar weight as the controls also had a similar GEC. It must be realized, however, that the range of liver weights is not the same in the two experimental groups, and that the regression line of the correlation between GEC and liver weight does not go through the origin. This explains why in table 5 the average GEC per gram of liver weight is significantly higher after PCA than in control animals.

Although the control animals and 5 of the shunted rats, in which blood pressures were recorded, kept their mean arterial pressures above 90 mm Hg (106 ± 10 mm

TABLE 4. *Infusion rates, attained plasma concentrations and plasma clearances of ICG in rats with PCA and in control animals*[a]

Rats	Body weight	Liver weight	Infusion rate of ICG	Plasma concentration of ICG	ICG clearance[b]	
	g	*g/100 g*	*nmole/min 100 g*	*nmole/ ml*	*ml/min/ 100 g*	*ml/min/g of liver*
With PCA (n = 7)	245 ± 16[c]	2.2 ± 0.1[d]	4.0 ± 0.3[d]	9.6 ± 0.7[c]	0.42 ± 0.02[d]	0.19 ± 0.01[c]
Controls (n = 14)	269 ± 12	4.1 ± 0.1	7.8 ± 0.6	9.1 ± 0.7	0.84 ± 0.03	0.21 ± 0.01

Values are means ± SE.

[a] ICG, indocyanine green; PCA, portacaval anastomosis.

[b] The ICG clearance (Cl_{ICG}) is significantly correlated with the body weight and the liver weight in the control group. Cl_{ICG} (ml per min) = 0.19 + 0.01 × g of body weight, r = 0.75; Cl_{ICG} (ml per min) = 0.68 + 0.14 × g of liver weight, r = 0.80.

[c] Not significantly different from the controls.

[d] Significantly different from the controls ($P < 0.01$).

TABLE 5. *GEC, slopes of the plasma disappearance curves of galactose and extrapolated galactose concentration at time of injection in rats with PCA and in appropriate controls*[a]

Rats	Body weight	Liver weight	GEC[b]		Slope of the disappearance curve of galactose	Extrapolated galactose concentration at $t = 0$[c]
	g	*g/100 g*	*μmole/min/ 100 g*	*μmole/min/ g of liver*	*μmole/ml/ min*	*μmole/ml*
With PCA ($n = 15$)	207 ± 12[d]	2.2 ± 0.1[d]	1.58 ± 0.06[d]	0.73 ± 0.03[d]	0.051 ± 0.002[d]	9.09 ± 0.35[e]
Controls[f]						
Anesthetized ($n = 9$)	218 ± 24	4.2 ± 0.1	2.52 ± 0.14	0.61 ± 0.04	0.070 ± 0.002	7.90 ± 0.46
Unanesthetized ($n = 17$)	252 ± 17	4.0 ± 0.1	2.30 ± 0.10	0.58 ± 0.02	0.068 ± 0.002	8.32 ± 0.32

Values are means ± SE.

[a] GEC, galactose elimination capacity; PCA, portacaval anastomosis.

[b] The equations for the regression lines of GEC on body weight are for the shunted rats: GEC (μmole per min) = 1.39 + 0.01 × g of body weight ($r = 0.73$); for the pooled control groups: GEC (μmole per min) = 1.92 + 0.015 × g of body weight ($r = 0.84$).

[c] The dose of galactose administered was standardized to 277 μmoles per 100 g.

[d] Statistically significant differences ($P < 0.01$) between the pooled values of the two control groups and the group with PCA.

[e] Difference to the combined control groups not significant statistically.

[f] The differences between the two control groups are statistically not significant.

Hg) throughout the experiment, 60 min after injection of galactose, 8 of the shunted rats showed a marked fall in pressure to 56 ± 5 mm Hg. No apparent cause for this hypotension (such as external or internal hemorrhage) could be found at autopsy. Since there was no difference in GEC between the animals with a normal blood pressure (0.68 ± 0.02 μmole per min per g of liver) or with low blood pressure (0.73 ± 0.04 μmole per min per g of liver) the results of the shunted group were pooled.

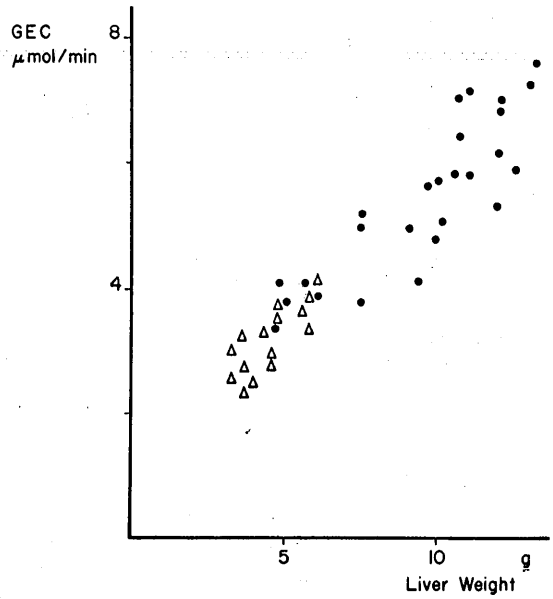

FIG. 3. Galactose elimination capacity (*GEC*) as a function of liver weight in 15 rats with portacaval anastomosis (PCA) (△) and in 26 control animals (●). The data of the anesthetized and unanesthetized control rats are pooled. The equations of the regression lines of GEC on liver weight are for the shunted group: GEC = 1.16 + 0.45 × liver weight ($r = 0.79$), and for the control group: GEC = 1.67 + 0.40 × liver weight ($r = 0.85$). The slopes of the two regression lines are not significantly different.

Discussion

If the tests used throughout this study may be considered as over-all indices of metabolic and excretory functional capacities of the liver, the well documented liver atrophy after a PCA[4, 26, 27] would be expected to be accompanied by corresponding reductions in liver function. Such a contention is further supported by the normal microscopic and ultrastructural aspect of the liver in the rat 14 days postoperatively.[27] The ICG clearance was indeed reduced in proportion to the loss in liver mass. In contrast to BSP, ICG was administered at submaximal doses and its hepatic handling is relatively simple. Removal of ICG from blood is mainly determined by hepatic perfusion and uptake. Once within hepatocytes, it is not conjugated, and cholestasis occurs only when infusions above the Tm are administered.[9] If a similar extraction of ICG is assumed in control rats and shunted rats, the comparable clearances per gram of liver weight in both experimental groups suggests that liver blood flow in shunted rats was reduced in proportion to the liver weight. This is in keeping with the direct measurements of hepatic perfusion in rats with a PCA reported by Ossenberg et al.[28]

The increase in bile salt output per gram of liver after PCA[20, 21] might have suggested a corresponding increase in BSP-Tm.[29-31] Unexpectedly, however, the PCA was followed by a disproportionate reduction of the BSP-Tm, indicating that hepatic handling of BSP in shunted rats is determined not only by the available cell mass, but might be affected also in another way. The decreased proportion of conjugated BSP found in the bile of shunted rats suggests that conjugation with glutathione was inadequate. The slight decrease in postoperative food intake hardly explains this finding, although protein deprivation has been used to produce hepatic glutathione depletion.[8, 32] The more likely explanation is the shunt-induced 10-fold increase in γ-glutamyl transpeptidase recently found by Colombo and Bircher.[33] It may be speculated that enhanced activity of this enzyme reduces the availability of the γ-linked peptide glutathione necessary for BSP conjugation.

Decreased excretion of conjugated BSP in the pres-

ence of an increased proportion of unconjugated dye in addition may explain the lack of the BSP-induced choleresis observed in the shunted rats. There is circumstantial evidence that the choleretic response is due mainly to the conjugates, whereas free BSP might be as anticholeretic as ICG.[9, 16, 22] Normally, the balance of the two simultaneously operative processes is in favor of a choleretic response, whereas the increased proportion of free BSP after PCA might produce a tendency toward anticholeresis. Defective BSP conjugation also could explain a reduction in BSP-Tm out of proportion to the decrease in liver mass. Conjugated BSP appears to be excreted with a larger Tm than is unconjugated dye,[34] and under certain circumstances conjugation appears to influence the rate-limiting step.[14-16]

Despite these qualitative and quantitative differences in the hepatic handling of BSP in rats with a PCA, several basic properties of the excretory apparatus appeared to remain intact. As shown in table 2, the correlation coefficients of the BSP-Tm with the body weight, the initial bile flow, and the bile flow at the Tm were surprisingly similar in both experimental groups.

Whether the GEC is reduced after PCA in proportion to the liver weight (fig. 3), or less (table 5), is a matter of conjecture. If figure 3 is analyzed, it appears more important that control livers of identical weight had practically the same GEC as the livers after PCA. Therefore, the statistically significant difference in average GEC per gram of liver (table 5), may more properly be regarded as a consequence of the intercept of the regression line on the ordinate, and the differences in actual liver weights between the two groups.

It appears unlikely that methodological problems significantly biased the results. In view of the complex hemodynamic changes to be expected after a PCA, the observed episodes of hypotension were not surprising. Their influence on the GEC could be evaluated and proved to be negligible, as expected from the investigations of Jacobsen et al. in man.[35] The well established relative independence of hepatic excretory function from hepatic perfusion[36, 37] suggests that possible episodes of hypotension also would not invalidate the BSP tests.

The relevance of these findings for the occurrence of hepatic failure in patients with cirrhosis of the liver remains speculative. At the least they demonstrate a set of quantitative and qualitative functional deteriorations of previously normal livers resulting from portal blood diversion. Consequently, they add support to the recent surgical efforts to treat portal hypertension while preserving as much portal flow as possible.[38]

APPENDIX

Master table of variables measured during determination of BSP-Tm in 12 rats with PCA and in 13 control rats[a]

Rats	Body weight	Liver weight	Initial bile flow[b]	Bile flow at Tm[c]	BSP-concentration in bile at Tm[c]	BSP-concentration in plasma at Tm[d]	Infusion rate
	g	*g*	*µl/min*		*µmole/ml*	*nmole/ml*	*µmole/min*
With PCA							
1	156	3.7	11.3	10.0	7.7	45.3	0.10
2	170	3.9	10.3	8.0	9.1	104.4	0.14
3	189	3.6	5.9	7.0	11.7	113.4	0.21
4	190	3.2	6.9	10.3	10.9	57.6	0.14
5	208	4.4	12.6	12.1	10.3	88.5	0.12
6	212	3.8	9.7	9.5	10.9	47.7	0.18
7	224	5.3	9.7	10.5	11.2	117.5	0.15
8	228	6.2	13.2	12.1	10.3	85.2	0.15
9	232	5.3	13.5	15.6	10.2	122.5	0.19
10	235	5.7	10.5	11.4	8.7	102.1	0.16
11	236	5.2	10.5	14.7	10.5	62.1	0.19
12	255	5.2	13.1	10.5	11.5	195.4	0.19
Controls							
13	176	6.6	13.0	16.6	15.9	237.0	0.40
14	180	7.3	10.4	12.8	18.2	272.9	0.24
15	182	7.2	10.5	12.9	17.8	200.5	0.41
16	207	9.0	20.1	26.1	12.8	110.8	0.44
17	216	8.6	16.1	19.2	13.7	166.7	0.32
18	221	9.8	9.5	16.1	17.3	182.8	0.38
19	227	10.7	15.3	24.4	15.4	94.5	0.38
20	230	11.1	18.3	26.8	18.1	131.2	0.60
21	232	10.0	24.0	27.1	13.5	181.6	0.50
22	240	9.0	27.6	32.3	15.1	141.9	0.60
23	252	10.1	22.6	30.4	16.6	236.7	0.66
24	255	9.6	13.0	16.5	18.9	442.5	0.63
25	272	11.8	16.8	24.5	19.0	249.3	0.71

[a] BSP-Tm, biliary transport maximum for sulfobromophthalein; PCA, portacaval anastomosis.
[b] Mean of two 10-min collecting periods before infusion of BSP.
[c] Mean of the three 10-min collecting periods when BSP output remained practically constant.
[d] At midtime of the three sampling periods used to calculate Tm.

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