

Effects of Portacaval Shunt and Portacaval Transposition on Hepatocellular and Hepatic Reticuloendothelial Cell Activity in the Dog

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Quantitative reduction of portal blood flow following a portacaval shunt (PCS) adversely affects hepatocyte function, but does not alter HRES activity [L. P. Edgcomb, J. A. Knol, and F. E. Eckhauser. *J. Surg. Res.* 33: 233, 1982]. To determine whether similar changes occur after qualitative alteration of portal blood flow, portacaval transpositions (PCT) were constructed in six conditioned mongrel dogs. Estimated hepatic blood flow (EHBF) was determined scintigraphically by the rate of hepatic uptake of a 500- μ Ci dose of 99m Tc-sulfur colloid (Tsc). Hepatic reticuloendothelial cell (RES) phagocytic (PI) and degradative (DI) indices were calculated from the half-time blood disappearance of 131 I-labeled RES test lipid emulsion, and the half-time urine appearance of free 131 I, respectively. Opsonic activity (OI) was determined by gelatin latex particle agglutination and normalized to control values. Hepatocellular function was assessed by serial determinations of albumin (Alb), and pyruvic and glutamic oxaloacetic transaminases (SGPT and SGOT). All studies were performed prior to and at 3, 6, and 9 weeks following PCS or PCT. Conclusions: In the dog, neither PCS nor PCT adversely affected HRES activity. Hepatocellular function and OI remained unchanged following PCT but deteriorated significantly after PCS. Observed changes in hepatocyte function and OI following PCS suggest that hepatocellular integrity and serum opsonic activity may be interrelated.

INTRODUCTION

Child in the early 1950s stressed that liver regeneration following portacaval transposition and partial hepatectomy was related directly to maintaining the "quantity" of portal blood flow [8]. Bollman also described progressive hepatic atrophy and loss of functional reserve following portal diversion and attributed this to deprivation of portal blood [4]. In contrast, Fischer and others have recently reemphasized the importance of hormonal and other factors in portal blood in sustaining liver regeneration and functional integrity [8, 12, 13, 29].

Phagocytic and metabolic (degradative) functions of the hepatic reticuloendothelial system (HRES) have recently been shown to be unaffected by portal diversion despite

marked hepatocellular dysfunction [11]. It is common knowledge that blockage of the HRES may result from depletion of circulating serum opsonic proteins [21, 24] and marked decreases in both HRES activity and serum levels of opsonic protein have been demonstrated after surgery, trauma, burns, and hepatic failure [17, 22, 27]. However, it is not known how portal diversion affects serum opsonic activity or the functional state of the HRES.

The purpose of this study was to determine the acute effects of complete portal blood flow diversion (PCS) on hepatocellular and HRES structure and function. Portacaval transpositions (PCT) were created to determine whether qualitative alteration of portal blood flow had similar effects on hepatocellular and HRES parameters. Finally, an attempt was

made to relate observed changes in hepatocellular function to long-term alterations in serum opsonic activity.

MATERIALS AND METHODS

Eighteen mongrel dogs 10–30 kg body wt were maintained on standard kennel chow and water *ad libitum*. Each animal underwent serial determinations of liver function tests and (HRES), phagocytic (PI), and degradative (DI) indices as well as determinations of serum opsonic activity (OI), and estimated hepatic blood flow (EHBF).

Liver function was assessed by determining serum levels of glutamic oxaloacetic transaminase (SGOT), glutamic pyruvic transaminase (SGPT), total protein (TP), and albumin (Alb). Changes in protein subgroups were determined by protein electrophoresis.

HRES phagocytic and degradative activity was determined with a gelatinized RES test lipid emulsion technique developed by DiLuzio and Riggi [10] and described previously [11]. This test lipid emulsion has been shown to be taken up selectively by the reticuloendothelial system and 90% of the emulsion is removed by the Kupffer cell population in the liver [9].

Each animal received an intravenous dose of 150 mg/kg of anhydrous base equivalent emulsion containing 30 to 50 μCi of ^{131}I . Ten drops of Lugol's solution was administered to all test animals to prevent thyroid uptake of the radiotracer. The test lipid emulsion was administered intravenously over 60 sec to awake, restrained animals. Four milliliters of central venous blood was withdrawn every minute for 10 min then every 15 min for a total of 2 hr. One-milliliter aliquots of protein and lipid devoid supernatant obtained by trichloroacetic acid precipitation were saved for assay of free serum ^{131}I . Urinary output was collected at 15-min intervals and recorded for the 2-hr test period. One-milliliter aliquots from each 5-min collection period were saved for measurements of urine ^{131}I . Deiodination of phagocytized ^{131}I -labeled lipid particles re-

sults from HRES metabolic activity. Serum levels of free ^{131}I activity were measured. Fifteen-minute urine samples were also assayed to determine the rate of appearance of free ^{131}I .

Serum opsonic activity was determined according to the method of Check *et al.* [7] measuring the ability of serum samples to cause agglutination of gelatin-coated carboxy-latex particles in the presence of heparin. Activity indices varied widely among study animals. Therefore, values were normalized to control values and plotted as mean percentage activity versus time.

Estimated hepatic blood flow was determined scintigraphically by measuring the rate of hepatic uptake of a "subcritical" dose of 500 μCi of $^{99\text{m}}\text{Tc}$ -sulfur colloid (Tsc) [15, 19]. After rapid intravenous injection of Tsc, radioactivity was counted using a 2.5-cm diameter NaI gamma probe positioned externally over the animal's liver, and read on a Tracor Northern multichannel analyzer at 140 keV \pm 30% windows.

Six animals underwent end-to-side portacaval shunt (PCS), six underwent portacaval transposition (PCT), and six underwent periportal and caval dissection only (controls). All animals were studied preoperatively and at 3, 6, and 9 weeks postoperatively. At the completion of the study, each animal was given 1 mCi of Tsc intravenously over 5 min and sacrificed. A subsequent open liver biopsy was immediately fixed in 10% buffered formalin and 2% glutaraldehyde for light and electron microscopy, respectively. Exsanguinated liver, spleen, lung, and proximal femur bone marrow were weighed. Each tissue was assayed for radioactivity/gram tissue weight in a well scintillation counter at 140 keV \pm 10% window for $^{99\text{m}}\text{Tc}$. Tissue distribution was expressed as the percentage injected dose phagocytized per gram tissue for each organ (% ID/g) and per total organ (% ID/TO). Bone marrow was assumed to represent 2% body wt. All data was represented as $\bar{x} \pm \text{SD}$ and analyzed using Student's *t* and unpaired *t* tests. Preoperative data were compared to that ob-

tained at 3, 6, and 9 weeks following operation and to controls when appropriate.

RESULTS

Following operation, serum levels of SGOT increased significantly ($P < 0.05$) in the PCS group compared to either the control or PCT group. There was no significant increase in SGOT following PCT. Similarly, serum levels of SGPT were significantly elevated following PCS compared to controls at 3 and 6 weeks, but returned toward normal by 9 weeks postoperatively. In the PCT group, the SGPT elevations observed at 3 weeks were not significant compared to controls. In addition, SGPT levels in PCS animals were significantly elevated ($P < 0.05$) to those observed in PCT animals at both 3 and 6 weeks postoperatively.

Serum levels of total protein and albumin declined following PCS. Serum total protein was significantly decreased in the PCS versus PCT group by 6 and 9 weeks, and was significantly depressed compared to controls by 9 weeks postoperatively. Albumin levels in the PCS versus control groups were significantly depressed by 6 and 9 weeks postoperatively, and significantly depressed as compared to the PCT group by 9 weeks postoperatively. There was no observable change in either serum total protein or albumin in the PCT group compared to controls after the 9-week study period (Table 1). Serum levels of α_2 -proteins did not change significantly fol-

lowing either PCS or PCT compared to controls by 9 weeks postoperatively.

Intravenous dosages of RES test lipid emulsion were adjusted during the study according to animal weight; no significant changes in total dosage or animal weight were observed after PCS or PCT compared to controls. There was no significant change observed in the half-time blood clearance of lipid at 3, 6, or 9 weeks following PCS or PCT. Similarly, there was no change observed in the half-time urine appearance of free ^{131}I after PCS or PCT compared to preoperative or control values.

Opsonic activity represented as a percentage of preoperative activity declined after PCS. At 6 and 9 weeks following PCS, these values were significantly less than levels measured in control and PCT groups ($P < 0.01$ and $P < 0.001$, respectively). A 23% decrease in opsonic activity was observed in the PCT group at 9 weeks but this was not significant compared to controls (Fig. 1).

Estimated hepatic blood flow (EHBF) declined significantly by 3 weeks following PCS from 49.1 ± 3.5 to 26.9 ± 2.7 ml/min/kg body wt ($P < 0.005$). Following PCT, EHBF rose significantly from control preoperative values to 62.5 ± 10.5 ml/min/kg body wt ($P < 0.005$). Attempts to autoregulate or return EHBF to normal levels were not observed in either PCT or PCS groups. Once blood flow had restabilized by 3 weeks postoperatively, no significant variation occurred in subsequent measurements at 6 or 9 weeks (Fig. 2).

TABLE 1
EFFECT OF PORTACAVAL SHUNT AND PORTACAVAL TRANSPOSITION ON SERUM
TOTAL PROTEIN AND ALBUMIN LEVELS^a

	TP (3 weeks)	Alb (3 weeks)	TP (6 weeks)	Alb (6 weeks)	TP (9 weeks)	Alb (9 weeks)
Control	6.08 ± 0.33	2.40 ± 0.35	6.25 ± 0.92	2.58 ± 0.18		
PCS	5.70 ± 0.70	2.32 ± 0.23	5.35 ± 0.68†	2.10 ± 0.24*	5.45 ± 0.42*†	2.07 ± 0.19*†
PCT	6.43 ± 0.31	2.52 ± 0.30	6.45 ± 0.24	2.48 ± 0.37	6.65 ± 0.37	2.55 ± 0.15

^a Serum levels of total protein (TP) and albumin (Alb) are in mg/dl.

* $P < 0.05$, PCS versus control.

† $P < 0.05$, PCS versus PCT.

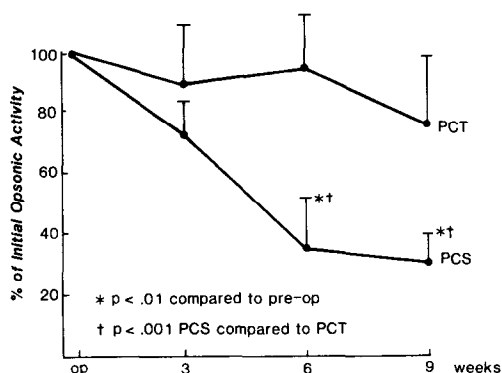


FIG. 1. Normalized serum opsonic activity declined gradually following PCT but by 9 weeks postoperatively was not significantly different than in controls. Corresponding serum opsonic activity following PCS was significantly reduced below preoperative and PCT values at 6 and 9 weeks, respectively.

There was no significant change in the organ weight-to-body weight ratio for liver, spleen, or lung following PCT. In contrast, the liver weight-to-body weight ratio following PCS decreased significantly compared to PCT ($P < 0.05$) and control ($P < 0.01$) groups. Similar changes were not observed for spleen or lung.

The organ distribution of phagocytized radiolabeled particles changed dramatically following PCT and PCS. Total liver radioactivity was significantly decreased after both PCS ($P < 0.01$) and PCT ($P < 0.05$). The 45% decrease in total liver radioactivity observed following PCS was significantly greater than that observed following PCT (33%, $P < 0.05$). Compared to controls or PCT, significantly greater amounts of phagocytized activity were found in spleen, lung, and bone marrow following PCS. Corresponding determinations of organ activity for spleen, lung, and bone marrow following PCT versus controls were not significantly different, but were significantly lower than similar values after PCS ($P < 0.05$) (Fig. 3). The tissue distribution of phagocytized activity following intravenous injection of 1 mCi of Tsc in the PCS group demonstrated a significant concentration of activity per gram tissue in both liver and spleen compared to control or PCT groups ($P < 0.05$). Following

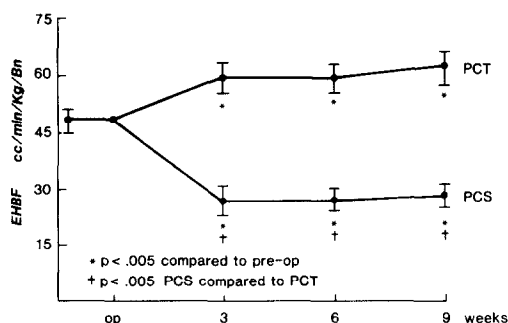


FIG. 2. Illustrates the significant fall in (estimated hepatic blood flow) EHBF following PCS and the significant rise in EHBF following PCT. Once new levels had been achieved, subsequent changes did not occur.

PCT no significant changes in the tissue concentrations of phagocytized activity were detected (Table 2).

Light and electron microscopy of liver from control animals was normal. In contrast, PCS and PCT caused demonstrable light and electron microscopic changes in liver morphology. Following both PCS and PCT, hepatocytes developed an eosinophilic, finely granular cytoplasm and appeared reduced in size. There appeared to be a greater loss of hepatocyte glycogen in the PCS group than in the PCT group. Dilatation of the hepatic sinusoids was observed following PCS and appeared to in-

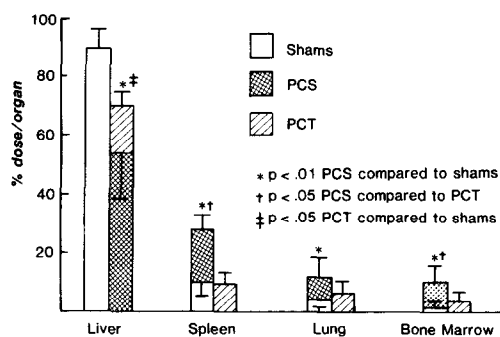


FIG. 3. Percentage tissue distribution of Tsc activity following PCS shows a significant shift away from liver to spleen, lung, and bone marrow. A similar but lesser reduction in liver activity was seen after PCT compared to controls. Spleen activity following PCT was similar to controls and both were significantly less than corresponding values after PCS.

TABLE 2
EFFECT OF PORTACAVAL SHUNT AND PORTACAVAL TRANSPOSITION ON TISSUE DISTRIBUTION
OF INTRAVENOUSLY INJECTED ^{99m}Tsc

Experimental groups	Liver		Lung		Spleen	
	%ID/g	%ID/TO	%ID/g	%ID/TO	%ID/g	%ID/TO
Control	0.14 ± 0.03	82.7 ± 6.3	0.07 ± 0.07	2.3 ± 1.3	0.05 ± 0.02	6.7 ± 2.7
PCS	0.23 ± 0.08*	53.4 ± 16.0*	0.01 ± 0.01	9.7 ± 8.0*	0.55 ± 0.23	26.8 ± 12*
PCT	0.11 ± 0.02†	67.2 ± 7.0† [∞]	0.01 ± 0.0	3.17 ± 2.5	0.03 ± 0.02†	3.6 ± 3.7†

Note. Tissue distribution data ($\bar{x} \pm \text{SE}$) were determined at 15 min after intravenous injection and expressed as percentage injected dose phagocytized per gram (%ID/g) and per total organ (%ID/TO).

* $P < 0.01$, PCS versus control.

† $P < 0.05$, PCS versus PCT.

[∞] $P < 0.05$, PCT versus control.

volve all three zones of the hepatic lobule. In contrast, only the central and terminal hepatic venule zones became dilated in the PCT group. In both PCS and PCT groups hepatic nuclei appeared variable in size. Kupffer cells in PCS livers were more abundant and contained more refractile amphophilic material as compared to PCT or controls.

Transmission electron microscopy demonstrated a significant reduction in hepatocyte glycogen following PCS. An intermediate loss of intracellular glycogen was noted in the PCT group. Mitochondria were more abundant in both groups compared to controls, but were more variable in size following PCS. Rough endoplasmic reticulum appeared less prominent and somewhat fragmented following both PCS and PCT, but these changes were most prominent after PCS. The Spaces of Disse were dilated in both groups, but increased collagen content in these spaces was found only after PCS. Following PCS, the Kupffer cells were markedly enlarged and contained abundant phagolysosomes filled with osmophilic debris. In contrast, after PCT, Kupffer cells were of more normal size and contained fewer phagolysosomes.

DISCUSSION

Early investigations of liver physiology stressed the importance of portal blood and hypothesized that hepatotrophic factors were

critical for normal hepatocellular regeneration [20]. Child and others later suggested that hepatic maintenance was determined not by trophic factors contained in portal blood but rather by total portal blood flow per se [8].

Although useful only as rough estimates of hepatic synthetic activity, serum levels of albumin and total protein remained near normal following PCT in the present study. Increased levels of SGOT and SGPT observed in the early postoperative period in PCS and PCT groups presumably represented a non-specific injury response to alterations in portal blood flow. The rapid return to normal of these values after operation and continued normal levels, especially after PCT, suggested restoration and maintenance of hepatocellular integrity. Serum total protein and albumin fell progressively in the PCS group, pointing to a defect in the liver's ability to synthesize these serum proteins. Transaminase levels in the PCS group were significantly elevated above control and PCT values in nearly all study periods. Presumably complete portal blood flow diversion had a long-lasting effect on hepatocyte integrity and function.

The liver weight-to-body weight ratio decreased significantly in the PCS group; this was not observed following PCT. After PCS there was significant microscopic evidence of hepatic atrophy with deglycogenation, loss of rough endoplasmic reticulum, and incomplete

restoration of hepatocellular mass. Although there was some loss of hepatocyte glycogen after PCT, the extent of loss was much less than after PCS and liver mass was better maintained. Maximum hepatocyte loss in PCT animals occurred mainly in the pericentral hepatic venous zone. Experimentally, acute diversion of portal blood flow in dogs results in hepatocyte loss and progressive hepatocellular dysfunction [4, 11, 20, 29]. These changes may be manifest long-term as organ atrophy and ultimately as hepatic failure resulting from organelle dysfunction. Our data would suggest that maintenance of total hepatic blood flow despite portal diversion can decrease the severity of morphological changes induced at both macro and microscopic levels.

Although estimated hepatic blood flow (EHBF) fell after PCS and increased sharply following PCT, estimated blood flow per gram of liver increased following both procedures. In fact, EHBF on a milliliter/minute/gram liver basis was similar between PCS and PCT groups. Following PCS the ratio of liver weight to body weight decreased by 38% compared to control and PCT ratios. These data suggest that maintenance of EHBF in the PCS group resulted from a reduction in perfused liver mass rather than from a compensatory increase in overall flow.

The total amount of radioactive tracer phagocytized by the liver decreased by 23 and 54% after PCT and PCS, respectively. There was no consistent increase in uptake in extrahepatic sites of reticuloendothelial activity such as spleen, lung, and bone marrow following PCT. In contrast, tracer activity in spleen and lung increased by 400 and 420%, respectively, after PCS (Table 1) and after PCS the percentage of injected Tsc per gram tissue increased in the liver by 39% despite a decrease in the ratio of liver weight to body weight. Acute portal diversion appeared to have a negligible effect on the hepatic RES system; in contrast, the marked decrease in liver weight/body weight and reduced serum protein levels observed after PCS were consistent with a defect at the hepatocyte level. Similar findings were not observed following PCT. The

10-fold increase in splenic tracer activity after PCS may simply be a manifestation of the "spillover phenomenon" described by Bradford [5] and Carr [6]. One would not expect this finding after PCT because hepatic blood flow and therefore colloid delivery remain normal. HRES extraction efficiency is determined largely by organ blood flow or the rate of delivery of particles to the macrophage system [3, 23, 24]. In fact, there is an inverse relationship between extraction efficiency and blood flow. The shift of Tsc activity to extrahepatic sites after PCT may also have been due to increased sinusoidal blood flow and therefore decreased extraction efficiency.

Recent work by Blumenstock and others [2, 3] has partially characterized serum opsonic factors which mediate RES clearance of blood-borne particulate matter. These substances appear to be glycoproteins, one of which may be identical to cold-insoluble globulin (CI_g) [25, 26] or fibronectin. CI_g is distributed in many tissues in bound and soluble forms and constitutes an important structural component of basement membranes [28]. High concentrations of this protein are also found along the sinusoids of the liver [28] and in tissue cultures of endothelial cells and can be demonstrated using immunofluorescent staining techniques on vascular endothelial surfaces [16, 18]. Although circulating CI_g and cell surface fibronectin appear to be antigenically similar, they may have distinctly different biologic roles [26].

In the present study serum opsonic activity decreased by 65% 6 weeks after PCS. In contrast, opsonic activity decreased transiently in the PCT group but stabilized at 77% of control values. These changes were accompanied by no measurable changes in the serum α_2 -protein levels as determined by serum protein electrophoresis in either PCS or PCT group up to 9 weeks after operation. The decreased levels of opsonic activity observed after PCS may have resulted from several factors. Progressive hepatocellular dysfunction may have led to decreased synthesis of α_2 -glycoprotein to a level insufficient for normal opsonophagocytosis. Alternatively, peripheral con-

sumption of opsonic proteins may have been increased because of iatrogenically induced portal-systemic shunting. Elevated peripheral levels of endotoxin or other potentially antigenic material which ordinarily would have been removed by the liver may have induced or contributed to this phenomenon.

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