Hemodynamic characterization of arterialized and nonarterialized liver transplants in the rat

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J Wong, Y Zhang, SS Lee. Hemodynamic characterization of arterialized and nonarterialized liver transplants in the rat. Can J Gastroenterol 2001;15(7):435-440. Persistent hyperkinetic circulation after liver transplantation has been described in humans, but similar changes have not been well characterized in the rat model. This study aimed to investigate the hemodynamics of the systemic and splanchnic circulations in both arterialized and nonarterialized hepatic allografts. Orthotopic liver transplantation was performed in four groups of Sprague-Dawley rats. Group A comprised sham-operated rats with hepatic artery ligation that did not receive transplants; group B comprised rats that received transplants without arterialization; group C comprised sham-operated rats with intact hepatic artery that did not receive transplants; and group D comprised rats that received transplants with arterialization. Blood flow measurements were performed three weeks after the surgical procedure, using the radioactive microsphere method. The results showed that rats that received transplants exhibited a significantly higher cardiac index and lower systemic vascular resistance than the control rats. Splanchnic hyperemia was also present with increased mesenteric blood flow. However, there was no difference in hemodynamics between rats that received arterialized transplants and those that received nonarterialized transplants. Arterial collateral vessels from adjacent tissues were observed in the nonarterialized grafts; this was confirmed histologically. It is concluded that rats that undergo orthotopic liver transplantation exhibit hyperdynamic circulation, regardless of the arterial reconstruction procedure, possibly due to extensive collateral formation in the hepatosplanchnic circulation.

Key Words: *Cardiovascular; Collaterals; Hepatic allograft; Hyperemia; Splanchnic hyperemia*

Caractéristiques hémodynamiques des transplantations du foie, avec ou sans reconstruction artérielle, chez le rat

RÉSUMÉ : La documentation scientifique fait état d'une circulation hypercinétique persistante après les transplantations du foie chez l'homme, mais les changements signalés ont été faiblement caractérisés chez le rat. La présente étude vise à mieux comprendre l'hémodynamique de la circulation générale et de la circulation splanchnique dans les cas d'allogreffe du foie, avec ou sans reconstruction artérielle. Nous avons pratiqué une transplantation orthotopique du foie dans quatre groupes de rats Sprague-Dawley. Le groupe A se composait de rats ayant subi une opération factice comportant la ligature de l'artère hépatique mais pas de transplantation du foie; le groupe B, de rats ayant reçu un foie sans reconstruction artérielle; le groupe C, de rats ayant également subi une opération factice mais sans ligature de l'artère hépatique ni transplantation du foie et le groupe D, de rats ayant reçu un foie avec reconstruction artérielle. Il y a eu mesure du débit sanguin trois semaines après l'opération selon la technique des microsphères radioactives. Les résultats ont révélé que les rats ayant subi une transplantation du foie avaient un index cardiaque significativement plus élevé et une résistance vasculaire générale significativement plus faible que les rats témoins. Nous avons également observé une hyperémie splanchnique, accompagnée d'une augmentation du débit sanguin mésentérique. Toutefois, aucune différence n'a été enregistrée quant à l'hémodynamique entre les rats ayant subi une reconstruction artérielle et ceux n'en ayant pas subi. Par ailleurs, nous avons noté la formation d'artères collatérales à partir des tissus adjacents dans les cas de greffe sans reconstruction artérielle, formation d'ailleurs confirmée à l'examen histologique. Aussi en arrivons-nous à la conclusion qu'une circulation hyperdynamique s'installe chez les rats ayant subi une transplantation orthotopique du foie, avec ou sans reconstruction artérielle, en raison peut-être de la formation importante de vaisseaux collatéraux dans la circulation hépato-splanchnique.

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Transplantation of the liver is an accepted mode of therapy for end-stage or acute fulminant liver disease. However, many aspects of hepatic transplantation physiology and pathophysiology remain poorly understood, and animal models of transplantation have been used extensively for experimental studies. The rat in particular has been widely used, with both arterialized and nonarterialized hepatic allografts described in this species (reviewed in 1). It is unclear whether the presence or absence of hepatic arterialization materially affects the local or regional hemodynamics. Furthermore, circulatory abnormalities, especially hyperdynamic circulation, in humans after transplantation have been described (2-6), and whether similar changes occur in rat models is controversial. The aims of this study, therefore, were to characterize the systemic and splanchnic circulation in rats with arterialized and nonarterialized hepatic allografts.

MATERIALS AND METHODS

The protocol was approved by the University of Calgary Animal Care Committee, and all animals received humane care in accordance with guidelines established by the Canadian Council on Animal Care. Male Sprague-Dawley rats (Charles River Canada) weighing 250 to 350 g were used as both donors and recipients and were subjected to one of four operations: either arterialized or nonarterialized liver transplantation, and their respective controls. The surgical technique employed was that described by Kamada and Calne (7,8) with minor modifications. The arterialized transplant grafts had a segment of aorta attached in an end-to-side manner to the recipient, as described by Zhao et al (9) to minimize the alteration of blood flow to other organs. All animals were fasted for 12 h before surgery.

Donor operation: The donor was anesthetized with intraperitoneal pentobarbital (50 mg/kg), and a midline abdominal incision was made. All ligamentous attachments around the liver were divided. The left phrenic, right adrenal and right renal veins were ligated. The portal vein was divided from the left gastric vein. The inferior vena cava was cleared from the connective tissues and dissected down to the left renal vein. The hepatic artery, celiac artery and abdominal aorta were cleared from all branches. The common bile duct was divided, and a 6 mm length of PE-50 tubing was inserted into the proximal end and secured by 5-0 silk suture. The animal was injected intravenously with 200 U of heparin in saline. The inferior vena cava and portal vein were then clamped. The liver was then flushed with 10 mL of cold (4°C) saline containing 50 U of heparin, through the aorta retrogradely. The portal vein, suprahepatic and infrahepatic vena cava were divided. The liver was removed from the donor into a 4°C saline bath.

Cuff preparation: The cuff for the portal vein (PE-240) and inferior vena cava (PE-280) consisted of a 0.3 cm length of tubing. The cuff preparation of both vessels was performed in the iced saline bath. With a clamp holding the tubing edge, a pair of fine forceps was used to pass the portal vein through the lumen of the tube and everted over it. The cuff was then secured with a circumferential 5-0 silk suture. The same method was applied to the inferior vena cava.

Recipient operation: The recipient was anesthetized with inhalant halothane. A midline abdominal incision was made. The left phrenic vein and right adrenal vein were ligated. The hepatic artery was ligated and divided. The bile duct was tied as close to the liver as possible. Isotonic saline (1 mL) was infused to compensate for blood loss. The infrahepatic inferior vena cava and the portal vein were clamped with microvascular clips. The suprahepatic vena cava was clamped by a teaspoon clamp. The vessels were divided and the recipient liver was removed. The donor liver was then placed in the orthotopic position immediately. The suprahepatic vena cava was first anastomosed end-to-end by 7-0 prolene continuous suture. The portal vein and infrahepatic vena cava were then connected to their corresponding cuffs by 5-0 silk ties. The vascular clamps were released after the connections were made. The bile duct was bridged by inserting the PE-50 tube into the recipient bile duct. Finally, end-to-side aorta-to-aorta anastomosis was performed by continuous 8-0 prolene suture under a dissecting microscope. The abdominal incision was closed with continuous 3-0 silk suture. The clamping time of the portal vein in all animals did not exceed 15 min.

The operation for nonarterialized grafts (Tx A–) was performed in the same manner except that the aortic segment was not anastomosed. Controls for the arterialized group (Sham A+) had ligation of the right adrenal and phrenic veins, and transection of hepatic nerves. Controls for the nonarterialized grafts (Shams A–) had the same procedures with the addition of hepatic artery ligation. Rats were then returned to their cages and allowed to recover. Operative mortality rates were approximately 10%.

Microsphere studies: Three weeks after the transplantation or control operations, cardiac output and regional blood flows were measured by radioactive microspheres and the reference sample method; the technique has been previously described in detail (10). In brief, rats were anesthetized with inhalant halothane, and PE-50 catheters were inserted into the femoral artery and left ventricle via the right carotid artery. The catheters were subcutaneously tunnelled to the dorsum of the neck and attached to a pressure transducer for arterial blood pressure monitoring. The incisions were treated with topical lidocaine 2% ointment and closed with silk sutures. The animals were then allowed to wake up in individual cages. Hemodynamics were measured when the rats had been fully conscious for at least 1 h, with complete stability of blood pressure and heart rate. No rat exhibited any behavioural signs of pain or stress.

For the hemodynamic study, a precounted aliquot of approximately 60,000 to 80,000 ^{113}tin-labelled microspheres of 16 µm diameter were injected into the ventricular catheter. The spheres were subsequently flushed with 0.6 mL of physiological saline. Starting 5 s before the injection, the reference blood sample was withdrawn from the femoral catheter via a withdrawal pump at 0.8 mL/min for 1 min. Immediately after the microsphere injections, the

TABLE 1
Systemic hemodynamics in rats that received liver transplants and control rats

	Group			
	Sham A– (n=7)	Tx A– (n=7)	Sham A+ (n=7)	Tx A+ (n=7)
Cardiac index (mL/min/kg)	335.7±17.0	463.7±35.8*	387.5±27.5	433.1±31.5
Mean arterial pressure (mmHg)	104±6	101±7	104±5	99±10
Systemic vascular resistance (mmHg·min·kg/mL)	0.31±0.02	0.20±0.02*	0.27±0.01	0.23±0.02
Heart rate (beats/min)	341±19	353±12	347±15	368±19
Renal blood flow (mL/min/kg)	53.2±6.2	64.2±17.7	56.1±10.3	67.7±6.4

*Values are means ± SEM. *Significantly different from nonarterialized shams, P<0.05. Sham A– Nonarterialized controls (hepatic artery ligated); Sham A+ Arterialized controls (hepatic artery intact); Tx A– Received nonarterialized transplants; Tx A+ Received arterialized transplants*

TABLE 2
Splanchnic hemodynamics in rats that received liver transplants and control rats

	Group			
	Sham A– (n=7)	Tx A– (n=7)	Sham A+ (n=7)	Tx A+ (n=7)
Portal pressure (mmHg)	7.0±1.0	8.8±2.8	8.0±1.3	9.6±0.8
Splanchnic blood flow (mL/min/kg)	71.4±6.5	117.7±14.0*	67.5±8.2	105.5±14.2†
PTBF (mL/min/kg)	54.9±3.2	89.3±8.6*	57.9±5.9	81.2±8.8†
PTBF/Cardiac index (%)	15.4±1.0	19.9±0.7*	15.2±1.2	19.0±1.2†

*Values are means ± SEM. Splanchnic blood flow = portal tributary blood flow (PTBF) + hepatic arterial blood flow. PTBF = stomach + spleen + intestine + colon + mesentery/pancreas flows. *Significantly different from nonarterialized shams, P<0.05; †Significantly different from arterialized shams, P<0.05. Sham A– Nonarterialized controls (hepatic artery ligated); Sham A+ Arterialized controls (hepatic artery intact); Tx A– Received nonarterialized transplants; Tx A+ Received arterialized transplants*

rats were reanesthetized with a small dose of sodium pentobarbital (4 to 6 mg) through the ventricular catheter, the abdomen opened through a small midline incision and portal pressure measured with a 23 gauge needle inserted through the superior mesenteric vein. The animals were then killed by an overdose of pentobarbital and the organs dissected for gamma-counting. Animals in which mixing was considered uneven, ie, with more than 15% difference in sphere counts between left and right kidneys, were rejected from further analysis.

Calculations: The cardiac index was calculated according to the following formula.

$$\text{Cardiac index (mL/min/kg body weight)} = \frac{(\text{counts injected/reference sample counts}) \times 0.8 \text{ mL/min}}{\text{kg body weight}}$$

Individual organ blood flows were calculated as follows.

$$\text{Organ blood flow (mL/min/kg body weight)} = (\text{organ counts/counts injected}) \times \text{cardiac index}$$

$$\text{Systemic vascular resistance (mmHg·min·kg/mL)} = \text{mean arterial pressure/cardiac index}$$

Portal tributary blood flow was calculated as the sum of stomach, spleen, intestine, colon and mesentery with pancreas flows. Splanchnic blood flow was calculated as the sum portal tributary flow and hepatic arterial flow.

Statistical analysis: The results are expressed as mean ± SEM. The data were analyzed by one-way ANOVA with a Newman-Keuls post hoc test. The significance level was set at P<0.05.

RESULTS

The systemic hemodynamics of rats with arterialized and nonarterialized grafts three weeks after the operation were generally very similar (Table 1). Cardiac index, mean arterial pressure, systemic vascular resistance and heart rate were not significantly different between the two types of grafts. Both groups that received transplants exhibited a higher cardiac index than their respective controls, although this difference reached statistical significance only in the group that received nonarterialized transplants. However, because both groups of controls and rats that received transplants had a similar cardiac index and systemic vascular resistance, a combined analysis was performed to determine the effect of transplantation on the systemic hemodynamics. Rats that received transplants (arterialized and nonarterialized) were compared with the controls (with and without hepatic artery ligation). Using an unpaired Student's *t* test, it was found that rats that received transplants had significantly higher cardiac index (451.1±24.3 mL/min/kg) than controls (363.1±17.4 mL/min/kg), and significantly lower systemic vascular resistance (0.22±0.01 mmHg·min·kg/mL) than the controls (0.29±0.01 mmHg·min·kg/mL).

Splanchnic hemodynamics showed no significant difference between the two groups that received transplants in terms of portal tributary flow and total splanchnic blood flow (Table 2). However, a significantly higher splanchnic blood flow was observed in the groups that received transplants than in the shams. In fact, in these animals that received transplants, the percentage of cardiac output going to the visceral organs was significantly increased. Portal

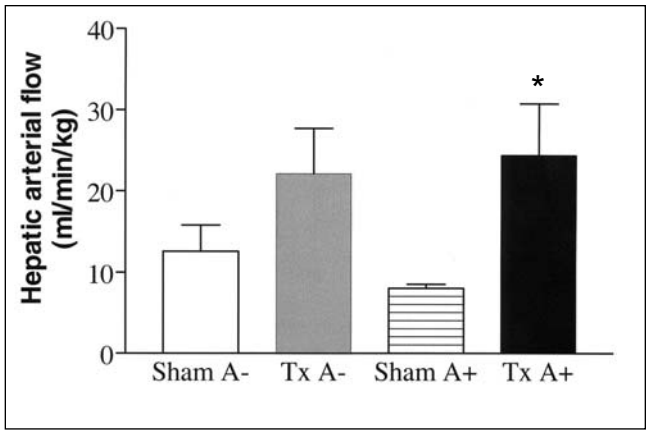

Figure 1) *Hepatic arterial blood flows in rats that received arterialized and nonarterialized liver transplants. Sham A– Nonarterialized controls (hepatic artery ligated); Sham A+ Arterialized controls (hepatic artery intact); Tx A– Received nonarterialized transplants; Tx A+ Received arterialized transplants. *P<0.05 compared with sham-operated controls*

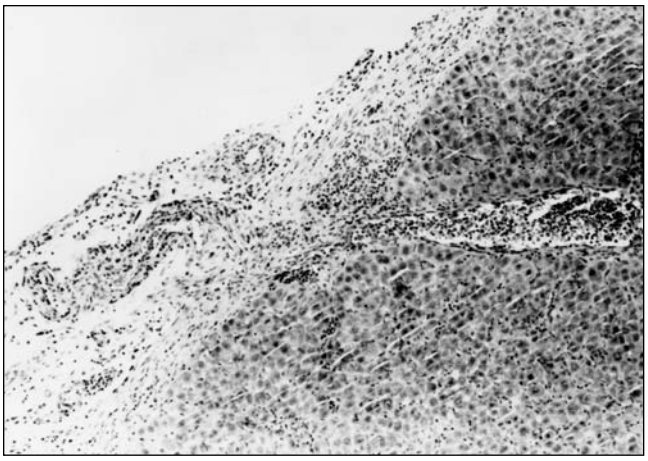

Figure 3) *Hematoxylin and eosin stain of a nonarterialized liver graft. A small vessel originating from the omentum is seen penetrating through the capsule into the liver parenchyma. Red blood cells are present within the arteriolar lumen*

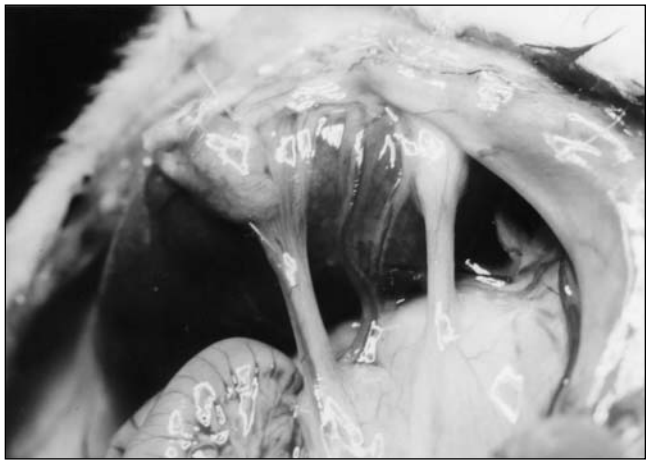

Figure 2) *Photograph of the abdominal cavity of a rat that received a nonarterialized liver transplant. Note the collateral vessels in the centre of the field, arising from the omentum and penetrating into the left lobe of the liver*

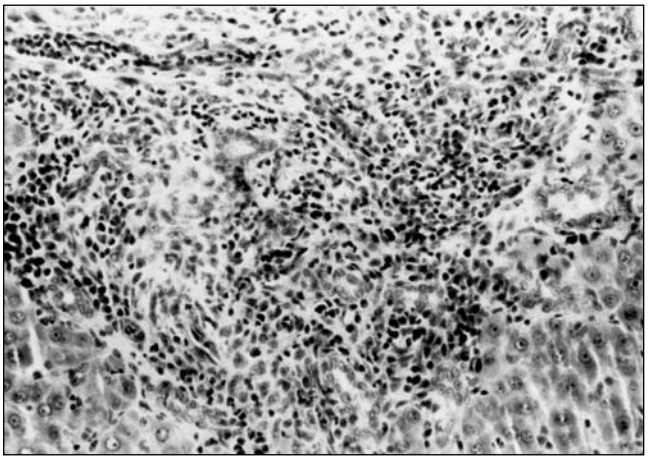

Figure 4) *Hematoxylin and eosin stain of a nonarterialized liver graft. Despite the neovascularization of arterial flow into the graft, the parenchyma still shows extensive portal mononuclear cell infiltration and bile ductular proliferation*

pressures did not differ among any of the four groups. The hepatic arterial blood flow in the arterialized group that received transplants was significantly higher than the sham-operated controls (Figure 1). Nonarterialized rats that received transplants also exhibited an increase in arterial flow into the liver compared with the shams, although a significant level was not reached.

The formation of arterial collateral vessels was confirmed by visual inspection (Figure 2). Small vessels from the omentum and peritoneal reflection penetrated the liver capsule into the parenchyma. These observations were further confirmed by microscopic histology of the liver surface (Figure 3). Despite the neovascularization of arterial flow into the nonarterialized liver graft, the parenchyma within a few millimetres of the capsule was still abnormal, with portal infiltrates and bile ductular proliferation (Figure 4). This contrasts with the normal histology from arterialized grafts (not shown).

DISCUSSION

Although these rat models of liver transplantation are widely used, there has been considerable controversy over the value of hepatic arterial reconstruction as part of the operation. The popularity of the nonarterialized allograft has been waning due to studies suggesting that arterialization is necessary to minimize biliary complications and improve general survival and hepatocellular function of the graft (1,11). However, other investigators have presented contradictory results (12,13). The present study demonstrates that hemodynamics are remarkably similar in the

arterialized and nonarterialized grafts, and suggests that occlusion of the hepatic artery per se is not associated with circulatory abnormalities in the rat model.

Several studies have shown that human liver transplantation is associated with persistent hyperdynamic circulation, even one to two years after successful grafting (2,3). However, in humans with cirrhosis, it appears that persistently increased flow through portosystemic collaterals and increased hepatic blood flow, with the implication that splanchnic visceral blood flow is increased, is mainly responsible for the persistence of hyperdynamic circulation. Moreover, direct measurement of total hepatic blood flow in human transplant recipients showed a persistently increased hepatic blood flow. The present study in rats suggests that this may be due to an increase in both mesenteric arterial (the portal tributary blood flow) and hepatic arterial inflows. In the present study, an increase in cardiac index was observed in rats after liver transplantation. In addition it was confirmed that splanchnic hyperemia was also present in rats that received transplants. Admittedly, direct clinical extrapolation from these rat models of transplantation to the human condition is hazardous. To date, no experimental animal models of transplantation have been reported that directly mirror the human situation, ie, transplantation of a healthy liver to replace the cirrhotic explant.

The issue of hyperdynamic circulation after liver transplantation in rats remains unsettled. There is some discrepancy in the literature, but we believe that this is explained by different timing of the hemodynamic studies. The present study, done three weeks after the operation, clearly showed a hyperdynamic circulation, even in the absence of significant portal hypertension. Our results agree with the work of Chaland and colleagues (14), who studied an arterialized hepatic allograft one week after transplantation and found hyperdynamic circulation. In contrast, Kuznetsova et al (15) showed portal hypertension and hyperdynamic circulation in rats 12 weeks after liver transplantation using the cuff method for portal vein and inferior vena cava anastomosis. Rats that underwent transplantation by using a suture method of anastomosis showed a normal circulation; thus, the authors concluded that the portal hypertension and hyperdynamic circulation were both caused by stenosis of the cuff lumens. Finally, Imamura and colleagues (16) examined the hemodynamics at 12 weeks in both arterialized and nonarterialized allografted rats, using the same sized cuffs that we and Kuznetsova et al (15) used. They found that, despite the presence of portal hypertension in all groups, hyperdynamic circulation developed only in a subgroup of nonarterialized rats that developed severe cholestasis and secondary biliary cirrhosis. Of note, no previous studies had examined the hemodynamics at any time periods between one week and 12 weeks after transplantation.

How can we reconcile these divergent previous findings with our current results? Despite using the same sized cuffs, we found no evidence of portal hypertension in any of our groups that underwent transplantation. Portal pressures were slightly and insignificantly higher in the rats that underwent transplantation than in the controls, and splenomegaly and ascites were not observed. Renal blood flows were also not significantly different from those of controls. Moreover, we demonstrated the patency of the cuffs at necropsy by passing a blunt-end probe through their lumens. We, therefore, presume that cuff stenosis occurs as a late complication somewhere between three weeks and three months after transplantation. We fully agree with the suggestion of Imamura and colleagues (16) that hyperdynamic circulation is not induced by the presence of portal hypertension or portosystemic collaterals, but rather by central neural factors. In that regard, we have previously demonstrated that afferent nervous signalling through capsaicin-sensitive pathways is abnormal in portal hypertension and cirrhosis, and that brainstem neuronal activation in the cardiovascular-regulatory nuclei such as the nucleus of the solitary tract, is necessary for the development of hyperdynamic circulation (10,17-19).

A major observation in the nonarterialized transplanted graft three weeks after the operation was the presence of arterial inflow into the liver. This was due to the recruitment of collateral vessels from the omentum, stomach, duodenum and retroperitoneum. It is interesting that this collateral circulation was eventually able to generate enough arterial flow to compensate fully for the lack of hepatic arterial supply. Similar extensive collateral vascularization has been described in the recipient liver with auxiliary heterotopic liver transplantation, although these collaterals were generally venous in origin (20). Svensson et al (21) also demonstrated hepatic arterial hyperemia 21 days after transplantation without arterial reconstruction, by angiographic means. The development of these collaterals in the present study may explain why nonarterialized grafts tend to function so well in some studies, with comparable rates of survival (8) and liver chemistry tests (22), as well as bile secretory function (23). Although this is a precarious speculation, perhaps similar collateral flow also occurs in humans and may explain why transplant recipients occasionally do well even with late occlusion of the hepatic artery.

Interestingly, rats appear to have impressive abilities to reroute circulation because not only rats that received nonarterialized liver transplants, but also control animals with hepatic artery ligation, were able to develop sufficient collaterals to eventually have enough arterial inflow to the liver to render them indistinguishable from nonligated controls. This agrees with many previous studies demonstrating that normal rats without transplants tolerate the hemodynamic consequences of hepatic artery ligation remarkably well.

Zhao and colleagues (9) also showed derangement of liver structure in the nonarterialized grafts compared with the arterialized ones. Although we did not detect quantitative differences in hemodynamics between these two groups, we confirmed the existence of abnormal hepatic histology in nonarterialized grafts, and agree that arterialization is preferable as a more clinically relevant experimental model.

In the present study, we chose to examine Sprague-Dawley strains rather than the inbred Lewis rats to mimic more closely the clinical situation in which modest rejection and portal cellular infiltrates are often present. Three weeks after grafting, no evidence of rejection was visible histologically in the arterialized grafts, whereas the nonarterialized grafts showed bile ductular proliferation and portal cellular infiltrate compatible with some degree of rejection. Similar changes were observed in the study by Zhao et al (9) in purebred Lewis strains that had no other evidence of rejection; therefore, we believe that these changes are secondary to bile duct damage secondary to an ischemic process rather than an immune-mediated rejection. On the other hand, rejection itself may cause endotheliitis and vasculitis, eventually leading to a pattern of bile duct injury indistinguishable from ischemic damage.

The effect of denervation of hepatic nerves on the hepatoportal hemodynamics is not fully understood (24), although the general belief is that hepatic innervation probably does not play a tonic role in the control of basal hepatic blood flow. The study by Wheatley et al (25) showed that four weeks after arterialized liver transplantation and seven days after chemical denervation, liver function and histological examination revealed no differences among transplant recipients, or denervated or sham-operated controls. Another study by Chan et al (26) also showed that biliary secretory function was not impaired after liver transplantation with its attendant denervation. In the present study, all animals undergoing surgery had their hepatic nerves transected, yet the rats that received transplants showed systemic and splanchnic hyperemia. Therefore, this argues against a role for hepatic denervation in the genesis of these circulatory changes associated with transplantation.

In summary, we showed that orthotopic liver transplantation at a relatively early stage is associated with hyperdynamic systemic and splanchnic circulations. However, there was no difference in hemodynamics between arterialized and nonarterialized liver grafts three weeks after the operation. The nonarterialized liver obtained adequate oxygenated blood by recruiting collaterals from adjacent tissues. The presence or absence of hyperdynamic circulation following liver transplantation may be dependent on the time after surgery when it is studied.

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