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Reversible hepatofugal portal flow after liver transplantation using a small-for-size graft from a living donor

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Abstract We describe a case of reversible hepatofugal portal flow 1 week after transplantation of a small-for-size liver graft from a living donor. A transient increase in intrahepatic portal vascular resistance was the suspected cause. The portal venous flow normalized after residual collateral channels had been interrupted surgically. The patient was discharged on the 90th postoperative day. Liver transplant clinicians should be aware that hepatofugal flow can occur with small-for-size liver grafts, despite sufficient portal venous flow immediately after transplantation.

Keywords Living related liver transplantation (LRLT) · Hepatofugal flow · Intrahepatic vascular resistance · Liver regeneration

Abbreviations *PT* Prothrombin time · *LRLT* Living related liver transplantation

Introduction

Living related liver transplantation (LRLT), an established treatment for children with end-stage liver disease, has recently also been performed in adults [11]. The physiological changes after small-for-size grafting are similar to those observed after hepatectomy, which leaves only a small remnant of the liver; however, transplant candidates with liver cirrhosis usually also have advanced portal hypertension before surgery. An experiment in rats has shown a transient increase in hepatic portal vascular resistance and transient narrowing of sinusoids after resection of two thirds of the liver [6].

We report a case of hepatofugal portal flow occurring 1 week after LRLT with a small-for-size graft [4]. A transient increase in intrahepatic portal vascular resistance was the suspected cause. Fortunately, portal venous flow recovered after residual collateral channels had been interrupted surgically. The patient was discharged on postoperative day (POD) 90.

Case report

A 53-year-old woman underwent LRLT for end-stage primary biliary cirrhosis. The patient's 25-year-old son was the donor. The recipient was 150 cm tall and weighed 48 kg. The donor was 162 cm tall and weighed 52 kg. Extremely large coronary and paraumbilical collateral veins were seen on pretransplantation imaging studies. Because the left liver of the donor was estimated to have a volume of 29% of the recipient's standard liver volume [16], the left liver (segments 2, 3, and 4) and the left caudate lobe (segment 1, the Spiegel lobe) were used for LRLT [13]. The left hepatic vein and the middle hepatic vein were included in the graft. The harvested graft, weighing 330 g, corresponded to 33% of the recipi-

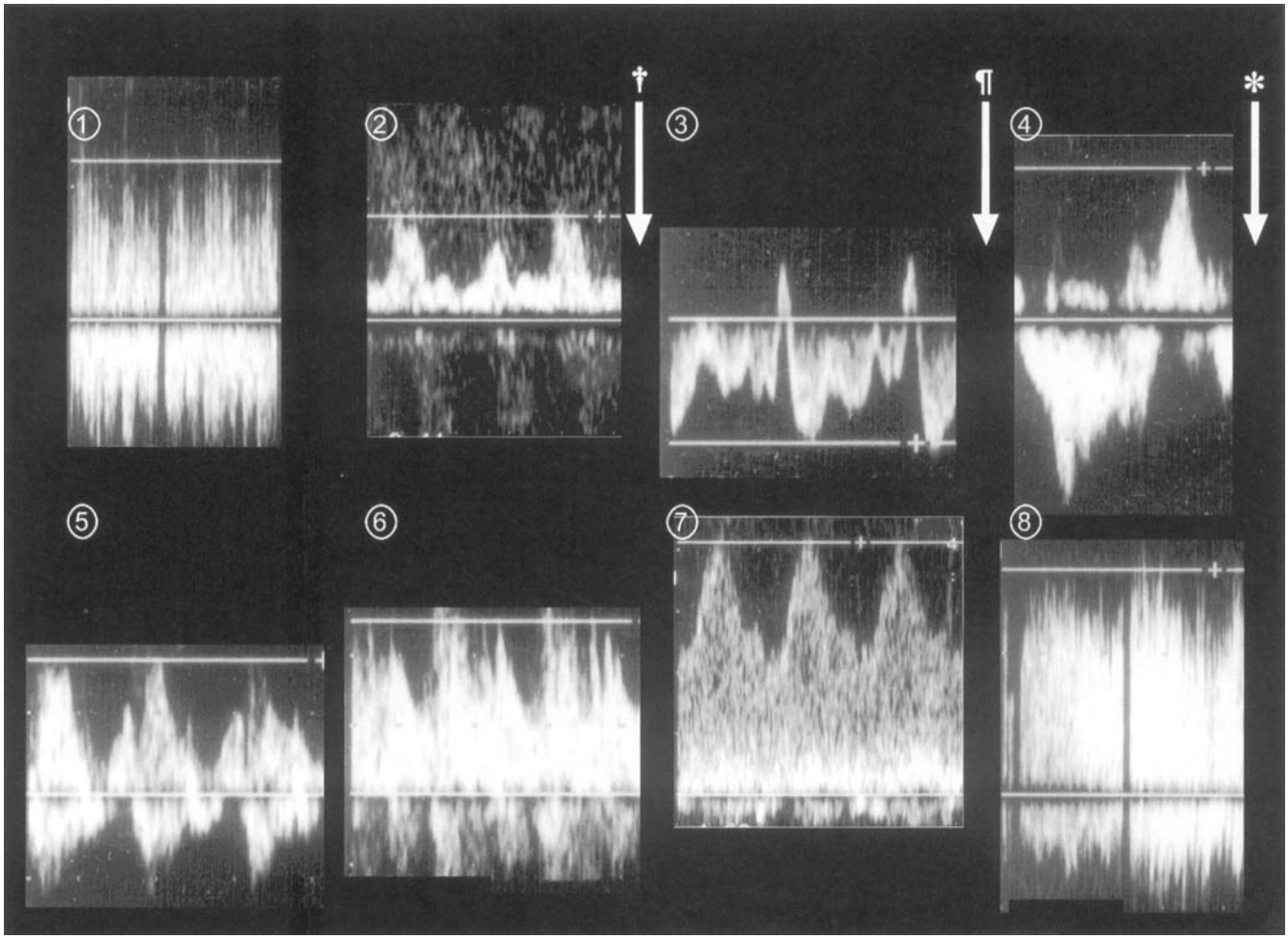

Fig. 1 Serial changes in waveform and peak flow velocity of the graft portal vein (umbilical portion) with Doppler US.

1 POD 1 The peak flow velocity was 59.4 cm/s.
2 POD 7 The peak flow velocity was 8.6 cm/s.
3 POD 8 The peak flow velocity was –7.8 cm/s (hepatofugal).
4 POD 9 The peak flow velocity was 12.6 cm/s (to-and-fro).
5 POD 10 The peak flow velocity was 16.3 cm/s.
6 POD 14 The peak flow velocity was 24.9 cm/s.
7 POD 28 The peak flow velocity was 41.1 cm/s.
8 POD 52 The peak flow velocity was 79.1 cm/s.
† lapalotomy, mobilization of the graft.
¶ splenectomy, ligation of collateral veins
* Embolization of the left gastric vein

ent's standard liver volume. Warm and cold ischemia times of the graft were 0 min and 88 min, respectively. The anhepatic period was 132 min. Blood loss in the recipient operation was 2463 g. Portal blood flow was evaluated with color Doppler ultrasound (US) as reported previously [5]. Hepatopetal portal blood flow at the umbilical portion of the graft was 46.6 ml/min per kg (peak flow velocity, 113 cm/sec) just after reperfusion.

After surgery, graft portal venous flow, hepatic venous flow, and hepatic arterial flow were routinely evaluated with color Doppler US twice a day. The portal blood flow of the umbilical portion was 34.8 ml/min per kg (peak flow velocity, 59.4 cm/sec) on POD 1 (Figure 1) but gradually decreased until POD 6. Hepatic venous flow had also decreased by POD 6, and its waveform had changed from triphasic to a continuous pattern by POD 7 (Figure 2). Hepatic arterial flow was maintained after surgery (Figure 3). Although the serum level of total bilirubin had decreased from 14.9 mg (POD 1) to 6.6 mg/dl (POD 5), it increased to 9.3 mg/dl on POD 6. A liver biopsy on POD 6 revealed significant hepatocyte regeneration. Neither acute cellular rejection (rejection activity index = 0) [1] nor hepatic veno-occlusive disease [3] was diagnosed (Figure 4).

On POD 7, portal venous flow decreased, and its waveform changed to the to-and-fro pattern (Figure 1). Laparotomy was performed because portal vein thrombosis was suspected, but no portal vein thrombosis was found. The transplanted liver was dark, swollen, and considerably more firm than at the time of transplantation. The portal venous flow increased with graft mobilization and fluid loading. On POD 8, hepatofugal flow in the main portal vein was observed with Doppler US (Figure 1). Splenectomy and ligation of the splenorenal shunt were performed, after which hepatopetal portal flow was observed. On POD 9 reversed flow at the portal trunk was again observed with Doppler US (Figure 1). Arterial portography revealed two large, spontaneous shunts: from the left gastric vein to the paraesophageal varices and from

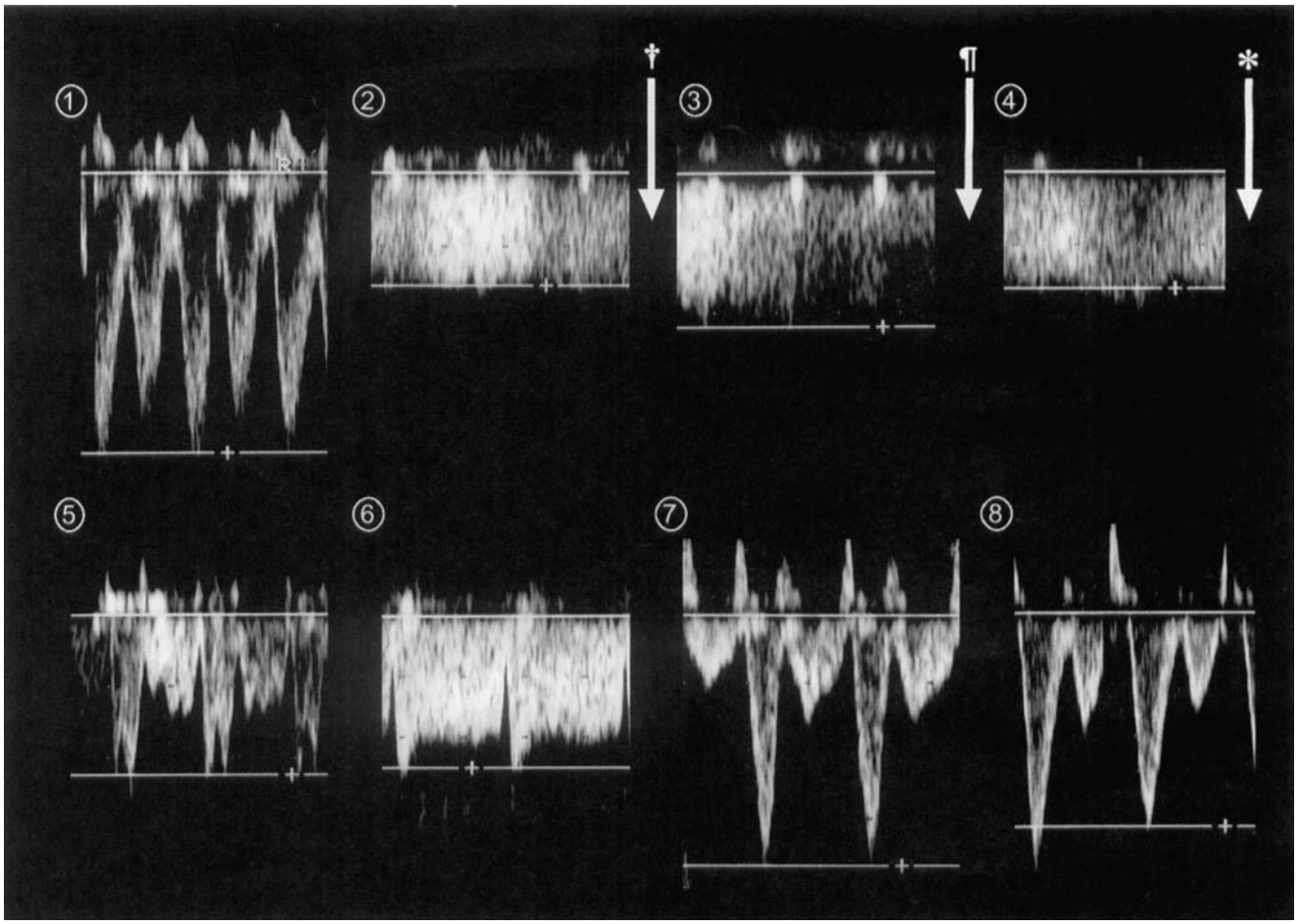

Fig. 2 Serial changes in waveform of a graft hepatic vein (middle hepatic vein) with Doppler US.
1 POD 1 The peak flow velocity was –76.2 cm/s (tri-phasic).
2 POD 7 The peak flow velocity was –6.2 cm/s (continuous).
3 POD 8 The peak flow velocity was –11.1 cm/s (continuous).
4 POD 9 The peak flow velocity was –16.1 cm/s (continuous).
5 POD 10 The peak flow velocity was –22.6 cm/s (continuous).
6 POD 14 The peak flow velocity was –25.3 cm/s (continuous).
7 POD 28 The peak flow velocity was –35.9 cm/s (tri-phasic).
8 POD 52 The peak flow velocity was –87.8 cm/s (tri-phasic)

retroperitoneal collaterals to the left ovarian vein. In addition, computed tomography (CT) during arterial portography showed poor parenchymal enhancement in the graft (Figure 5 upper). To maximize portal inflow to the graft, the left gastric vein was embolized with metallic coils through the inferior mesenteric vein. In addition, the retroperitoneal collaterals to the left ovarian vein were ligated. The portal venous pressure increased to 30 mm Hg after these procedures. In addition, to exclude hepatic vein anastomotic stenosis, the pressure gradient between the intragraft hepatic vein and the inferior vena cava was directly measured with a catheter. The pressure in the vena cava and in the graft hepatic vein was 0–3 mm Hg; no pressure gradient was found. Other possible causes of hepatofugal flow, such as kinking or stretching of the reconstructed portal vein or the arterioportal fistula [8], were ruled out with Doppler US and by intraoperative findings.

As evidence for graft injury, the level of serum aspartate aminotransferase (AST) reached a first peak of 149 IU/L on POD 1, but had normalized by POD 7. The level of AST reached a second peak of 281 IU/L on POD 8 but had normalized by POD 12. As a reflection of the synthetic function of the graft, prothrombin time (PT) improved gradually from 17.0 s (33.8%) on POD 2 to 11.6 s (83.9%) on POD 13, when it was considered normal.

Thereafter, the portal venous flow gradually increased, but its waveform was pulsatile (Figure 1). A CT scan performed on POD 31 showed that the graft had increased in volume to 887 ml and was almost uniformly enhanced (Figure 5 lower). By POD 52, portal venous flow had increased to 79.1 ml/s, and the wave form had changed to a continuous pattern at the umbilical portion of the left portal vein of the graft (Figure 1) A considerable amount of ascitic fluid and a pleural effusion (1000 to 2000 ml/day) were observed until POD 60. The patient was discharged with normal graft function on POD 90. The patient has a high social rehabilitation status and visited the outpatient clinic 21 months after undergoing transplantation.

Discussion

Fujimoto et al have suggested that patient collaterals should be ligated during LRLT in patients with a portal

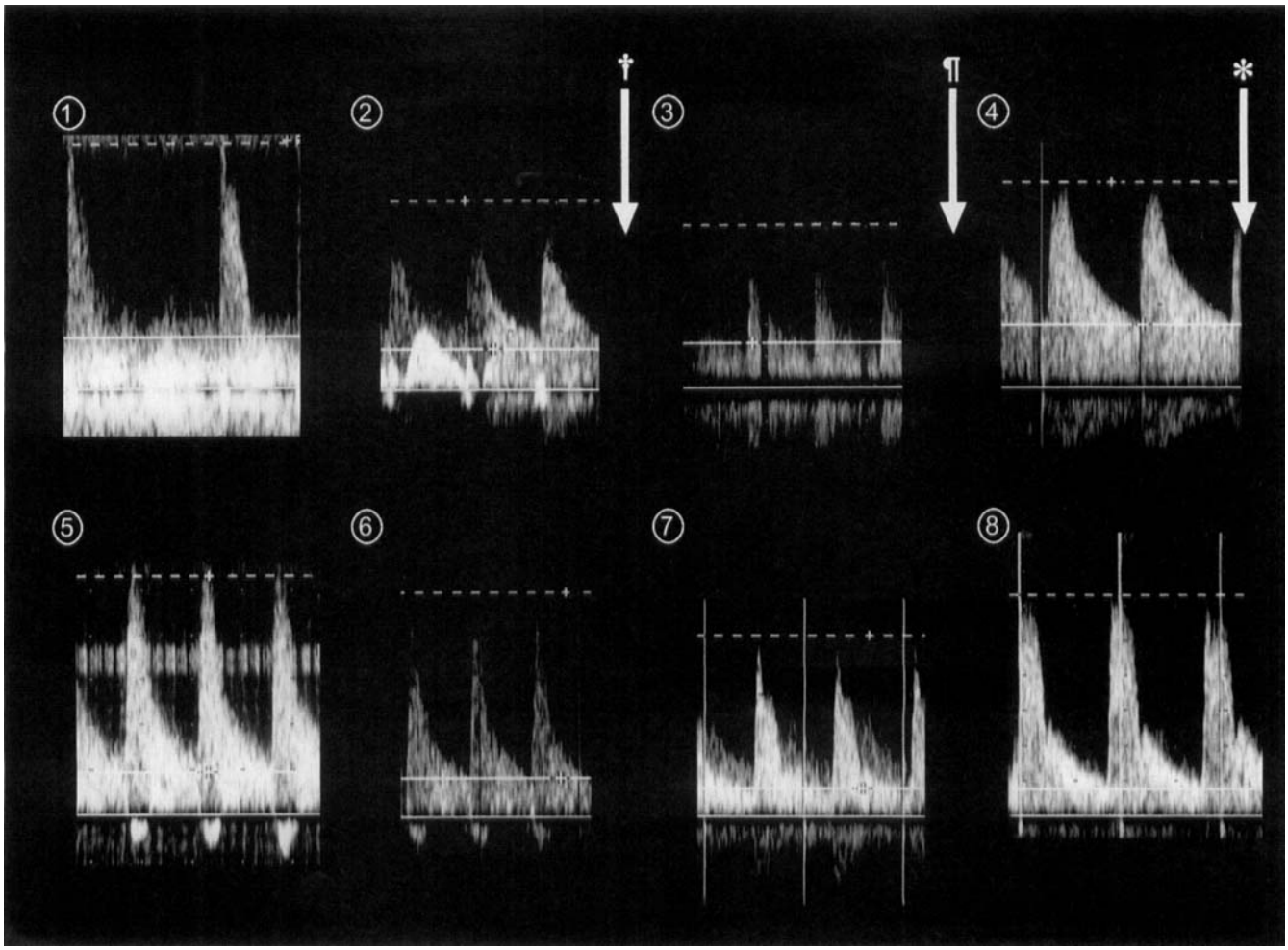

Fig. 3 Serial changes in waveform of a graft artery (A3) with Doppler US. The serial number corresponds to those of the portal vein and hepatic vein

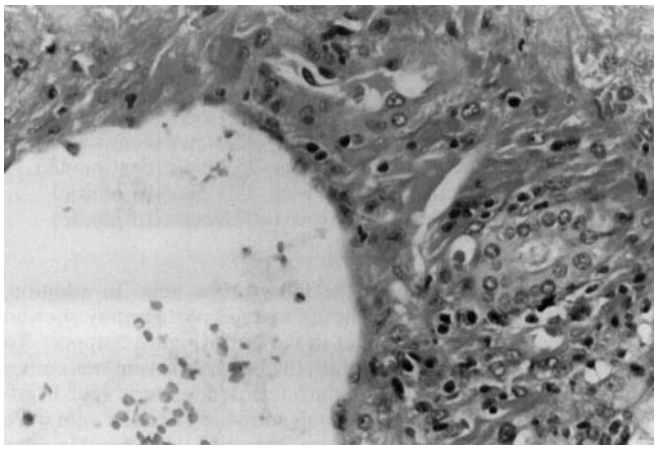

Fig. 4 Histological features of a liver biopsy obtained on POD 6 (HE × 100). No evidence of acute cellular rejection was found

blood flow less under 10 ml/min per kg [5]. In our patient, hepatofugal portal flow was observed 1 week after transplantation, although sufficient portal venous flow (46.6 ml/min per kg) was observed just after reperfusion.

Liver transplantation with a full-size cadaver donor graft promptly resolves hemodynamic changes due to portal hypertension by interposing a new, adequately-sized graft with normal vascular resistance between the splanchnic and systemic circulations [15]. In contrast, splanchnic pooling of blood may be more or less continuous after LRLT with small-for-size grafts. Physiological and metabolical changes associated with rapid liver regeneration after this procedure are compatible with those after extensive hepatic resection. Nagasue et al [14] has reported substantial increases in portal vein

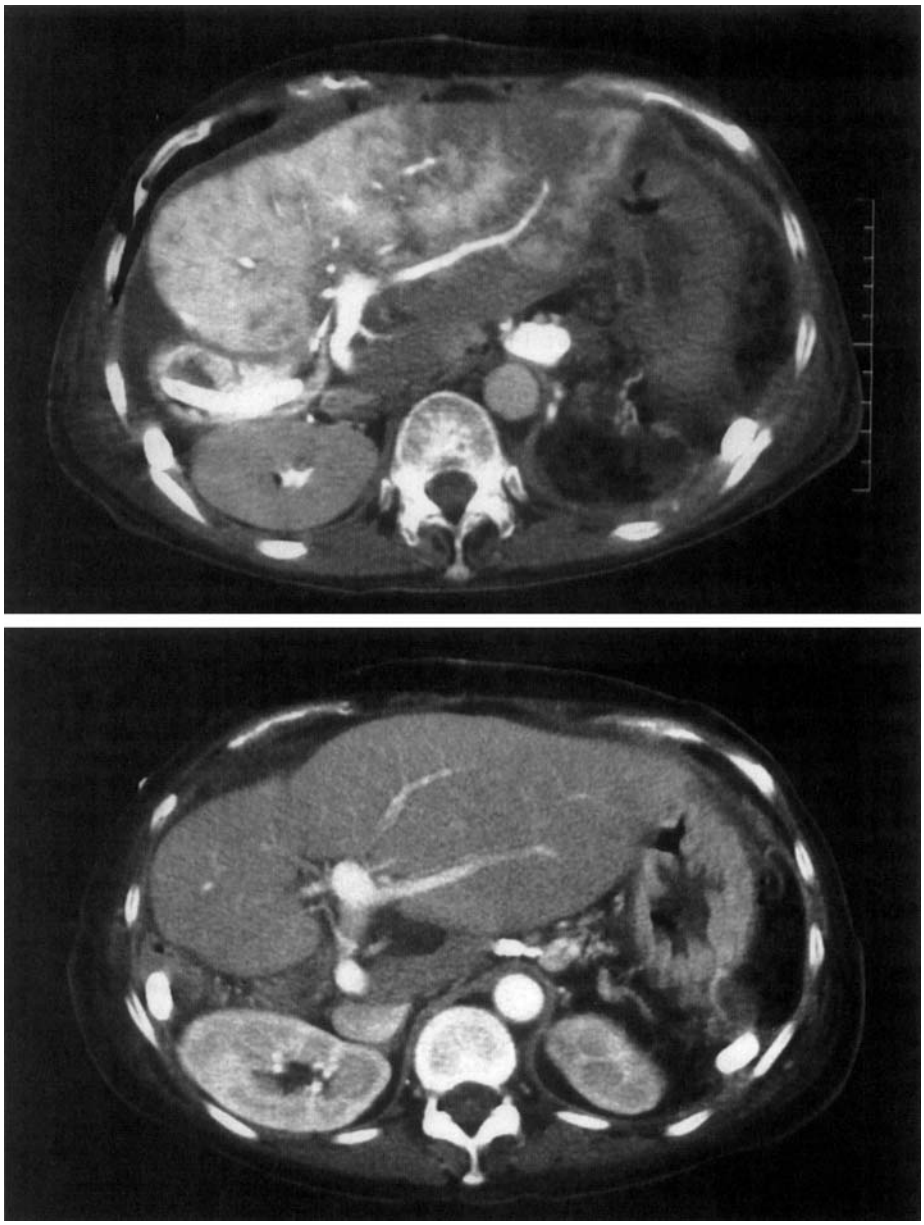

Fig. 5 A CT scan during arterial portography on POD 9 (*upper*) and a CT with contrast enhancement on POD 31 (*lower*)

pressure in 17 of 18 patients, regardless of the presence or absence of cirrhosis, after resection of more than 30% of the liver. Kanematsu et al [9] have also reported significant increases in portal pressure in 17 patients with cirrhosis and 14 patients without cirrhosis after resection of more than 30% of the liver.

Like liver remnants after extensive hepatic resection, small-for-size grafts are exposed to excessive portal blood flow (portal hyperperfusion). Portal hyperperfusion may cause graft dysfunction. Ku et al [12] have suggested that acute portal hypertension of the liver is harmful but they have also reported improved results with portal decompression in a canine quarter orthotopic liver transplantation model. However, in our present case, the hepatopetal flow was sufficient both at reperfusion and soon after transplantation. Therefore, acute portal hypertension did not occur early after transplantation.

The cause of hepatofugal blood flow in our patient might have been a transient increase in the vascular resistance of the graft. The most common cause of portal hypertension occurring 1 week after transplantation is acute rejection. Hadengue et al [7] have reported that portal pressure increases sharply during rejection episodes but subsides after treatment. DeCarlis et al [2] have also reported a "steal phenomenon (hepatofugal

flow)" through large patent shunts during three acute rejection episodes, possibly because increases in intrahepatic vascular resistance due to inflammation in the portal triad diverted blood flow from the graft. In our patient, however, no evidence of acute rejection was found on a liver biopsy on POD 6.

Another possible cause of increased vascular resistance in a small graft is rapid regeneration. Livers from small donors transplanted into larger recipients undergo hypertrophy and hyperplasia until their volume is appropriate to the recipient [10, 17]. Gertsch et al [6] have reported that hepatic portal resistance increased, reaching maxima 3 and 7 days after a two-thirds hepatectomy in rats, but returned to baseline values after 56 days. Furthermore, the width of the sinusoid was lowest 3–7 days after hepatectomy but returned to nearly to baseline values within 56 days after hepatectomy. These findings suggest that rapidly regenerating hepatocytes may compress the hepatic sinusoids, thereby further enhancing portal hypertension during early liver regeneration.

In conclusion, liver transplant clinicians should be aware that hepatofugal flow can occur with small-for-size grafts, despite sufficient portal venous flow just after transplantation. However, hepatofugal flow can be successfully treated by occluding major portosystemic shunts.

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