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The role of spontaneous portosystemic shunts in the course of orthotopic liver transplantation

Luciano De Carlis[1], Ernesto Del Favero[1], Gianfranco Rondinara[1], Luca S. Belli[1], Cosimo V. Sansalone[1], Bruno Zani[1], Alberto Cazzulani[2], Giorgio Brambilla[2], Antonio Rampoldi[2], and Lino Belli[1]

[1] Department of Surgery, Transplantation Unit, "Pizzamiglio 2'", and [2] Institute of Radiology, Niguarda Hospital, I-20162 Milan, Italy

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Abstract. Spontaneous portosystemic shunts are commonly found in cirrhotic patients. Not yet established is their role after orthotopic liver transplantation (OLTx), especially when an increase in portal pressure develops, as during early acute rejection. In this study, 34 cirrhotic patients in a series of 70 OLTx are considered. Each patient had preoperative angiographic assessment, and, in 21 (62%), large spontaneous portosystemic shunts were evident. In 12 cases the shunts were not affected by the surgical procedure and were present during the postoperative period; in 9 the hepatectomy itself involved interruption of the shunts. The patient population was divided into two groups: patients with postoperative shunts ($n = 12$) and those without ($n = 22$). The two groups were similar in age, sex, Child's stage, transplantation variables, and number and grade of rejection episodes. However, mean transaminases (AST) values in the first 2 weeks were significantly higher levels in shunt versus nonshunt patients (421 ± 335 vs 183 ± 126; $P < 0.025$), and this was even more evident when rejection occurred (626 ± 375 vs 195 ± 129; $P < 0.001$). Furthermore, during an acute rejection reaction, three cases showed a true "steal phenomenon" through the large reopened shunts with ischemic damage to the grafts. The data indicate a possible detrimental effect of the spontaneous shunts on graft perfusion and suggest the prophylactic surgical interruption of the residual shunts during the transplantation.

Key words: Liver transplantation, portosystemic shunts – Portosystemic shunts, liver transplantation

An almost constant feature of portal hypertension is the spontaneous diversion of portal blood flow through a wide variety of collateral vessels that bypass the liver into the systemic circulation. The esophageal and periesophageal plexus represent the main routes of diversion. Reopened embryonic channels provide an alternate outflow in approximately 9%–14% of all patients [1, 6, 8, 13].

Offprint requests to: L. De Carlis

These collateral vessels sometimes have a very large caliber, thus draining a significant amount of blood out of the cirrhotic liver. In advanced stages, portal flow becomes hepatofugal and may determine a 'steal phenomenon' with a dramatic decrease in hepatic perfusion.

The possibility of blood diversion with its negative effects on liver function is well known and justifies the new trends in surgical management of portal hypertension that recommend a selective, extended interruption of the main portal-mesenteric collaterals in order to preserve portal prograde flow in Warren's operation [9].

Also, in the field of liver transplantation, attention has been focused on the probable detrimental effects of previous surgical splenorenal shunts on graft perfusion when an increase in vascular resistances occur within the new liver [7]. In fact, after orthotopic liver transplantation (OLTx), collateral channels virtually disappear by removing the cirrhotic liver, which represents an obstacle to portal circulation. Some conditions, however, such as rejection, severe ischemic damage, and fluid overload, may cause portal hypertension with reopening of the spontaneous shunts and diversion of blood away from the liver.

The purpose of the present paper is to analyze the role of spontaneous portosystemic shunts on the outcome of liver transplantation and, on the basis of the postoperative course of three patients in our series in whom an evident clinical and radiological "steal phenomenon" has been observed, to propose surgical prophylactic management of these shunts.

Materials and methods

From January 1987 to April 1990, 70 OLTx were performed in our department on 62 patients with end-stage liver disease. Indications for liver grafting are shown in Table 1.

All but ten patients were preoperatively assessed with selective coeliac superior mesenteric arteriography with late-phase portal venography.

Five patients with the diagnosis of fulminant hepatic failure were referred to our center from other institutes when a donor was available and there was no time for routine angiographic evaluation. In

Table 1. Indications for orthotopic liver transplantation. PBC, Primary biliary cirrhosis; HCC, hepato cellular carcinoma

Cirrhosis	33
PBC	1
HCC in cirrhosis	12
Cholangiocarcinoma	6
HCC in normal liver	2
Other hepatic tumors	3
Fulminant hepatic failure	5
Retransplantation	8
Total	70

Table 2. Classification of rejection on liver biopsies

	Infiltrates	Canalicular lesions	Endothelitis
Mild	+ +	< 50%	−
Moderate	+ + +	> 50%	±
Severe	+ + +[a]	> 50%	+ +

[a] Panlobular infiltration with initial ischemia and necrosis

Table 3. Distribution of the study population across three groups according to angiographic findings. A, Highly situated coronary vein + short gastric veins; B, juxtaduodenal coronary vein + short gastric veins; C, inferior mesenteric vein; D, umbilical vein; E, splenorenocaval inflow

Group 1	Group 2	Group 3
1) OLTx 4	1) OLTx 10 A	1) OLTx 20 B
2) OLTx 7	2) OLTx 11 A	2) OLTx 23 B
3) OLTx 12	3) OLTx 26 D	3) OLTx 28 B
4) OLTx 13	4) OLTx 37 D	4) OLTx 29 B + E
5) OLTx 14	5) OLTx 45 A + D	5) OLTx 32 B + E
6) OLTx 27	6) OLTx 48 D	6) OLTx 33 B + D
7) OLTx 36	7) OLTx 52 A	7) OLTx 34 B + C
8) OLTx 43	8) OLTx 55 A + D	8) OLTx 35 A + C + D
9) OLTx 46	9) OLTx 68 A	9) OLTx 38 B + E
10) OLTx 50		10) OLTx 39 B + D
11) OLTx 58		11) OLTx 44 B + E
12) OLTx 62		12) OLTx 49 B + C
13) OLTx 66		

the other five patients, severe hepatorenal failure contraindicated arteriography and a Doppler scan was used to assess vascular anatomy. Of the 52 patients submitted to angiographic evaluation, 13 were excluded from this study because of the absence of portal hypertension (hepatic tumors), 2 because their courses were complicated by early vascular problems, and 3 due to death in the immediate perioperative period.

The angiograms of the remaining 34 patients were retrospectively and accurately reviewed together with a trained vascular radiologist for the purpose of detecting type and size of the preoperative, spontaneous portosystemic shunts, and they were compared, when available, with post-transplant findings in order to verify the changes that had occurred after OLTx. Arteriographic postoperative studies were not performed routinely but only when vascular complications were suspected.

Patients were divided into three groups according to the arteriographic findings. In group 1 there was no angiographic evidence of large portosystemic collectors (> 5 mm) nor of multiple, smaller shunts having the same hemodynamic effect; in these cases, only mild portal hypertension was present. In group 2, portosystemic collaterals were angiographically well expressed but all were interrupted during the hepatectomy. In these cases, the shunts were present through the umbilical vein or through a highly situated coronary vein. In group 3 there was evidence of large venous collaterals that the transplant procedure itself does not usually affect. This occurs when the shunts are formed by the inferior mesenteric vein, the juxtaduodenal coronary vein, or by direct inflow into the inferior vena cava via the left renal vein (spontaneous shunts from the splenic or mesenteric region).

The magnification of the radiographic pictures was the same, as all examinations were performed in the same institute by only two vascular radiologists.

The donor and recipient operations were performed according to the techniques described by Starzl and his team [12]. Belzer's UW solution for cold organ storage was used, starting with OLTx no. 30. Donor-recipient AB0 compatibility was observed in all the cases studied, as were negative crossmatch tests.

Initially, immunosuppression was maintained with cyclosporin and steroids. Starting with OLTx no. 30, a triple-drug therapy was adopted including cyclosporin, azathioprine, and steroids. Rejection episodes were treated with steroid boluses (1 g Solu-Cortef on days 1, 2, and 3, plus 500 mg on days 5 and 7) and, if unresponsive, with administration of OKT3 monoclonal antibodies (5 mg daily) for 10–14 days.

Hepatic biopsies were performed at regular intervals during the postoperative course on days 0, 7, 14, and whenever complications were suspected.

Acute rejection was diagnosed when infiltrates in the portal triads, vacuolar lesions of biliary epithelial cells, and endothelitis were present, in varying degrees, in liver biopsies. Rejection was described as "mild", "moderate", or "severe", according to the criteria shown in Table 2.

Mean values of transaminases (AST), total bilirubin, and prothrombin time were considered between the 1st and the 14th postoperative days and compared within each group of patients.

Statistical analysis was done using Student's *t*-test; statistical significance was assumed when $P < 0.05$.

Results

All principal collateral pathways of blood outflow from the portal to systemic circulation, with relative incidence in our series, are represented in Fig. 1.

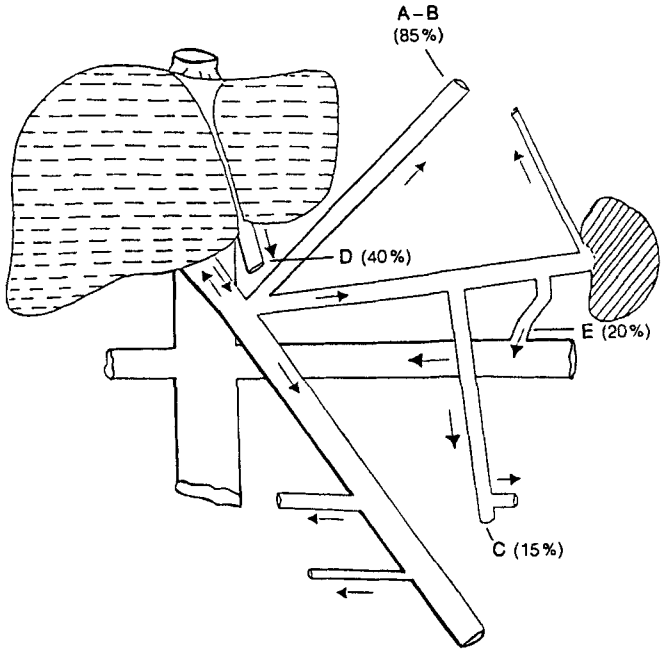


Fig. 1. The main collateral pathways of blood outflow from the portal to systemic circulation in cirrhotics and their relative incidences in the patients included in this study. *A–B* Coronary vein + short gastric vessels; *C* inferior mesenteric vein; *D* umbilical vein; *E* splenorenocaval shunts

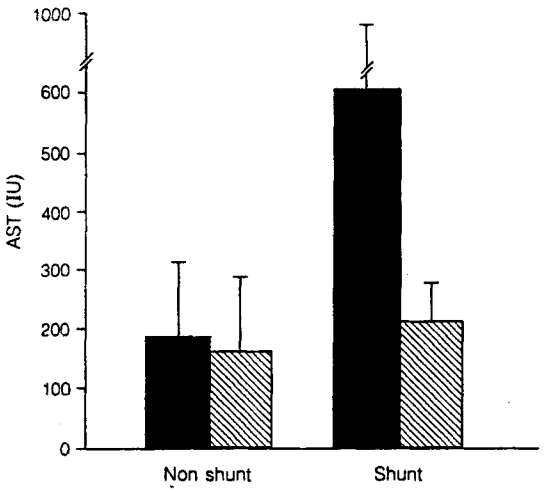


Fig. 2. Mean AST profiles from 1st to 14th day after OLTx in patients with and without postoperative spontaneous shunts. There is a significant difference between the two groups in cases where acute rejection has occurred ($P < 0.001$). ■ Rejection; ▨ no rejection

Table 3 shows the study population, which was divided on the basis of the angiographic findings into the three groups previously described. There were 13, 9, and 12 patients in groups 1, 2, and 3, respectively. The last group, in particular, included 35% of the patient population.

In Table 4, the angiographic data and the clinical courses of group 3 patients are reported. No patient submitted to angiography experienced complications related to the procedure, except for groin hematoma in six cases.

The three groups were statistically comparable with respect to age, sex, Child's stage, graft ischemic lesions (i.e., AST values > 1000 IU in the immediate postoperative period), use of UW cold storage solution, and number and grade of rejection episodes. No significant differences were found when the same parameters were compared between group 3 and groups 1 and 2 together (i.e., between patients in whom the shunts were or were not present in the post-transplant period; P = NS; Table 5).

In particular, a biopsy-proven acute rejection was evident in 6 out of 12 shunt patients (50%) and in 12 out of 22 nonshunt patients (54.5%) during the first 2 weeks after transplantation. Rejection reactions in the shunt population were considered mild in two cases, moderate in two cases, and moderate-to-severe in the last two cases (Table 4), while in nonshunt patients they were mild in five cases, moderate in three, moderate-to-severe in three, and severe in one. No correlation was found between severity of rejection in the two groups of patients and AST levels.

The use of double or triple drug immunosuppressive treatment had no influence on the results since the ratio between the two protocols was respectively 8:14 in nonshunt and 4:8 in shunt patients (P = NS).

When considering AST profiles in the first 2 postoperative weeks, significant differences were found between the shunt and nonshunt populations; (421 ± 335 vs 183 ± 126, respectively; mean ± SD, $t = 2.35$, $P < 0.025$). Also significant was the comparison between the two subgroups of patients (shunt vs nonshunt) in which a biopsy-proven rejection was present (626 ± 375 vs 195 ± 129, respectively; mean ± SD, $t = 2.72$, $P < 0.001$) (Fig. 2). No statistical differences were found in bilirubin or prothrombin time profiles between the two groups and subgroups of cases (P = NS).

Three patients in group 3 require a separate description.

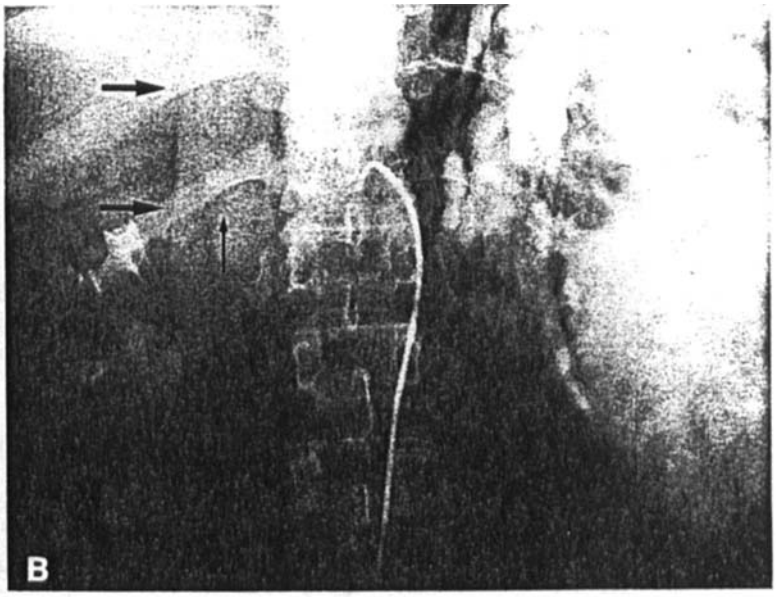
OLTx no. 29

This was a 36-year-old male, affected by hepatocellular carcinoma in posthepatitis cirrhosis. Preoperative angiography revealed a large splenorenal shunt (Fig. 3). An angiographic study on the 1st postoperative day, performed to rule out vascular problems, showed disappearance of the preoperative shunt (Fig. 4). On the 6th day, a moderate-to-severe rejection became evident on liver biopsy, and ischemic damage to the graft was soon evidenced by high AST levels (Fig. 5). Further SMA arteriography demonstrated the reopening of the shunt and the lack of liver perfusion during the late venous phases (Fig. 6). The patient died on the 9th postoperative day with no possibility for retransplantation because of the absence of a suitable donor.

Table 4. Arteriographic data and clinical course of group 3 patients

OLTx no.	Angiography	Rejection	Mean AST[a]	Rx Control
OLTx 20	B (5 mm)	Mild	421	–
OLTx 23	B (6 mm)	Moderate	388	–
OLTx 28	B (8 mm)	None	115	–
OLTx 29	B (12 mm) + E (10 mm)	Moderate-severe	1293	Reopened shunts
OLTx 32	B (8 mm) + E (8 mm)	Moderate	496	Reopened shunts
OLTx 33	B (7 mm) + D (10 mm)	None	265	–
OLTx 34	B (5 mm) + C (10 mm)	Moderate-severe	848	Reopened shunts
OLTx 35	A (9 mm) + C (8 mm) + D (12 mm)	None	191	–
OLTx 38	B (9 mm) + E (8 mm)	None	198	–
OLTx 39	B (8 mm) + D (12 mm)	None	321	–
OLTx 44	B (7 mm) + E (5 mm)	Mild	315	–
OLTx 49	B (9 mm) + C (15 mm)	None	210	–

[a] Mean AST value from 1st to 14th postoperative day



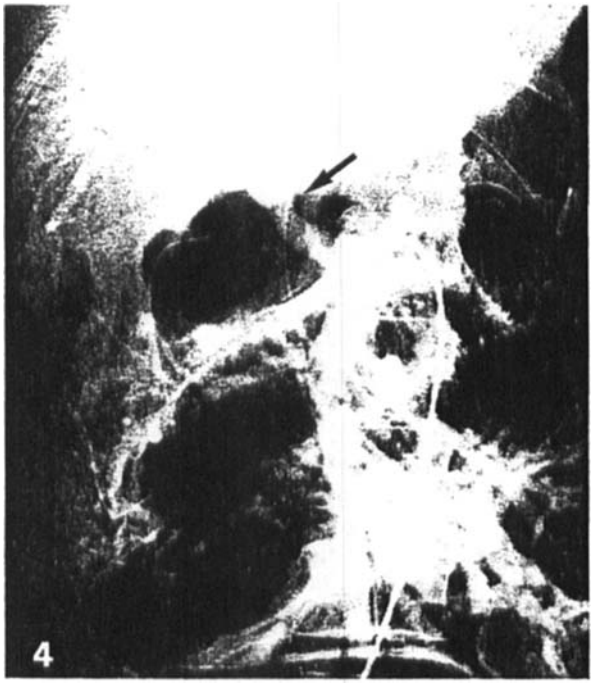


Fig. 3. **A** Venous phase of preoperative selective SMA arteriography shows normal dimension and patency of the superior mesenteric vein and portal trunk with late opacification of intrahepatic portal branches.
B The spleen is enlarged and, in the late phases of selective splenic arteriography, large and tortuous parahilar splenic collaterals drain into the left renal vein, thus creating a spontaneous splenorenal shunt: the dye has contrasted the inferior vena cava *(arrow)*

Fig. 4. Venogram during selective SMA angiography on the 1st postoperative day shows a patent portal anastomosis *(arrow)* with excellent inflow to the graft. Intrahepatic portal branches are well contrasted. Preoperative shunts are not evident on radiograms

OLTx no. 32

This was a 58-year-old female, transplanted for Child C cryptogenetic cirrhosis. Preoperative angiography showed a large splenorenocaval shunt from a large juxtaduodenal coronary vein and tortuous parahilar splenic collateral draining into the left renal vein. After an uneventful operation and normalization of liver tests, a moderate rejection was revealed by a liver biopsy on the 6th postoperative day. AST increased nearly tenfold, their values ranging from 78 to 843 IU. US scan demonstrated an enlarged and tense liver graft. Angiography revealed patency of the spontaneous shunts with diversion of the blood out of the liver. The patients is alive and well 28 months after transplantation with complete reversal of rejection after OKT3 treatment.

OLTx no. 34

This was a 49-year-old female affected by primary biliary cirrhosis. On preoperative arteriography a juxtaduodenal coronary vein and a large shunt through the inferior mesenteric vein were present. A moderate-to-severe

Table 5. Pre- and post-transplant variables in patients with and without postoperative shunts

	Nonshunt patients	Shunt patients	*P* value
Age	33 ± 8	32 ± 9	NS
Sex (m:f)	14:8	8:4	NS
Child: A	2	2	NS
B	3	2	NS
C	13	8	NS
Ischemic time (h)	7.3 ± 4.1	8.2 ± 3.9	NS
Ischemic lesions	3	1	NS
Rejection < 14 days	12	6	NS
> 14 days	2	1	NS
Mean (days 1–14)			
AST (IU)	183 ± 126	421 ± 335	< 0.0025
Bilirubin (mg/dl)	4.6 ± 3.8	5.2 ± 3.3	NS
Prothrombin time (%)	78 ± 24	69 ± 31	NS
UW solution (yes/no)	13/9	8/4	NS

acute rejection was evidenced by liver biopsy on the 7th postoperative day and was completely reversed with OKT3 therapy. AST increased from 95 to 1058 IU. Angiography revealed a significant reduction in portal perfusion with an evident 'steal phenomenon' through the spontaneous shunts. The patient is alive and well 25 months after OLTx.

Discussion

OLTx resolves the hemodynamic changes of portal hypertension by interposing a new, low-resistance, vascular bed between the splanchnic and systemic circulation. This causes a significant reduction in portal pressure with obliteration of collateral channels, either spontaneously or surgically, during the transplant procedure. However, in the postoperative course, changes in intrahepatic vascular resistance, as a result of inflammation or infiltration during rejection episodes, may cause reopening of the preexisting shunts.

The question is, do these spontaneous shunts negatively affect the fate of the transplant? To the best of our knowledge, only occasionally, in a few papers, have the possible effects of spontaneous or surgical shunts been reported, and in no specific study that has been undertaken. Starzl's group has presented some evidence of the negative effects of Warren's splenorenal shunts or of spontaneous shunts via the coronary vein after liver grafting and their closure is recommended [7, 11, 15]. On the other hand, a report from UCLA, considering two patients with Warren's operation, does not deem the division of the shunt necessary for the outcome of OLTx [2, 3].

Our study is unique in that it focuses on spontaneous portosystemic shunts and because our entire patient population was preoperatively assessed by angiography. In our series, 35% of the transplant recipients in whom cirrhosis was the major indication for grafting showed angiographic evidence of spontaneous shunts, unaffected by the transplant procedure, that were large enough to steal blood out of the liver if and when portal hypertension reappeared. In the remaining 65% of the patients, shunts were not significant or were interrupted during the hepatectomy.

Ischemic changes in the early postoperative period were significantly more evident in the shunt group and, in particular, when rejection occurred, as evidenced by AST profiles. This fact needs to be confirmed in a prospective, randomized trial; our series is too small – even if the analysis is mathematically significant – to give real credit to our hypothesis. The data, however, show that liver grafts in the shunt population are more prone to exhibit ischemic damage, probably as a consequence of blood diversion through the reopened spontaneous shunts. The grade of the rejection reaction did not significantly influence AST levels. In our opinion, AST peaks were correlated with the degree of ischemia derived from the diversion of the portal blood flow, rather than with the severity of the rejection.

The 'steal phenomenon' is well represented in the three case reports and particularly in OLTx no. 29 (Figs. 3–6). In this patient we strongly feel that the blood diversion was the main cause of the massive hemorrhagic necrosis of the graft, evidenced at autopsy, that caused the death of the patient [4, 5, 10, 14].

In conclusion, our data strongly suggest that the presence of spontaneous portosystemic shunts after OLTx has a detrimental effect on graft perfusion when portal hypertension reappears in early postoperative stages, as during rejection episodes. A 'steal syndrome', with ischemic changes in the transplant, was demonstrated in three patients; moreover, AST levels were significantly higher in the first 2 weeks after OLTx in the shunt population than in patients without postoperative shunts. This difference was even more significant when acute rejection was present in their courses, independent of the severity

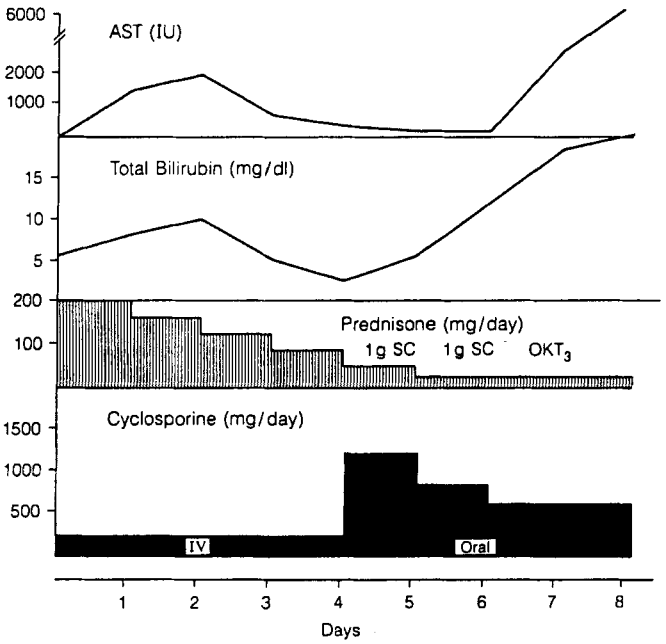


Fig. 5. Postoperative course of OLTx no. 29 from the 1st to the 8th day, showing AST and bilirubin profiles, together with immunosuppressive treatment. Starting on the 5th postoperative day, steroid boluses (1 g Solu-Cortef IV) and OKT3 were administered to treat a moderate-to severe acute rejection

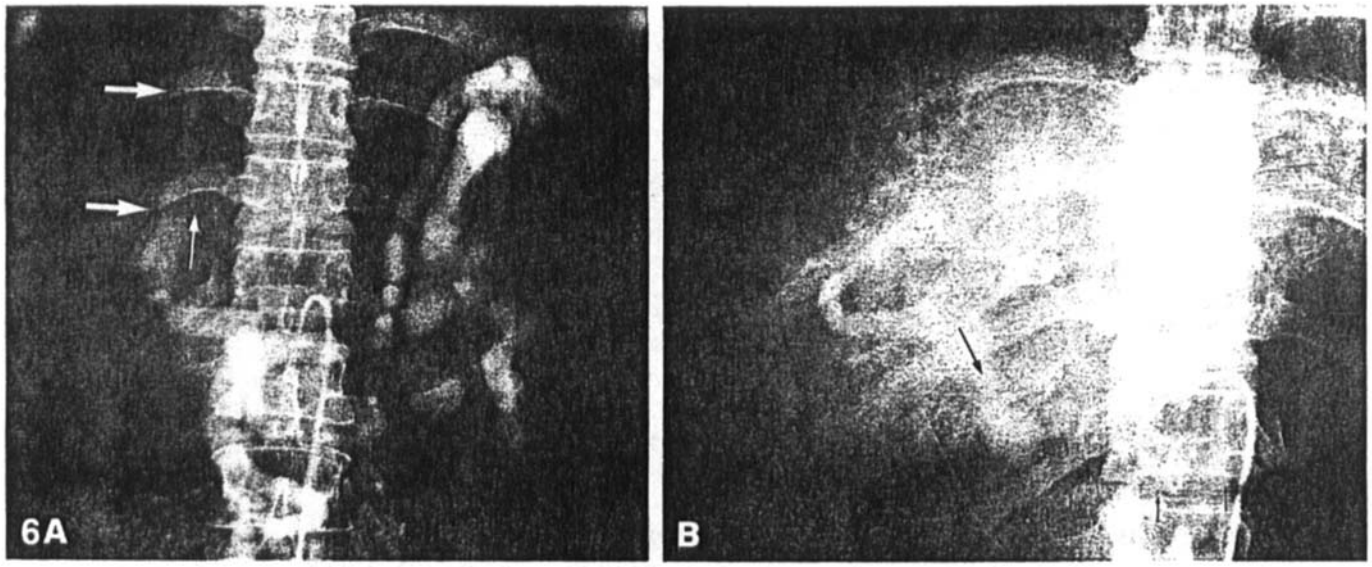


Fig. 6. A On the 7th postoperative day, a late phase of selective SMA angiography shows a retrograde flow in the splenic vein toward the perisplenic collaterals with reappearance of the spontaneous splenorenocaval shunt *(arrow)*. **B** In the late phases of the selective hepatic arteriography, the 'steal phenomenon' is depicted with diversion of the portal blood flow out of the liver graft *(arrow)*. Intrahepatic portal perfusion is absent on venogram

of the rejection. We therefore advocate, during the transplant procedure, the interruption of those shunts unaffected by the hepatectomy (i.e., juxta-duodenal coronary vein, inferior mesenteric vein, or splenorenal spontaneous shunts) if angiographically evident and large in caliber, as these additional surgical manoeuvres are rapid and do not add particular risks to the operation. Other studies will clearly be required to elucidate the role of these prophylactic procedures.

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