Transplant International

Transplant International ISSN 0934-0874

ORIGINAL ARTICLE

Evolving experience with prevention and treatment of splenic artery syndrome after orthotopic liver transplantation

Martina T. Mogl,[1] Natascha C. Nüssler,[2] Sabine J. Presser,[1] Petr Podrabsky,[3] Timm Denecke,[3] Christian Grieser,[3] Peter Neuhaus[1] and Olaf Guckelberger[1]

1 Department of General, Visceral and Transplant Surgery, Charité Campus Virchow, Humboldt-University Berlin, Germany
2 Department of Surgery, Klinikum Neuperlach, Munich, Germany
3 Department of Radiology, Charité Campus Virchow, Humboldt-University Berlin, Germany

Keywords
liver graft dysfunction, liver transplantation, splenic artery syndrome, vascular complication.

Correspondence
Dr Martina T. Mogl, Department of General, Visceral and Transplant Surgery, Charité Campus Virchow, Humboldt-University Berlin, Augustenburger Platz 1, 13353 Berlin, Germany. Tel.: +49 30 450 652 124; fax: +49 30 450 552 900; e-mail: martina.mogl@charite.de

Received: 21 July 2009
Revision requested: 14 September 2009
Accepted: 21 January 2010
Published online: 18 February 2010

doi:10.1111/j.1432-2277.2010.01062.x

Summary

Impaired hepatic arterial perfusion after orthotopic liver transplantation (OLT) may lead to ischemic biliary tract lesions and graft-loss. Hampered hepatic arterial blood flow is observed in patients with hypersplenism, often described as arterial steal syndrome (ASS). However, arterial and portal perfusions are directly linked via the hepatic arterial buffer response (HABR). Recently, the term 'splenic artery syndrome' (SAS) was coined to describe the effect of portal hyperperfusion leading to diminished hepatic arterial blood flow. We retrospectively analyzed 650 transplantations in 585 patients. According to preoperative imaging, 78 patients underwent prophylactic intraoperative ligation of the splenic artery. In case of postoperative SAS, coil-embolization of the splenic artery was performed. After exclusion of 14 2nd and 3rd retransplantations and 83 procedures with arterial interposition grafts, SAS was diagnosed in 28 of 553 transplantations (5.1%). Twenty-six patients were treated with coil-embolization, leading to improved liver function, but requiring postinterventional splenectomy in two patients. Additionally, two patients with SAS underwent splenectomy or retransplantation without preceding embolization. Prophylactic ligation could not prevent SAS entirely ($n = 2$), but resulted in a significantly lower rate of complications than postoperative coil-embolization. We recommend prophylactic ligation of the splenic artery for patients at risk of developing SAS. Post-transplant coil-embolization of the splenic artery corrected hemodynamic changes of SAS, but was associated with a significant morbidity.

Introduction

Surgical techniques in liver transplantation are still evolving, mostly focusing on venous outflow reconstruction or bile-duct anastomosis. Another focus lies on the improvement of partial liver transplantation techniques, either in the living-donation setting or in deceased-donor splits for two recipients.

Over the years there have repeatedly been reports on the arterial steal syndrome (ASS), a phenomenon describing the impaired hepatic artery flow by shifting of the main blood flow to the splenic or gastroduodenal artery [1,2]. The incidence of ASS varies considerably between 3.1% [3] and as much as 11.5% after orthotopic liver transplantation [4]. While reports about this phenomenon mainly focus on the hampered arterial inflow, another mechanism has to be taken into account. Portal hyperperfusion also leads to a decelerated arterial inflow with an increase in hepatic resistive index (RI) in Doppler ultrasound [5]. A potential physiological explanation might be the adenosine washout into portal blood leading to decreased adenosine concentrations around hepatic

arterial resistance vessels with consecutive arteriolar vasoconstriction and reduced arterial blood flow [6,7]. This condition can be reversed by reduction of portal hyperperfusion via ligation of the splenic artery [8]. Accordingly, reports have shown that a small-for-size liver graft also may result in portal hyperperfusion eventually leading to primary nonfunction. The sudden portal hyperperfusion after split-liver transplantation seems to trigger the deterioration of arterial inflow, which can be improved by embolization of the splenic artery [3,9]. This immediate relationship between portal hyperperfusion and diminished hepatic arterial perfusion is contradictory to the above postulated ASS via the celiac trunc. Recently, Quintini *et al.* [10] supported this theory and coined the term 'splenic artery syndrome' (SAS) to postulate that a so-called steal phenomenon does not exist.

In 2003, we reported our experience in diagnosis and treatment of ASS in liver transplant recipients, suggesting that prophylactic banding of the splenic artery during the transplantation procedure in selected patients may prevent development of ASS after orthotopic liver transplantation [11]. Now we report on evolving experience in diagnosis and treatment of – generally speaking – SAS leading to hepatic arterial malperfusion. Furthermore, we will summarize currently known mechanisms influencing liver-graft perfusion including portal hyperperfusion in different clinical settings.

Patients and methods

Patient population, preoperative diagnostic work-up

We retrospectively analyzed 650 consecutive liver transplantations performed between September 2000 and February 2006. Of these, 60 (9.2%) partial liver transplants have been performed with 27 (4.2%) living-related adult-to-adult liver transplantations using a right liver lobe, 15 (2.3%) split-liver transplantations with cadaveric splits and 18 (2.8%) living-related adult-to-child liver transplantations using a left liver lobe.

All primary transplantations and first retransplantations were included in the study, 14 second and third retransplantations were excluded. Demographic details are presented in Table 1, follow-up at time of the analysis was 35 months (median) ranging from 8 to 68 months.

All patients received routine preoperative imaging of liver vascular anatomy with either catheter angiography visualizing celiac trunk and portal vein, computed tomography scan or magnetic resonance imaging with vascular reconstruction techniques. While initially nearly all patients received invasive digital subtraction angiography (DSA), we changed our routine to computed tomography angiography (CTA) in 2003 with the evolution of scanner technology (multislice detectors). In case the CTA raised suspicion of a celiac trunk stenosis, DSA was performed to further evaluate the type of stenosis (fixed or unfixed) and to decide about the surgical technique of arterial anastomosis (aortic interposition or dissection of the arcuate ligament). In patients with contraindications to iodine contrast media, magnetic resonance angiography was performed with visualization of the vascular anatomy of the liver using a gadolinium-based extracellular contrast agent.

Operative procedure and patient collectives

Liver transplantations were performed following standard techniques with either caval interposition using a veno-venous bypass until 2005 or the piggy-back technique with side-to-side anastomosis of the recipient and donor vena cava in the majority of patients after 2005. Anastomosis of the portal vein was performed as an end-to-end anastomosis. Of the 636 primary transplantations or first retransplantations, altogether in 553 procedures (492 patients, 87%) arterial reconstruction was performed as end-to-side anastomosis between the donor celiac trunk

Table 1. Demographic data for patients receiving first and second liver transplantation. Table showing distribution of gender, age at orthotopic liver transplantation, diagnosis as well as number of retransplantations and partial liver transplants.

n (%)

Sex		Age at OLT (years)		Diagnosis					Partial liver	
Male	Female	Range	Median	Alcoholic cir.	HCV	HCC	Other†	Re-OLT	Child	Adult
357 (62.8)	211 (37.2)	0.4–70	53	143 (22.5)	112 (17.6)	97 (15.3)	284 (44.6)	68 (10.7)‡	18 (2.8)	42 (6.6)
$\sum$ 568 patients (100)				$\sum$ 636 procedures (100)						

Alcoholic cir., alcoholic cirrhosis; HCV, chronic hepatitis C virus infection with cirrhosis; HCC, hepatocellular carcinoma; OLT, orthotopic liver transplantation; re-OLT, first re-transplantation.

$\sum$ *n* = 636 procedures in 568 patients (100%).

†Other = autoimmune and metabolic disorders, HBV, acute liver failure, biliary atresia, trauma, cholangiocellular carcinoma etc.

‡68 patients retransplanted within the study period.

or common hepatic artery and the recipient common hepatic artery or orifice of the gastroduodenal artery. In 76 patients (83 transplantations, 13%) with celiac trunk stenosis, the arterial anastomosis was carried out by interposition of a donor iliac artery graft between recipient aorta and donor common hepatic artery to improve arterial blood flow. These patients were excluded from the analysis. Ninety-eight (15.4%) cadaveric whole-organ transplantations were performed in 86 patients with hypersplenism and the splenic artery being the dominant branch of the celiac trunk in preoperative diagnostic imaging. These patients received either prophylactic banding (20 transplantations, 3.1%) or ligation (78 transplantations, 12.3%) of the splenic artery intraoperatively. None of these grafts was split-liver transplantations. The banding procedure was carried out as described by Nüssler *et al.* [11] with administration of an artificial and predefined stenosis to the splenic artery by tying a nonabsorbable suture around the tip of a surgical clamp together with the splenic artery close to the celiac trunc, thereby realizing a standardized diameter of the vessel after removal of the clamp. Despite banding of the splenic artery during 20 transplantations, two patients presented with SAS (10%) shortly after the operation. As the procedure proved to be unreliable, it was stopped further on and those patients were excluded from the analysis. Ligation of the splenic artery on the other hand signifies a complete occlusion of the vessel with a nonabsorbable suture. Of the remaining 455 procedures without prophylactic treatment (71.5%, 406 patients), 395 (62.1%) whole-organ deceased-donor liver grafts were transplanted with standard arterial anastomosis. Adult living-related and cadaveric split-liver transplantations were performed using the piggy-back technique with end-to-end anastomosis of the donor right hepatic artery and the recipient hepatic artery (42 procedures, 6.6%), while adult-to-child living-related transplantations of the left or left-lateral liver were performed using the donor left hepatic artery (18 procedures, 2.8%) (Fig. 1).

For further analysis, transplantations with splenic artery ligation as prophylactic treatment were compared with transplantations without prophylactic treatment after exclusion of all transplantations with arterial interposition grafts and banding of the splenic artery.

Postoperative regimen

All patients received immunosuppressive therapy consisting of either tacrolimus- or cyclosporin-based regimens. Doppler ultrasound examinations of hepatic perfusion were undertaken daily during the first postoperative week, routinely after 6 and 12 months and yearly thereafter as well as in case of an unexpected elevation of transaminases. Laboratory values were taken daily during the first 21 days after transplantation, including total bilirubin, liver enzymes (AST, aspartate transaminase; ALT, alanine transaminase), albumin, platelet count and coagulation parameters. During follow-up, routine laboratory testing was de-escalated from twice a week during the first 2 months to once a month after 4 months and thereafter. Exceptions were made in case of clinical problems or unusually elevated test results. In case of a coiling procedure, laboratory tests were taken immediately before as well as after the intervention until normalization of test results. For statistical evaluation, laboratory tests and doppler ultrasound examinations were analyzed 1 to

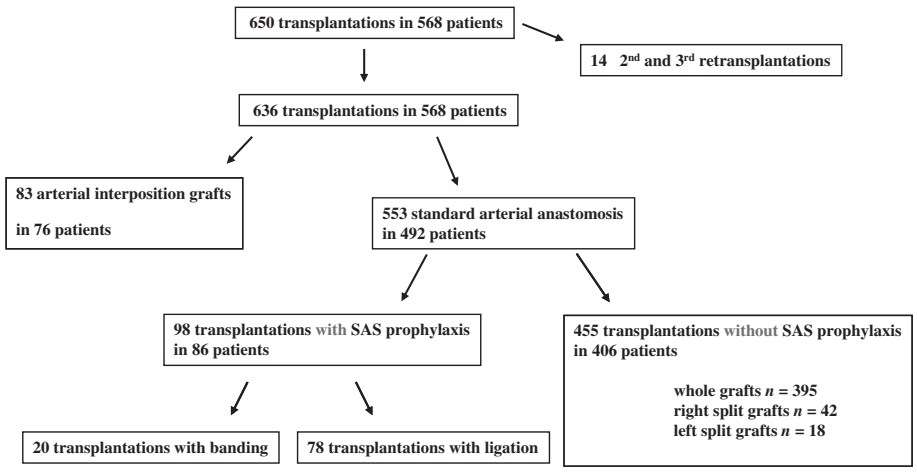

Figure 1 Patient groups according to operative procedure. Flow-diagram displaying the different patient groups according to operative procedure: transplantations with arterial interposition grafts, transplantations with standard arterial anastomosis, transplantations with or without prophylactic treatment.

3 days prior to coiling and 3 to 7 days after the intervention. Liver biopsies were performed routinely after 12 months and every other year thereafter, as well as in times of suspected acute cellular rejection.

Diagnosis of SAS

Splenic artery syndrome was assumed when elevation of transaminases and bilirubin, or persistent ascites were observed in the absence of acute cellular rejection, infection or toxicity.

Diagnosis was supported by an unusually weak blood flow in the hepatic artery (<35 cm/s) associated with an increased hepatic artery resistance index (RI > 0.8) as described by Garcia-Criado *et al.* [12] in Doppler ultrasound examinations, always confirmed by DSA. Analogous, portal hyperperfusion was presumed via ultrasound, if mean velocity of portal venous blood flow exceeded 25 cm/s or calculated blood flow measured via Duplex ultrasound was >1000 ml/min following the description by Ignee *et al.* [13]. Only if dynamic findings of DSA verified relative arterial hypoperfusion of the graft together with an enlarged splenic artery and good portal perfusion, diagnosis of an SAS was confirmed. Typical dynamic angiographic features are early perfusion of the splenic or gastroduodenal artery together with delayed or dim perfusion of the hepatic artery along with early portal venous contrast filling indicating hampered hepatic arterial blood flow, as described by Uflacker *et al.* [3] (Fig. 2). Underlying medical or morphological conditions like vasoconstrictive drugs or anastomotic stenoses had to be excluded.

Statistics

Data are expressed as mean ± standard deviation of mean, unless noted otherwise. Continuous variables with gaussian distributions were compared using Student's paired *t*-test. Categorial variables were compared using chi-square test. All calculations were performed using the SPSS software package (Version 16.0 for Windows, SPSS Inc., Chicago, IL, USA). A *P*-value of <0.05 was considered statistically significant.

Results

Incidence of SAS and arterial reconstruction

Of the 455 transplantations (406 patients) without prophylactic ligation of the splenic artery, SAS was diagnosed after 24 procedures, reaching an incidence of 5.3%. One of these patients had received a first retransplantation. None of the 15 cadaveric split- or 15 adult-to-child living-related transplantations with an end-to-end anastomosis using the donor right (cadaveric split) respective left (adult-to-child living-related) hepatic artery resulted in SAS. Among the adult living-related liver transplant recipients with an arterial anastomosis between donor right hepatic artery and recipient common hepatic artery, two of 27 patients (7.4%) were diagnosed with SAS and treated accordingly.

In 78 transplantations with prophylactic ligation, another two patients (2.6%) developed SAS. Interestingly, one of the patients with ligation of the splenic artery displayed radiological features of a gastroduodenal artery 'steal' syndrome. The other patient presented with massive collateralization and hypersplenism despite ligation of the splenic artery, leading to SAS.

Diagnosis and treatment of SAS

Diagnosis and treatment of SAS were equal in all patient groups. The majority of patients were diagnosed within the first 2 months after orthotopic liver transplantation

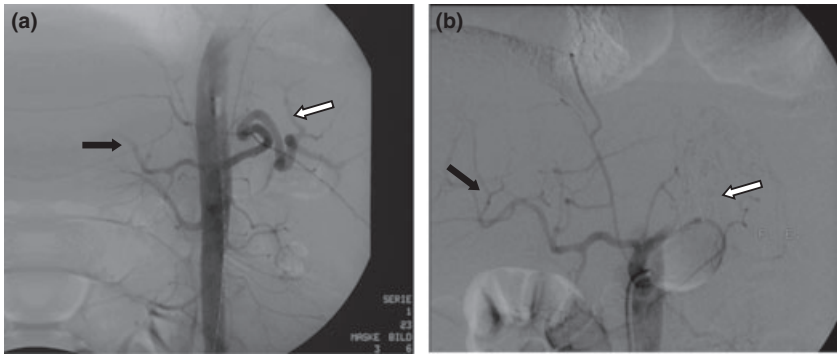

Figure 2 Typical angiography of splenic artery syndrome before and after coil-embolization. (a) Catheter angiography of the abdominal aorta before coiling displays celiac trunk and superior mesenteric artery with a predominant contrast of the splenic artery (white arrow) and dim contrast of the hepatic artery (black arrow). (b) Catheter angiography after coiling of the splenic artery with the coils placed centrally (white arrow) and a prominent contrast of the hepatic artery (black arrow).

(OLT). In five patients, diagnosis was established between 4 months and as late as 52 months after transplantation. In all patients, immunological, toxic or infectious causes for graft dysfunction were ruled out by percutaneous liver biopsy. Most of the patients presented with elevated liver enzymes and bilirubin levels. Mean AST-value of patients with SAS immediately prior to embolization was 233.7 ± 227.8 IU/l (normal range for male patients AST < 50 IU/l). The majority of patients displayed a concomitant elevation of total bilirubin (mean 3.1 ± 2.3 mg/dl, normal range of total bilirubin <1 mg/dl), while in two patients a sole elevation of bilirubin levels could be observed. Two patients presented with only mildly elevated transaminases but refractory ascites as main feature leading to diagnosis and nine patients additionally displayed low platelet counts. One patient repeatedly demonstrated uncharacteristic parenchymal changes in liver biopsies suspicious for hypoxemia which disappeared after the coiling procedure.

Suspicious findings in routine Doppler ultrasound examinations were observed inconsistently. There was a statistically significant difference ($P = 0.02$) in hepatic artery RI before (mean 0.79 ± 0.14) and after coil-embolization (mean 0.65 ± 0.09). Considering the mean velocity of portal venous blood flow, coil-embolization resulted in a significant decrease in patients after embolization (mean before 37.3 ± 12.8; mean after 29.4 ± 9.3, $P = 0.023$).

Nearly all ($n = 25$) of the patients throughout the groups diagnosed with SAS received therapeutic interventions as soon as they presented with graft dysfunction. To enhance arterial hepatic perfusion, altogether 24 patients were treated by coil-embolization of the splenic (23 patients) or gastroduodenal artery (1 patient). One patient was treated with secondary splenectomy as therapeutic intervention and one patient was not treated immediately but underwent retransplantation later on. Looking at the patient groups in more detail, two of the 78 patients (2.6%) with prophylactic ligation of the splenic artery were diagnosed with SAS and required different treatment options: despite ligation of the splenic artery during initial transplantation, one patient required splenectomy for massive collateralization with consecutive portal hyperperfusion and one patient underwent early revision of the hepatic artery anastomosis for relevant kinking of the vessel with simultaneous ligation of the splenic artery to enhance hepatic arterial blood flow, but needed coiling of the gastroduodenal artery for subsequent presentation of a gastroduodenal artery 'steal' syndrome.

Of the remaining 455 procedures without prophylactic treatment, 24 patients were identified with SAS after transplantation (5.3%). Twenty-three of them were successfully treated with coil-embolization of the splenic artery. The remaining patient was diagnosed 4 months after OLT with already severe biliary tract destruction and was not treated immediately but underwent retransplantation with simultaneous ligation of the splenic artery 34 months later. She had been transplanted for acute viral hepatitis and organ function was stable shortly after OLT. During waiting-time, the patient underwent continuous endoscopic treatment with internal and external stenting of the biliary tree and had to be treated for biliary abscesses intermittently. However, after retransplantation this patient did not recover and died of septic multiorgan failure. Included in the group without prophylactic treatment were two patients receiving a living-related liver transplantation who both successfully underwent coil-embolization of the splenic artery after diagnosis of SAS.

After treatment of SAS all of the patients experienced a rapid and statistically highly significant improvement in liver function tests (AST: $P < 0.001$; bilirubin: $P < 0.001$) (Fig. 3) and statistically significant recovery of platelet counts ($P = 0.017$). All but one had an overall successful recovery without further signs of disturbed perfusion or graft malfunction. During follow-up, one patient died of recurrent hepatocellular carcinoma, none required retransplantation.

Complications and prophylactic ligation

Among all the 568 patients, a total of 68 patients required one re-OLT (12%) during the study period, seven re-OLTs occured in the group with aortic interposition graft and were not included into the analysis. The remaining 61 retransplantations were necessary for

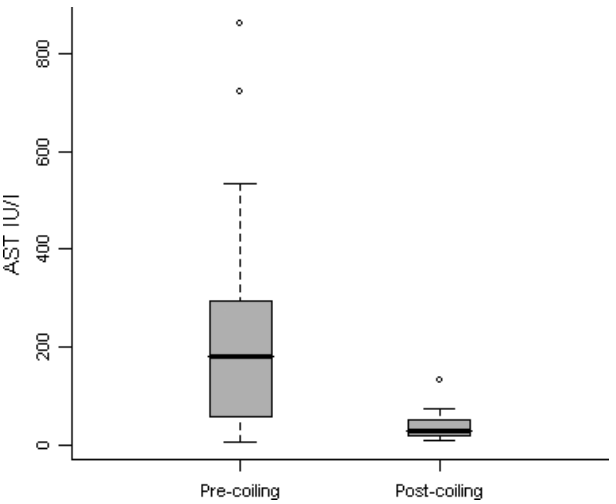

Figure 3 Aspartate transaminase-values in patients with splenic artery syndrome before and after coil-embolization. Box plots of AST-values pre and postcoiling of the splenic artery demonstrate a significant decrease (233.7 IU/l ± 227.8 vs. 38.35 ± 28.8 IU/l, $P < 0.001$).

various reasons including 17 OLTs (27.9%) with detrimental hepatic artery thrombosis and 28 transplantations (45.9%) in patients with initial nonfunction (INF). Eleven of the hepatic artery thromboses occurred within the first days after OLT resulting from either technical problems with back-table reconstruction of accessory arteries, incongruency of hepatic artery diameter, massive cardiocirculatory problems with high-dose catecholamine administration during or after OLT or exaggerated use of prothrombotic substances and delay of heparin-administration during or early after OLT for excessive bleeding. These 11 patients were retransplanted immediately. Another six patients with arterial thrombosis were diagnosed during follow-up (up to 1 year post-transplant) and underwent re-OLT with waiting-time. All of the patients with early hepatic artery thrombosis were diagnosed with CT-scans or angiographies. Here additionally two patients displayed hyperperfusion of the spleen via a prominent splenic artery that was ligated during retransplantation. Other reasons for retransplantation were organ failure for recurrent viral hepatitis (five patients; 8.2%), chronic rejection (three patients; 4.9%), biliary tract complications (two patients; 3,3%) or portal vein thrombosis (6 patients; 1.1%).

The 20 patients receiving intraoperative banding of the splenic artery developed a total of nine complications (45%), including two diagnoses of SAS, one secondary splenectomy, and three biliarytract complications requiring interventions.

Of the 78 patients undergoing prophylactic ligation intraoperatively, 15.4% (12 patients) required retransplantation compared with 49 patients without prophylactic treatment (10.8%) showing no statistically significant difference ($P = 0.248$) (Table 2). Retransplantations in the group with prophylactic ligation were necessary for INF (four patients; 5.1%), chronic rejection (three patients; 3.8%), portal vein thrombosis (two patients; 2.6%), hepatic artery thrombosis (one patient; 1.3%) and ischemia type biliary lesion (two patient; 2.6%). Among these 78 patients, only once an asymptomatic splenic infarction was diagnosed without any further consequences. However, two patients (2.6%) with ligation of the splenic artery developed portal vein thrombosis leading to early retransplantation, yet this reached no significant difference compared with the other patients ($n = 4$, $P = 0.214$). Additionally, one patient developed substantial peripancreatic bleeding after ligation of the splenic artery, requiring reoperation, but the total number of complications in the group with prophylactic ligation was not statistically different than in patients without prophylactic treatment ($P = 0.262$). The previously described higher rate of complications for ligation-treatment [11] could not be observed anymore, probably because of a successful learning curve. In other terms, prophylactic treatment was associated with a certain number of complications, but only two patients were diagnosed with SAS or gastroduodenal artery 'steal' syndrome (2.6%), compared with 24 patients without prophylactic ligation (5.3%).

Table 2. Incidence of complications related to prophylactic splenic artery ligation. Table displaying number and percentage of major complications related to prophylactic ligation of the splenic artery. Splenectomy only occured in the group without prophylactic treatment. For portal vein thrombosis leading to early retransplantation ($P = 0.214$), the total number of retransplantations ($P = 0.248$) and the total number of complications ($P = 0.262$) no statistically significant differences can be calculated.

	No prophylaxis $n = 455$†	Ligation $n = 78$	Total‡ $n = 533$	
Complications	*n* (%)	*n* (%)	*n* (%)	*P*-value
Splenectomy	4 (0.9)	–	4 (0.8)	
Portal vein thrombosis leading to early re-OLT	4 (0.9)	2 (2.6)	6 (1.1)	0.214
Reoperation related to ligation	–	1 (1.3)		
Re-OLT total¶	49 (10.8)	12 (15.4)	61 (11.4)	0.248
Total no. of complications	53 (11.6)	13 (16.7)	66 (12.4)	0.262

OLT, orthotopic liver transplantation; re-OLT, retransplantation.

†455 procedures including 27 with living-related adult-to-adult liver transplantations using a right liver lobe, 15 partial liver transplantations with right cadaveric splits and 15 living-related adult-to-child liver transplantations using a left liver lobe.

‡Total = 533 procedures = 636 procedures minus 83 transplantations with aortic interposition graft, minus 20 transplantations with intraoperative banding.

¶Total = 61 retransplantations within the study period = 68 retransplantations minus 7 retransplantations in patients with aortic interposition graft.

Table 3. Incidence of complications related to splenic artery syndrome (SAS). Table displaying number and percentage of major complications related to SAS. For splenectomy ($P = 0.030$) and long-term endoscopy for I(T)BL ($P = 0.015$) a statistically significant difference can be calculated. The total number of retransplantations ($P = 0.343$) was not significantly different in developing patients with SAS, while the total number of complications is statistically significantly higher ($P = 0.006$).

Complications	Transplantations without consecutive SAS *n* = 507† *n* (%)	SAS *n* = 26 *n* (%)	Total‡ *n* = 533 *n* (%)	*P*-value
Splenectomy	4 (0.8)	2 (7.7)	6 (1.1)	0.030
Portal vein thrombosis leading to early re-OLT	6 (1.2)	–		
Reoperation related to treatment	–	3 (11.5)		
Long-term endoscopy for I(T)BL	17 (3.4)	4 (15.4)	21 (3.9)	0.015
Re-OLT total¶	60 (11.8)	1 (3.8)	61 (11.4)	0.343
Total no. of complications	81 (16)	10 (38.5)	91 (17.1)	0.006

SAS, splenic artery syndrome; OLT, orthotopic liver transplantation; re-OLT, retransplantation; I(T)BL, ischemic (type) biliary lesion requiring long-term endoscopic treatment.

†507 procedures including 455 transplantations without prophylactic treatment and 78 transplantations with prophylactic ligation of the splenic artery.

‡Total = 533 procedures = 636 procedures minus 83 transplantations with aortic interposition graft, minus 20 transplantations with intraoperative banding.

¶Total = 61 retransplantations within study period = 68 retransplantations minus 7 retransplantations in patients with aortic interposition graft.

Complications in patients with SAS

When looking more closely at patients developing SAS, the rate of complications was even higher: secondary splenectomy occurred at significantly higher frequencies (7.7%, $P = 0.030$) compared to patients without SAS (0.8%) (Table 3). Considering biliary complications with the need for long-term endoscopic treatment, patients developing SAS appeared to have a statistically significant higher rate of 15.4% ($P = 0.015$) compared with those without SAS (3.4%). Among patients diagnosed with SAS only one retransplantation was carried out, thus no statistically significant difference could be observed. Complications related to catheterization for the coiling procedure did not occur. However, two patients had to undergo hepatojejunostomy, one for biliary leakage and another one for anastomotic stricture, later developing an arterial aneurysm that was treated by homograft-replacement of the hepatic artery. As well, three patients required endoscopic retrograde cholangiography (ERC) with papillotomy (EPT) and short-term follow-up endoscopic dilatation and one patient presented with hepatic artery thrombosis 4 weeks after coil-embolization of the splenic artery with spontaneous revascularization later on. A possible explanation for this thrombosis or arterial malperfusion 4 weeks after embolization most likely was a severe steroid-resistent rejection with the need for OKT-3-antibody treatment at the time of diagnosis. One patient had an eventful postoperative course with long-term percutaneous stenting for biliary strictures and leakage, needed operative revision for rupture of the diaphragm and developed recurring PTLD and CMV-infection with eventually fatal septic multiorgan failure.

The total number of serious complications reached a significantly higher rate in the group of patients with SAS (38.5%) compared with patients not developing SAS (16%, $P = 0.006$). So overall, prophylactic ligation of the splenic artery was associated with a certain morbidity; however, post-transplant coil-embolization of the splenic artery with correction of hemodynamic changes of SAS was associated with a significantly higher rate of specific complications.

Discussion

While much effort lies on the improvement of surgical techniques in liver transplantation, little focus seems to lie on the problems deriving from hypersplenism and consecutive reduction of hepatic arterial blood flow. In various reports, this was designated to result from a shifting of the arterial blood flow toward the splenic artery and termed 'arterial steal syndrome' (ASS). Over the years, repeatedly case-series about ASS have been reported and standard treatment options like coil-embolization of

the steal-artery have been suggested. Only few publications have come up with an estimated incidence of ASS between 3.1% and 11.5% after OLT [1–4].

With growing experience in split-liver transplantation and extended hepatic resections another phenomenon reached attention, the small-for-size syndrome (SFSS). It is basically defined as postoperative liver dysfunction as a result of insufficient functional liver mass [15]. The development of SFSS is influenced by liver-graft quality, portal hyperperfusion and size of the remnant liver volume. Here a graft-to-recipient body weight ratio ≥ 0.8% should be achieved to avoid SFSS in the first place. Animal models showed the prevention of SFSS by avoiding portal hyperperfusion and graft dysfunction via splenectomy [9]. A case report by Lo *et al.* and a prospective study by Troisi *et al.* could show that modulation of the recipient portal inflow by ligation or embolization of the splenic artery led to improved liver function with an increase in recipient hepatic arterial inflow and resolution of ascites [8,16].

The reciprocity between hepatic artery and portal venous inflow, termed the hepatic arterial buffer response (HABR) by Lautt *et al.* [17] and confirmed experimentally by Richter *et al.* [18], seems to be the pathophysiological link explaining successful treatment of both ASS and SFSS by coil-embolization of the splenic artery. Just recently Quintini *et al.* [10] published an observational study about four patients with ultrasound diagnostics displaying what they termed the 'splenic artery syndrome' (SAS). They proposed that splenic artery embolization reduces hepatic arterial resistance by decreasing blood flow in the splenic circulation and consecutively portal venous flow toward the liver. They suggested that patients display hepatic artery vasoconstriction via portal hyperperfusion and an exaggerated HABR, which can be reversed by splenic artery embolization.

In our previous report [11], we stated an estimated incidence of more than 6% SAS/ASS, based on the fact that we applied a prophylactic procedure including splenectomy, banding or ligation of the splenic artery for patients during OLT suspicious for developing an SAS afterwards. In our current series, we observed an incidence of 5.1% (28 of 553 procedures). Still the diagnosis of SAS is difficult to obtain as the clinical picture varies immensely and reaches from elevated liver enzymes without clinical symptoms to biliary tract lesions and even graft failure. Of course every effort has to be made to rule out any other cause of graft impairment such as acute rejection, infectious or toxic problems, as well as influence of vasoconstrictors and impaired circulation in critically ill patients. Overall, dynamic DSA with the typical finding of a dim hepatic artery and 'steal-flow' toward the splenic or gastroduodenal artery in our opinion is the gold standard for the diagnosis of SAS. As shown elsewhere [19], Doppler ultrasound findings were not indicative for diagnosis, but in some cases raised the suspicion for SAS which was then confirmed by angiography. It should be clear that ultrasound is very operator dependent and rather nonspecific. Ultrasound examinations were performed by a great number of people with different experience levels and at least three different ultrasound machines, additionally flow volumetry was not measured routinely. Generally, measurement of hepatic artery RI is useful to detect stenosis in the hepatic artery as this leads to the typical poststenotic 'tardus et parvus'-profile with diminished systolic acceleration time and peak systolic velocity. Increased RI in kidney transplantation has been described to diagnose graft dysfunction, as it occurs in acute cellular rejection with a rapid decline in renal function [20]. Whether the same findings are true for acute cellular rejection and graft dysfunction after liver transplantation is still under discussion [12,21]. Here as well dynamic angiography helps to distinguish between hepatic artery problems with a typical 'pearl-chain'-picture in acute cellular rejection with vascular involvement and anastomotic stenoses because of operation technique. Nonetheless acute or chronic rejection always should be ruled out histologically by percutaneous liver biopsy. Interestingly several reports show spontaneous normalization of both hepatic artery RI as well as portal venous flow over time in liver transplant recipients [19,22]. Intraoperative Doppler ultrasound/flowmetry in case of unsatisfying hepatic artery flow after reperfusion was implemented in 2005 to immediately measure the effect of splenic artery ligation especially in case of reoperation for hepatic artery thrombosis or stenosis.

Concerning complications of treatment for SAS by embolization of the splenic artery, a clear reduction could be noticed after conversion of embolization techniques to a central placement of coils in the splenic artery as to allow collateral blood supply of the spleen as described by Madoff *et al.* [23]. Prophylactic splenectomy during OLT cannot be suggested as this would mean a considerably higher risk for the procedure in fairly ill patients (average lab-MELD approximately 19). Moreover, routine splenectomy during transplantation in patients suspicious for development of SAS as described in our first report was abandoned after a significant reduction of complications related directly to the coiling procedure. However, another change consisted in prophylactic routine intraoperative ligation of the splenic artery for patients with preoperative imaging displaying a high likelihood for the development of postoperative steal-phenomena. This risk was defined by preoperative imaging showing an enlarged diameter of the splenic artery compared with the hepatic artery combined with hypersplenism. This recently could be confirmed with a retrospective radiological evaluation

by Grieser *et al.* [24]. As contraindication for prophylactic treatment, we defined patients with portal vein thrombosis, transjugular intrahepatic portosystemic shunt (TIPSS) or other porto-caval shunts as they seem to be at a higher risk of developing portal venous thrombosis after OLT [25–29]. Of 20 procedures with prophylactic banding of the splenic artery to prevent SAS, we observed one splenic infarction requiring secondary splenectomy. Additionally, two patients developed SAS and successfully underwent standard coiling procedures completing the obviously unsuccessful banding procedure. We changed routine prophylactic treatment to complete ligation of the splenic artery for the unreliable banding procedure thereafter.

Complications directly related to prophylactic ligation of the splenic artery were comparatively low. Considering retransplantation rates, we observed no statistically significant difference between patients with or without prophylactic treatment ($P = 0.248$). Looking at this figure in more detail, 28 of altogether 61 retransplantations (45.9%) were performed for INF, not linked to technical problems. Additionally, 17 of 61 (27.9%) patients were retransplanted for detrimental hepatic artery thrombosis, mostly related to technical circumstances like backtable-reconstruction of donor accessory arteries, or incongruency of artery diameter which are known to be related with a higher risk for complications [14]. So in our opinion the high number of retransplantations has no relation to the prophylactic procedure. Overall, the total number of complications related to prophylactic treatment was not statistically different from the number of complications in patients without prophylactic ligation of the splenic artery ($P = 0.262$) (Table 2).

Remarkably enough, two patients were diagnosed with SAS in the group with successful prophylactic ligation of the splenic artery, one because of massive collateralization which was treated by splenectomy, one with a 'steal' syndrome involving the gastroduodenal artery which was sucessfully treated by coil-embolization. The existence of a 'steal' phenomenon via the gastroduodenal artery in a way weakens the 'SAS' theory. Of course, portal venous flow via duodenum, pancreas and mesenteric veins or collaterals exists, but substantial portal hyperperfusion from increased mesenteric inflow triggering an HABR in our opinion seems unlikely and should be proven experimentally.

Overall, the rate of complications related to prophylactic treatment was lower than following embolization as treatment of postoperative SAS. We demonstrated a statistically significantly higher number of secondary splenectomies ($P = 0.030$), altogether three reoperations related to the coiling procedure and a significantly higher number of long-term endoscopic treatments for ischemia type biliary strictures ($P = 0.015$). The rate of retransplantations was not significantly different ($P = 0.343$), but the total number of complications in the group of patients diagnosed with SAS reached a statistically significant higher rate ($P = 0.006$). After coil-embolization, we noticed no complications related to catheterization of the

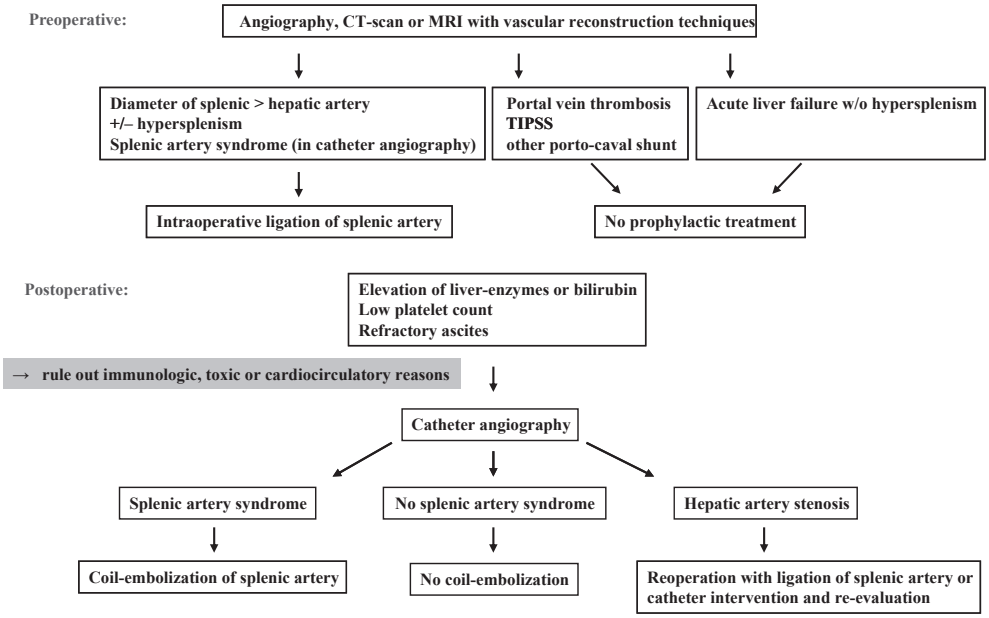

Figure 4 Algorithm for diagnosis and treatment of splenic artery syndrome (SAS). Flow-chart displaying diagnostic tree to preoperatively identify patients at risk for developing SAS, and postoperatively define those who benefit from coil-embolization of the splenic artery.

femoral artery, none of the grafts or patients was lost because of septic complications following embolization (Table 3).

Splenic artery syndrome also developed in two recipients of living-related split-liver grafts. In both cases, the graft-to-recipient body weight ratio was >0.8% as calculated preoperatively by diagnostic imaging with volumetry and controlled intraoperatively. Interestingly, both patients showed only minor signs of graft dysfunction without typical clinical problems, but developed significantly elevated transaminase levels that resolved after embolization of the splenic artery. Looking at Doppler ultrasound findings, no hint for portal hyperperfusion was observed in both patients and hepatic artery RI was normal before embolization. However, hepatic artery inflow improved persistently during and after angiographic intervention.

Combining these observations and looking at the potentially underlying pathophysiology it can be concluded that both conditions – SAS and portal hyperperfusion in SFSS – are linked and only are labeled according to their predominant feature in the respective patient, but may respond to the same treatment.

We therefore recommend a stepwise procedure to prevent and treat SAS in OLT. Primarily, thorough preoperative imaging of the celiac trunk and its branches as well as the portal vein should be established to define patients at risk of developing SAS. Supposedly, these are patients with hypersplenism and bigger diameter of the splenic compared with the hepatic artery. In case of already preoperative dynamic catheter angiography, the existence of an SAS can directly be ruled out or defined with a typical early contrasting of the spleen together with dim or late contrasting of the liver. In this case, intraoperative ligation of the splenic artery should be performed to avoid possible complications following coil-embolization in usually fairly ill patients with end-stage liver disease. All patients at risk of developing SAS identified by noninvasive preoperative diagnostics are recommended to receive prophylactic treatment with intraoperative ligation of the splenic artery. Exceptions should only be made for patients with portal vein thrombosis, TIPSS or other major portocaval shunts, under the presumption of resulting in a higher incidence of portal vein thrombosis after OLT, ranging from 5% to 21% [24–28].

Following OLT, attention should be paid to portal hyperperfusion or SAS after ruling out immunological, toxic or infectious causes for postoperative liver dysfunction. To correctly diagnose SAS, dynamic catheter angiography should be the main diagnostic tool and could result in immediate coil-embolization of the splenic artery. In case of hepatic artery stenosis, either a catheter intervention or reoperation with revision of the hepatic artery anastomosis and concomitant ligation of the splenic artery to enhance arterial perfusion of the liver could be performed (Fig. 4).

In conclusion, prophylactic treatment with ligation of the splenic artery for all patients at risk of developing SAS after OLT should be established. It is associated with a low number of complications and effectively prevents SAS. The high rate of complications, especially biliary problems, resulting from SAS postoperatively underlines the importance of an effective prophylactic treatment. In case of postoperative diagnosis of SAS, coil-embolization of the splenic artery can be recommended as treatment of choice with a low risk profile and good outcome for grafts and patients.

Authorship

M.T.M.: wrote the article, collected and analyzed the data. N.C.N., P.N.: designed analysis. S.J.P., T.D., C.G.: collected the data. P.P.: performed intervention, collected the data. O.G.: analyzed the data and wrote the article.

Funding

No financial funding or commercial associations for any of the authors.

References

1. De Carlis L, Sansalone CV, Rondinara GF, *et al.* Splenic artery steal syndrome after orthotopic liver transplantation: diagnosis and treatment. *Transplant Proc* 1993; **25**: 2594.
2. Geissler I, Lamesch P, Witzigmann H, *et al.* Splenohepatic arterial steal syndrome in liver transplantation: clinical features and management. *Transpl Int* 2002; **3**: 139.
3. Uflacker R, Selby JB, Chavin K, *et al.* Transcatheter splenic artery occlusion for treatment of splenic artery steal syndrome after orthotopic liver transplantation. *Cardiovasc Intervent Radiol* 2002; **25**: 300.
4. Lüsebrink R, Blumhardt G, Lohmann R, *et al.* Does concomitant splenectomy raise the mortality of liver transplant recipients? *Transpl Int* 1994; **7**(Suppl. 1): 634.
5. Jakab F, Rath Z, Schmal F, *et al.* The interaction between hepatic arterial and portal venous blood flows; simultaneous measurement by transit time ultrasonic volume flowmetry. *Hepatogastroenterology* 1995; **42**: 18.
6. Ezzat WR, Lautt WW. Hepatic arterial pressure-flow autoregulation is adenosine mediated. *Am J Physiol* 1987; **2**: H836.
7. Jakab F, Sugar I, Rath Z, *et al.* The relationship between portal venous and hepatic arterial blood flow. I. Experimental liver transplantation. *HPB Surg* 1996; **10**: 21.
8. Lo CM, Liu CL, Fan ST. Portal hyperperfusion injury as the cause of primary nonfunction in a small-for-size liver

graft-successful treatment with splenic artery ligation. *Liver Transpl* 2003; **9**: 626.
9. Glanemann M, Eipel C, Nussler AK, *et al.* Hyperperfusion syndrome in small-for-size livers. *Eur Surg Res* 2005; **37**: 335.
10. Quintini C, Hirose K, Hashimoto K, *et al.* 'Splenic artery steal syndrome' is a misnomer: the cause is portal hyperperfusion, not arterial siphon. *Liver Transpl* 2008; **14**: 374.
11. Nussler NC, Settmacher U, Haase R, *et al.* Diagnosis and treatment of arterial steal syndromes in liver transplant recipients. *Liver Transpl* 2003; **9**: 596.
12. Garcia-Criado A, Gilabert R, Salmeron JM, *et al.* Significance of and contributing factors for a high resistive index on Doppler sonography of the hepatic artery immediately after surgery: prognostic implications for liver transplant recipients. *AJR Am J Roentgenol* 2003; **181**: 831.
13. Ignee A, Gebel M, Caspary WF, Dietrich CF. Doppler imaging of hepatic vessels – review. *Z Gastroenterol* 2002; **40**: 21.
14. Stange BJ, Glanemann M, Nuessler NC, *et al.* Hepatic artery thrombosis after adult liver transplantation. *Liver Transpl* 2003; **9**: 612.
15. Tucker ON, Heaton N. The 'small for size' liver syndrome. *Curr Opin Crit Care* 2005; **11**: 150.
16. Troisi R, Cammu G, Militerno G, *et al.* Modulation of portal graft inflow: a necessity in adult living-donor liver transplantation? *Ann Surg* 2003; **237**: 429.
17. Lautt WW. Relationship between hepatic blood flow and overall metabolism: the hepatic arterial buffer response. *Fed Proc* 1983; **42**: 1662.
18. Richter S, Vollmar B, Mucke I, *et al.* Hepatic arteriolo-portal venular shunting guarantees maintenance of nutritional microvascular supply in hepatic arterial buffer response of rat livers. *J Physiol* 2001; **1**: 193.
19. Stell D, Downey D, Marotta P, *et al.* Prospective evaluation of the role of quantitative Doppler ultrasound surveillance in liver transplantation. *Liver Transpl* 2004; **10**: 1183.
20. Petersen LJ, Petersen JR, Ladefoged SD, *et al.* The pulsatility index and the resistive index in renal arteries in patients with hypertension and chronic renal failure. *Nephrol Dial Transplant* 1995; **10**: 2060.
21. Harms J, Ringe B, Pichlmayr R. Postoperative liver allograft dysfunction: the use of quantitative duplex Doppler signal analysis in adult liver transplant patients. *Bildgebung* 1995; **62**: 124.
22. Bolognesi M, Sacerdoti D, Bombonato G, *et al.* Change in portal flow after liver transplantation: effect on hepatic arterial resistance indices and role of spleen size. *Hepatology* 2002; **35**: 601.
23. Madoff DC, Denys A, Wallace MJ, *et al.* Splenic Arterial Interventions: anatomy, Indications, Technical Considerations and Potential Complications. *RadioGraphics* 2005; **25**(Suppl. 1): S191.
24. Grieser C, Denecke T, Steffen I, *et al.* Multidetector row computed tomography for preoperative assessment of hepatic vasculature and prediction of splenic artery steal syndrome in patients with liver cirrhosis before transplantation. *Eur Radiol* 2010; **20**: 108.
25. Settmacher U, Nüssler NC, Glanemann M, *et al.* Venous complications after orthotopic liver transplantation. *Clin Transplant* 2000; **14**: 235.
26. Davidson BR, Gibson M, Dick R, *et al.* Incidence, risk factors, management, and outcome of portal vein abnormalities at orthotopic liver transplantation. *Transplantation* 1994; **57**: 1174.
27. Yerdel MA, Gunson B, Mirza D, *et al.* Portal vein thrombosis in adults undergoing liver transplantation: risk factors, screening, management, and outcome. *Transplantation* 2000; **69**: 1873.
28. Manzanet G, Sanjuán F, Orbis P, *et al.* Liver transplantation in patients with portal vein thrombosis. *Liver Transpl* 2001; **7**: 125.
29. Kyoden Y, Tamura S, Sugawara Y, *et al.* Portal vein complications after adult-to-adult living donor liver transplantation. *Transplant Int* 2008; **21**: 1136.

