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Temporary intraoperative porto-caval shunt: useless or beneficial in piggy back liver transplantation?

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extended criteria donors, graft survival, ischemia-reperfusion injury, liver function, orthotopic liver transplantation, porto-caval shunt.

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Summary

The role of intraoperative porto-caval shunts in orthotopic liver transplantation (OLT) is controversial. Aim of this study was to analyze the effects of an intraoperative, porto-caval catheter-shunt on graft function and survival following cava sparing OLT. Four hundred and forty-eight piggy back liver transplantations with or without a temporary spontaneous porto-caval shunt between 1997 and 2010 were analyzed (shunt $n = 274$ vs. no shunt $n = 174$). Lab MELD scores and donor risk indices (DRI) were calculated. Hepatic injury (ALT, AST), -function (bilirubin, prothrombin ratio), postreperfusion liver blood flow and graft survival were registered [mean follow-up: 50.5 (0–163.0) months]. The impact of a shunt on graft survival was determined using multivariate analysis. Usage of a porto-caval shunt was associated with reduced hepatic injury (ALT, AST), whereas graft function was not affected. The shunt group showed a significantly increased portal venous blood flow after reperfusion. Retransplantation rate was decreased (7.7% vs. 20.1%, $P = 0.001$) and long-term graft survival was significantly increased with a porto-caval shunt (hazard ratio 2.1, $P < 0.001$). This effect was even more pronounced for marginal organs. Usage of intraoperative porto-caval catheter-shunts is beneficial in cava sparing OLT and is associated with reduced ischemia-reperfusion injury and improved organ survival in particular for recipients of marginal organs.

Introduction

Ischemia-reperfusion injury following orthotopic liver transplantation (OLT) contributes to postoperative organ dysfunction and may result in graft loss [1,2]. The use of marginal livers, made necessary by an increasing shortage of organ donors, further aggravates ischemia-reperfusion injury [3]. The activation of Kupffer cells plays a pivotal role in the pathophysiology of reperfusion injury [4,5]. Several experimental studies demonstrate that gut-derived mediators are involved in the activation of Kupffer cells during reperfusion following temporary occlusion of the portal vein [6–9]. Portal hypertension during liver transplantation may cause intestinal edema leading to increased gut permeability and resulting in bacterial translocation and the release of various mediators, that is chemokines, cytokines, and endotoxin into the portal circulation [5,7].

Cava sparing surgical techniques for liver transplantation (i.e. piggy back technique or side-to-side cavo-caval anastomosis according to Belghiti [10]) have been developed to minimize blood flow stasis in the inferior caval vein during surgery [10–13]. This results in improved hemodynamic stability during transplantation and reperfusion [11–13]. Combining cava sparing OLT or piggy back technique with a temporary porto caval shunt [12,14,15] additionally reduces venous stasis by connecting the portal venous system with the inferior caval vein. This technique avoids splanchnic congestion and therefore may decrease the release of endotoxin and other mediators from the gut into the graft and consecutively into the systemic circulation

after reperfusion. Furthermore, a reduction in intraoperative blood loss through preservation of the retroperitoneum has been reported [15].

Tzakis and Belghiti described a temporary end-to-side porto-caval anastomosis to establish a shunt for patients with a lack of adequate portosystemic collaterals [14,15]. Alternatively, an extracorporeal spontaneous porto-caval shunt-catheter can be inserted using a plastic tube to connect the portal- to the femoral vein. This shunt technique, which does not require anticoagulation or an additional pump supply (Fig. 1), is commonly used at the transplantation center of the University of Munich.

The aim of this study was to determine whether the use of temporary porto-caval shunt-catheters reduces hepatic injury, improves cardiovascular stability and intraoperative blood loss, and improves short- and long-term organ survival during and after cava sparing OLT.

Methods

Study design

The study was performed at the surgical department of the University of Munich – Campus Grosshadern, Munich, Germany. The study period extended from January 1997 to April 2010. A retrospective search of the liver transplant database, including all consecutive patients who received a cava preserving OLT was performed. Pediatric and split liver transplantations were excluded. The retrospective data analysis of the liver transplant database was approved by the local institutional review board.

Surgical procedures

All patients included in this study received a cava preserving OLT with an end-to-side or side-to-side caval anastomosis. For the piggy back technique, it is attempted to partially clamp the caval vein allowing blood flow to the right atrium through the inferior caval vein. Shunt application was performed by all transplant surgeons. Moreover, insertion of the femoral and portal catheter is standardized at our institution and carried out similarly by all surgeons according to an standard opening procedure (SOP). This minimizes the risk for heterogeneity within the groups because of the surgical procedure. The use of temporary intraoperative spontaneous extracorporeal porto-caval shunts was based on the transplant surgeons' assessment of the recipient's general condition and the presence of adequate porto systemic collaterals. In brief, a 17 F cannula (50 cm, CB 96535 015; Medtronic Inc., Meerbusch, Germany) was inserted into the femoral vein by direct puncture (Seldinger technique). Another catheter was placed in the portal vein and fixed by tourniquet ligation (24 F, 35 cm, CB 66124; Medtronic Inc.). The catheters were connected, allowing porto systemic blood pressure differences to establish spontaneous porto-caval blood flow. Insertion of the femoral and portal catheter accounts for approximately 20 min, which does not represent a relevant addition in operative time to the transplantation. It should be emphasized that this technique does not require a centrifugal pump or additional anticoagulation (Fig. 1).

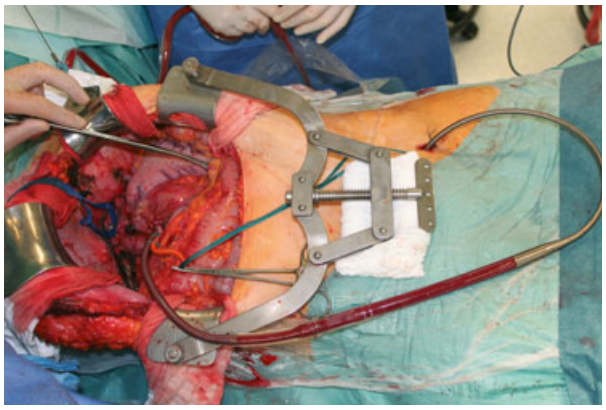

Figure 1 Intraoperative picture of a temporarily inserted porto-caval shunt catheter after cava preserving hepatectomy prior to liver transplantation.

Donor and recipient characteristics

The following data was collected for each donor and recipient: Age, sex, blood group, United Network for Organ Sharing (UNOS) status of the recipient [high urgency versus T-status listing on the transplant list], retransplantation, cold ischemia time, and type of graft preservation solution [University of Wisconsin (UW)- or Histidine-Tryptophan-Ketoglutarate (HTK)-solutions]. Based on the preoperative serum creatinine, bilirubin, and INR levels, the lab MELD Score was calculated as described previously [16]. Furthermore, the donor risk index (DRI) was calculated according to Feng *et al.* [17]. The indications for liver transplantations were classified as follows: alcoholic cirrhosis, malignancy, acute liver failure, viral hepatitis, primary biliary cirrhosis, and others.

For the detection of graft steatosis, liver biopsies of donor organs were routinely obtained after reperfusion using a Menghini needle (Hepafix; Braun, Melsungen, Germany) or wedge biopsy. In each biopsy, the percentage of hepatocytes showing macrovesicular steatosis, was determined. For analysis, steatosis was classified as mild (<30%) and moderate/severe (more than 30%). These categories were based on a previous study in which donor steatosis of more than 30% donor steatosis was associated with impaired postoperative organ function [18].

Intraoperative parameters

Continuous intraoperative hemodynamic monitoring was performed according to standard hospital procedures. Hepatic arterial and portal vein blood flow were measured intraoperatively following reperfusion using transit time flow measurement as described previously [19]. The average consumption of catecholamines (norepinephrine or epinephrine) during the entire surgical procedure was used as a surrogate marker for hemodynamic stability [20], and intraoperative transfusion requirements were recorded (substitution of red cell units and fresh frozen plasma concentrates).

Serum parameters

The prothrombin ratio [Quick (%)], AST, ALT, bilirubin-, and serum creatinine levels were recorded on the first, second, and seventh postoperative day as a measure of postreperfusion liver injury, graft function, and renal function.

Short- and long-term outcome

Graft survival and the frequency of primary graft nonfunction (PNF) resulting in acute retransplantation within the first postoperative month after initial transplantation were assessed. Long-term organ survival status was registered for all patients (median observation period: 32.0 months). In addition, retransplantation rates caused by chronic organ dysfunction were documented. To verify the effect of shunt usage on long-term graft survival, the data werealso analyzed excluding patients with PNF.

Statistical analysis

The statistical analysis was performed using statistical software PASW statistics 18.0.0 (SPSS Inc., Chicago, IL, USA). For all statistical tests, a testwise α level of 5% was used. *P*-values of <0.05 were considered statistically significant.

The effect of variables on cumulative organ survival was assessed using the log rank test in Kaplan–Meier survival analysis. In addition to hepatic and portal venous blood flow other variables that may influence the outcome following liver transplantation according to the survey of the European database [21] were evaluated using univariate analysis. Continuous variables, such as recipient and donor age, were dichotomized based on the values published by Adam *et al.* [21]. Variables were considered as potential confounders in a multivariate analysis performed using Cox proportional-hazard regression using the forward Wald method. Besides gender and recipient and donor age, those variables with a *P*-value of <0.05 in the univariate analysis were entered into the multivariate analysis model.

The results of continuous variables are presented as mean ± SEM. To determine the differences between the values on day 1 and 2, the Mann–Whitney *U*-test was applied. Categorical parameters, such as retransplantation and complication rate, were compared using chi-square test or the Fisher′s exact test, as appropriate.

Results

Within the observation period, a total of 448 liver transplantations were performed in 392 patients [mean age 51.0 (±11.0) years, sex ratio m:f = 2.05:1]. A porto-caval shunt was established in 274 patients (61%) vs. 174 patients (39%) without a shunt. The morbidity rate due to the insertion of a shunt was 0.73% with two lymphatic fistulas documented. The mean follow-up was 50.5 [0–163.0] months.

Patient characterization with respect to shunt application

The median Lab MELD score and the rate of high urgency transplantations did not differ whether a shunt was inserted or not (Table 1). The average recipient age was lower in patients receiving a shunt than in those without a shunt: 46.0 [10.0–84.0] vs. 52.0 [11.0–79.0] years, $P < 0.001$. Furthermore, the percentage of indications within the compared groups did not differ with respect to the insertion of a shunt, except in the group of transplantations not classifiable to those categories (Table 1).

Intraoperative course

Transfusion requirement, vasopressor support, organ blood flow

The number of transfused packed red blood cells did not differ between the groups: 5.0 ± 4.0 (shunt) vs. 4.4 ± 5.0,

Table 1. Recipient characteristics.

	Shunt		
	Yes (*n* = 274)	No (*n* = 174)	*P*-value
Recipient age	46.0 (10.0–84.0)	52.0 (11.0–79.0)	<0.001
MELD Score	20 (2–40)	21 (5–40)	0.103
High urgency-transplantation (%)	11 (44)	14 (56)	>0.05
Indications for liver transplantation: *N* (% within groups shunt versus no shunt)			
Alcoholic cirrhosis	57 (20.8)	37 (21.3)	0.907
Malignancy	65 (23.7)	29 (16.7)	0.074
Acute liver failure	18 (6.5)	16 (9.2)	0.306
Viral hepatitis	65 (23.7)	32 (18.4)	0.182
Primary biliary cirrhosis	30 (10.9)	16 (9.2)	0.551
Others	39 (14.2)	44 (25.3)	0.003

(no shunt), $P = 0.80$. Moreover, the number of fresh frozen plasma concentrates transferred could not be correlated with the use of a shunt: 21.1 ± 1.2 (shunt) vs. 19.6 ± 1.1 (no shunt), $P = 0.806$.

Continuous infusion of vasopressors was significantly reduced in patients receiving a shunt: The infusion rate of norepinephrine in patients receiving a shunt was 1.60 ± 0.8 mg/h vs. 1.88 ± 1.0 mg/h without shunt, $P = 0.012$. Similarly, the infusion rate of epinephrine was decreased in patients receiving a shunt: 0.08 ± 0.03 mg/h vs. 0.09 ± 0.02 mg/h, $P = 0.002$).

Intraoperative portal venous blood flow following reperfusion significantly correlated with the usage of a temporary porto-caval shunt-catheter and was elevated to 1727 ± 48 ml/min in patients with a shunt compared with 1431 ± 63 ml/min in patients without a shunt ($P < 0.001$). In contrast, no such correlation was evident with respect to hepatic arterial blood flow ($P = 0.792$) (Table 2).

Postoperative course

Hepatic cellular injury

ALT and AST levels were significantly decreased on the first, second, and seventh postoperative day in patients transplanted with a temporary porto-caval shunt ($P < 0.001$) compared to patients without a shunt (Fig. 2a and b).

Hepatic- and renal function

Establishment of an intraoperative shunt was associated with a significant reduction in serum bilirubin levels on the first day following liver transplantation ($P = 0.023$) (Fig. 2c). In contrast, prothrombin ratio [Quick (%)] was not affected by the usage of a shunt (Fig. 2d).

Serum creatinine levels measured on the first, second, and seventh postoperative day were also not affected by the application of a shunt ($P > 0.05$).

Causes of early graft loss

Within the study period, a total of 13 grafts failed within the first postoperative month with consecutive retransplantation. While 12 cases of early graft loss occurred in grafts without a shunt, only one graft loss was apparent following transplantation with a shunt ($P < 0.001$). The causes of early graft loss were categorized into the following subgroups: PNF, vascular and others. Graft losses were distributed as follows: No shunt: PNF 7 (58%), Vascular 4 (33%), others 1 (8%); shunt: PNF 1 (100%).

Table 2. Application of a shunt and correlation with liver blood flow.

	Shunt	No shunt	*P* (Mann–Whitney *U*-test)
n (%)	274 (61.2)	174 (38.8)	
Portal vein	1724 ± 48	1431 ± 63	<0.001
Hepatic artery	205 ± 8	205 ± 10	0.792

A subgroup analysis also indicates that patient and donor characteristics were equal in patients undergoing retransplantation with respect to the insertion of a shunt. DRI did not differ significantly in patients retransplanted whether a shunt was utilized or not ($P = 0.484$): 1.63 ± 0.08 (shunt) vs. 1.74 ± 0.07 (no shunt) (mean ± SEM; Mann–Whitney *U* test.). The lab MELD score did also not show differences between the subgroups: 26 ± 2 (shunt) vs. 27 ± 2 (no shunt), $P = 0.729$. According to univariate, not multivariate regression analysis, the insertion of a shunt significantly reduced the risk of graft loss within the early phase following liver transplantation ($P = 0.04$). DRI and lab MELD score did not affect early graft loss.

Retransplantation

Forty-three retransplantations were performed during the whole observation period after the first month. Within this period, significantly less retransplantations were evident in patients receiving a shunt compared to those transplanted without a shunt [*n* (%)]: 20 (7.3) vs. 23 (13.2), $P = 0.038$.

Altogether, 56 patients underwent retransplantation over the entire observation period. Within this group, 35 reoperations (20%) were performed in patients that had been initially operated without a shunt compared with 21 reoperations in patients that had not been receiving a shunt.

Graft survival

Univariate analysis revealed an increased long-term graft survival when a porto-caval shunt was applicated with a mean survival (CI) of 106 [98.0–115.7] months vs. 86.5 [73.5–99.5] months, $P = 0.001$ (Table 3; Fig. 3a). When patients with PNF were excluded from the analysis, these results did not change: 108.0 [99.1–116.9] vs. 88.5 [75.4–101.6] month, $P = 0.002$ (Table 3).

In 2007, the MELD score was introduced in the Eurotransplant allocation system. Therefore, the study period was divided into periods from 1997 till 2006 and 2007 till 2010. In this respect, the mean survival did not differ between the periods (Table 3).

A subgroup analysis with respect to recipients' lab MELD scores (MELD <35 vs. $\geq$ 35) and the application of a shunt revealed an increased graft survival in patients with a MELD Score $\geq$ 35 when a shunt was established. Mean survival increased from 39.9 [21.5–58] months to 101.2 [73.2–129.1] month, $P = 0.049$ (Fig. 3b; Table 3). Moreover, in recipients with a MELD Score <35 graft survival rose from 70.9 [60.8–80.9] to 110.0 [100.1–113.9] month, when a shunt was inserted, P (log rank) = 0.001 (Fig. 2b).

According to CRT-analysis, grafts were divided into groups with a donor risk index < or $\geq$ 1.25 with regard to

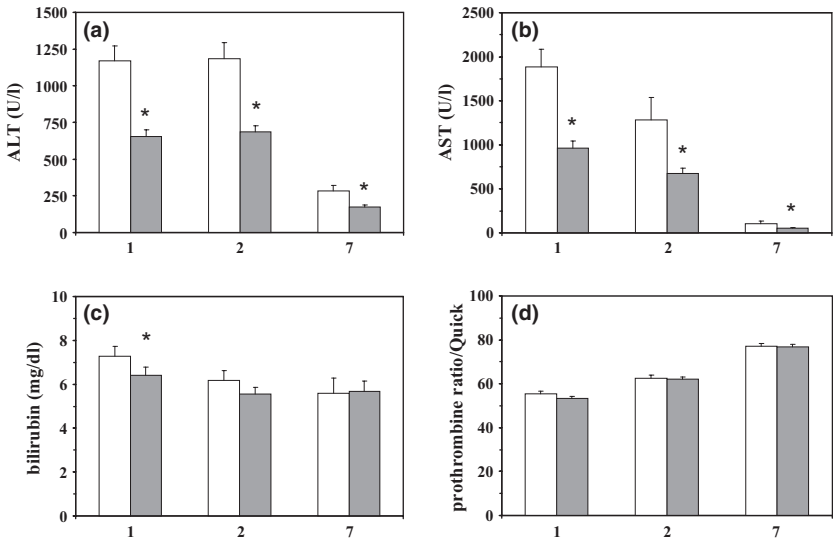

Figure 2 Serum ALT levels (U/l) (a), AST levels (U/l) (b), bilirubin levels (ml/dl) (c), and prothrombin ratio [Quick (%)] (d) were determined on the first, second, and seventh postoperative day following liver transplantation with respect to the insertion of a porto systemic shunt (white column: no shunt, gray column: shunt). Values are presented as mean ± SEM. (a–c): *$P < 0.001$ shunt versus no shunt.

the application of a shunt. In this respect, graft survival increased from 77.7 [62.7–92.7] to 99.6 [88.9–110.3] months in grafts with a donor risk index ≥ 1.25 if a shunt had been applicated, $P = 0.002$ (Fig. 3c).

Other potential confounders: multivariate analysis

Associations of collected variables with long-term graft survival (Cox model) in the univariate analysis are shown in Table 3. Donor age (>65 years), recipient age (>60 years), degree of steatosis, type of preservation solution (UW versus HTK), high urgency transplantation, malignancy, epinephrine treatment in donor, total ischemic time ≥ 12 h, or a lab MELD Score ≥ 35 did not affect survival ($P > 0.10$).

Potential confounders with a p value <0.05 in the univariate analysis were included in the multivariate model: retransplantation, arterial flow <100 ml/min, no use of a shunt and a DRI $\geq$ 1.25. No shunt, hepatic arterial blood flow <100 ml/min as well as a donor risk index ≥ 1.25 were identified as independent risk factors for decreased graft survival in the covariate–adjusted model (Table 4).

Discussion

Cava sparing liver transplantation in piggy back technique in combination with partial cava clamping during implantation may provide better hemodynamic stability as compared with full cava clamping in conventional technique [10]. Early division of the recipient portal vein substantially facilitates hepatectomy in piggy back technique. However, prolonged portal venous clamping during hepatectomy may lead to portal venous hypertension and splanchnic congesting with this technique. To decompress the portal venous system during hepatectomy, two principal shunting techniques have been established: (i) *In situ* portal venous shunt by an temporary end-to-side anastomosis of the the PV to the infrahepatic vena cava (ii) a spontaneous *ex situ* shunt. In animal models, an interruption of portal flow for up to 90 min resulted in increased permeability of splanchnic vessels, intestinal edema of the gut, and the accumulation of acute inflammatory cells with evidence of mucosal cell damage [22,23]. In light of those pathophysiological changes caused by an acute rise in portal venous pressure, the use of a temporary porto-caval shunt has been described by Tzakis *et al.* [14]. In those studies, a temporary end-to-side anastomosis was formed between the recipient's portal vein and the infrahepatic inferior vena cava. In contrast, an extracorporal shunt catheter is used at our institution, which is directly placed in the portal vein after dissection and connected to a catheter previously placed in the femoral vein to establish a spontaneous temporary porto-caval blood flow. Utilization of temporary porto-caval shunts was initially recommended for patients with portal hypertension caused by acute or subacute liver failure who are expected not to have adequate portosystemic venous collaterals [14]. Surprisingly, a subgroup analysis of patients transplanted for acute liver failure revealed no statistical difference in organ survival compared with patients transplanted for chronic liver diseases (data not shown). The small number of transplantations for acute liver failure ($n = 34$) may account for the lack of statistical significance. Therefore, experimental studies are required to further

Table 3. Univariate analysis.

	n (%)	Mean survival [months] [CI]	*P* (log rank) univariate analysis
Total	448 (100)		
Recipient age			
<60 years	377 (84.2)	99.6 [91.7–107.5]	0.494
≥60 years	71 (15.8)	92.9 [74.8–111.0]	
High urgency			
No	423 (94.2)	98.4 [90.9–105.8]	0.720
Yes	25 (5.8)	105.4 [78.0–132.7]	
Retransplantation			
1. LTx	381 (85.0)	102.8 [95.0–110.6]	0.003
Re-LTx	67 (15.0)	73.6 [54.0–93.1]	
Shunt			
No	174 (38.8)	86.5 [73.5–99.5]	0.001
Yes	274 (61.2)	106.8 [98.0–115.7]	
Shunt (excl. primary graft nonfunction)			
No	170 (38.5)	88.5 [75.4–101.6]	0.002
Yes		108.0 [73.5–99.5]	
Time period			
1997–2006	303 (67.6)	97.6 [89.3–105.9]	0.537
2007–2010	145 (32.4)	31.8 [28.9–34.7]	
Total ischemia time			
<12 h	339 (81.7)	99.6 [91.3–108.0]	0.831
≥12 h	76 (18.3)	98.3 [80.8–115.8]	
Donor age			
<65 years	324 (81.4)	100.4 [92.1–108.7]	0.367
≥65 years	74 (18.6)	95.3 [75.1–115.6]	
Resuscitation donor			
No	353 (86.9)	100.0 [91.8–108.1]	0.986
Yes	53 (13.1)	90.8 [71.6–109.9]	
Shock donor			
No	313 (77.5)	101.2 [92.6–109.9]	0.538
Yes	91 (22.5)	87.9 [73.9–101.9]	
LabMELD Score			
<35	317 (79.4)	101.4 [92.9–110.0]	0.023
≥35	82 (20.6)	85.6 [68.1–103.0]	
Shunt and LabMELD Score			
I: Shunt/MELD < 35	207 (51.9)	110.0 [100.1–119.9]	I vs. II 0.001
II: No Shunt/MELD < 35	141 (35.3)	70.9 [60.8–80.9]	
III: Shunt/MELD ≥ 35	28 (7.0)	101.2 [73.2–129.1]	III vs. IV 0.049
IV: No Shunt/MELD ≥ 35	23 (5.8)	39.9 [21.5–58.3]	
Donor risk indices (DRI)			
DRI < 0.125	88 (20.0)	125.6 [112.3–138.9]	<0.001
DRI ≥ 0.125	351 (80.0)	90.4 [81.9–98.8]	
Shunt and DRI			
I. Shunt/DRI < 1.25	201 (45.8)	123.7 [108.2–139.3]	III vs. IV 0.002
II. No Shunt/DRI < 1.25	150 (34.2)	106.3 [86.1–126.4]	
III. Shunt/DRI ≥ 1.25	66 (15.0)	99.6 [88.9–110.3]	
IV. No Shunt/DRI ≥ 1.25	22 (5.0)	77.7 [62.7–92.7]	

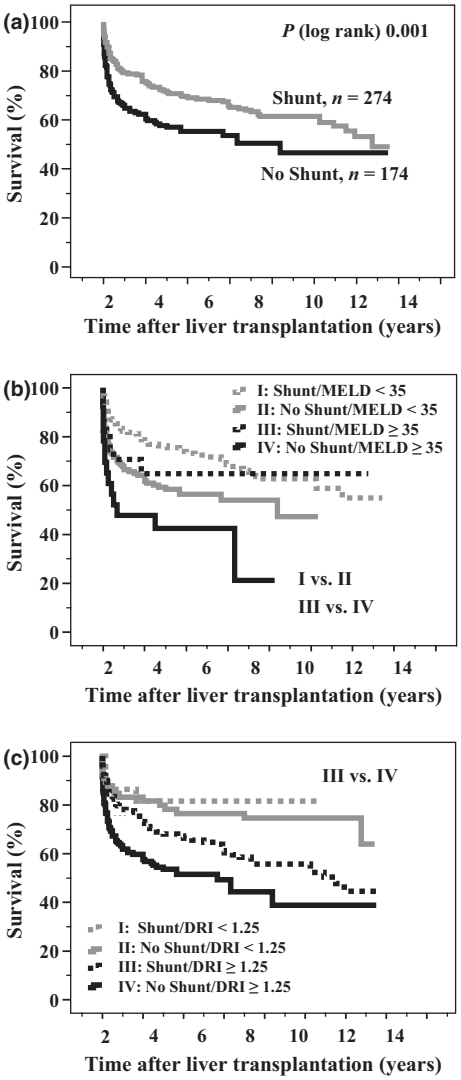

Figure 3 (a) Cumulative graft survival (10 years) after liver transplantation with regard to the insertion of a spontaneous porto caval shunt. Shunt (gray line), no shunt (black line). 106.8 [98.0–115.7] vs. no shunt 88.5 [73.5–99.5] months; $P = 0.001$. (b) Cumulative graft survival after liver transplantation with regard to the insertion of a spontaneous porto caval shunt and the recipients' lab MELD Scores. I: Shunt and MELD < 35 (gray perforated line); II: shunt and MELD ≥ 35 (gray line); III: no shunt and MELD < 35 (black perforated line); IV: no shunt and MELD ≥35 (black line). I vs. III: $P = 0.001$; II vs. IV: $P = 0.049$. C: Cumulative graft survival after liver transplantation with regard to the insertion of a spontaneous porto caval shunt and the Donor Risk Index. I: Shunt and donor risk indices (DRI) < 1.25 (gray perforated line); II: no shunt and DRI < 1.25 (gray line); III: shunt and DRI ≥ 1.25 (black perforated line); IV: no shunt and DRI ≥ 1.25 (black line). I: Shunt and DRI < 1.25 (gray perforated line); II: no shunt and DRI < 1.25; III: shunt and DRI ≥ 1.25; IV: no shunt and DRI ≥ 1.25. III vs. IV: $P = 0{,}002$. Values are presented as mean ± SEM.

clarify the underlying mechanisms of the protective effects of intraoperative shunts. The routine use of temporary porto-caval shunts in liver transplantation, however, is

Table 4. Multivariate analysis.

Prognostic factors	Hazard rate ratio [CI]	*P*
Transplantation without shunt	2.1 [1.4–3.0]	<0.001
Flow hepatic artery <100 ml/min	2.1 [1.3–3.2]	0.001
DRI $\geq$ 1.25	3.2 [1.7–5.9]	<0.001

discussed controversially in the literature [24]. Despite the theoretical arguments in favor of a systematic use of porto-caval shunts, their clinical benefit remains the subject of controversy [25,26]. Hoffmann *et al.* [25] state in their review that shunts are not required for successful liver transplantation. Although this review analyzed utilization of shunts during en bloc transplantation with resection of the caval vein, it must be stated that the rationale for the insertion of a shunt, a reduction in venous stasis, is the same in both techniques. Nevertheless, basic differences between cava sparing and cava resecting liver transplantation may account for the discrepancy in the results. In particular, the mechanisms and effects of portosystemic shunts on hepatic injury remain unclear. Thus, it was the aim of this study to determine whether usage of a temporary porto-caval shunt-catheter may reduce liver damage after ischemia reperfusion and affect long-term graft survival.

The use of a portal venous shunt was associated with lower levels of aminotransferases for up to 7 days, suggesting a lowered degree of postischemic injury in this group of patients. In contrast, Ghinolfi *et al.* [26] could not show such effects in their retrospective analysis in 148 cava sparing liver transplantations. The smaller number of patients compared to this study may account for this discrepancy. Figueras *et al.* [12] also failed to demonstrate beneficial effects of porto-caval shunts on postoperative aminotransferase levels. Four-months graft survival rates in this study, however, were more than 97% in both groups suggesting differences in the patient collectives in terms of donor and recipient characteristics compared to the Eurotransplant allocation area [27]. Moreover, only 80 patients were included in this prospective trial. In addition to liver injury, beneficial effects of porto caval shunt utilization on blood product transfusion, intraoperative hemodynamics, and ease of retrohepatic dissection with a shorter operative time have been observed in liver transplantation with the use of a porto-caval shunt [24,26]. The subjective surgeon's impression at our institution suggests that establishment of a porto-caval shunt helps to control intraoperative blood loss. This impression, however, was not reflected in reduced blood product substitution in patients with porto-caval shunt.

A recent study reports beneficial effects of porto-caval shunting on postreperfusion hemodynamic instability, which is associated with significantly adverse postoperative outcome [28]. In this respect, increased organ survival in recipients transplanted with a temporary shunt using multivariate analysis considering all known potential confounders was shown. The absence of an intraoperative shunt in this study was identified as a significant risk factor for diminished organ survival with a hazard ratio of 2.1. As opposed to this finding, Ghinolfi *et al.* [26] failed to demonstrate such an effect in multivariate analysis. Even excluding patients with a primary nonfunction, this survival benefit was still present in our study. Our results imply that intraoperative portal-caval shunting may be associated with improved long-term survival.

Utilization of a temporary intraoperative porto-caval shunt was based on subjective assessment of the responsible surgeon, including personal preference or the presence of potentially adequate portosystemic collaterals. This represents an obvious limitation. Despite significant effects of the MELD score on organ survival in univariate analysis, this parameter failed to reach statistical significance in multivariate analysis. One potential explanation could be that the number of cases with a MELD score $\geq$35 is too small (n = 82). Moreover, sick patients with a MELD score $\geq$35 generally receive grafts with good quality. This policy may to some extent compensate for the reduced health condition of those patients.

The recipient age was significantly higher in patients transplanted with a porto-caval shunt (52 vs. 46 years, respectively). In uni- and multivariate analysis, however, recipient age was not identified as a significant risk factor for organ survival. Nonetheless, a potential bias cannot be excluded in this study. In contrast to previous trials, a donor age $\geq$65 years as well as a recipient's age >60 years did not influence graft survival in this study ($P > 0.05$). In an analysis incorporating 22089 liver transplant patients, Adam *et al.* [21] showed statistical significance for these risk factors in multivariate analysis. A risk ratio of <1.3 was evident for a recipient age $\geq$60 years (RR 1.29) and for a donor age >55 years (RR 1.14). This relatively small effect may suggest limited clinical relevance in light of critical organ shortage. In this respect, the large number of patients included in the study of Adam *et al.* could explain the discrepancy in significance levels. Moreover, only a relatively small number of older recipients and grafts has been transplanted compared to the rest of the population in this study (recipients: 377 vs. 71; donors: 324 vs. 74), which may be another explanation of the lack of statistical significance.

Previous studies indicate the importance of portal blood flow and gradient measurements prior to hepatectomy in deciding who should be selected for shunt utilization [12,29]. Patients with high portal flow and elevated porto-caval gradient benefited particularly on post-transplant renal function when using a temporary porto-caval shunt. Margarit *et al.* defined the cut-off for high versus low portal flow prior to hepatectomy as 800 ml/min. Based on

those findings, measurement of portal blood flow prior to hepatectomy might represent an objective tool for selecting patients who should be transplanted with a temporary porto-caval shunt. This, however, should be clarified in a prospective trial.

As liver transplantation faces serious problems concerning extended criteria donors and recipients in poor conditions represented by high MELD scores, a subgroup analysis on the efficacy of shunt utilization was performed in this study with respect to the donor risk index and the recipients' MELD score. Ghinolfi *et al.* [26] however, failed to show such effects when stratifying the population by low and high MELD scores. Interestingly, the application of a shunt exhibited beneficial effects on graft survival especially in high risk transplantations, that is with poor graft quality (DRI $\geq$ 1.25) and a high Lab MELD score ($\geq$35). Although the relevance of poor graft quality and bad recipient conditions differs regionally, a general advice for shunt utilization might be supported by the present data. In contrast to our own results, Mehrabi *et al.* [30] postulated that usage of porto-caval shunts is not required when performing piggy back technique liver transplantation. This center, however, utilized porto-caval shunts in only 1.4% of 500 patients. Thus, this manuscript does not allow drawing valid conclusions of shunt utilization on organ outcome.

The exact underlying mechanisms for the protective properties of a temporary porto-caval shunt remain unknown. Nonetheless, in our series, application of a porto-caval shunt catheter was associated with significantly increased portal blood flow following reperfusion. This result may in part explain the beneficial effects of shunt usage, as enhanced portal blood flow has been shown to be associated with reduced liver injury previously [19]. Furthermore, incidence of postreperfusion syndrome was reduced after utilization of a temporary porto-caval shunt [28]. Whether solely those improvements in hemodynamics account for the ameliorated postoperative transaminase levels in patients with porto-caval shunt remains unknown. Alternatively, mediators released from the gut that is proinflammatory cytokines, endotoxin, chemokines etc. caused by splanchnic congestion, may be responsible for the observed liver injury in patients without a shunt. In this respect, induction of inflammatory responses in the liver, that is expression heat shock proteins [31] as well as remote organ injury following portal vein occlusion have been reported [32]. The implication of those potential mechanisms for the beneficial effects of maintained portal drainage versus portal occlusion during liver transplantation, however, has to be further investigated.

In summary, the insertion of a temporary porto-caval shunt catheter reduces cellular damage in patients with cava sparing liver transplantation. Shunt usage was associated with increased portal blood flow following reperfusion, which may in part explain the beneficial effects on hepatic injury. Moreover, the insertion of a shunt was associated with an improved graft survival. This effect was more pronounced in recipients with high MELD scores and recipients of marginal donor organs. Therefore, the application of a temporary porto-caval shunt catheter is advisable in cava sparing OLT especially for recipients of marginal organs. Nonetheless, a prospective randomized multicenter trial should be initiated to confirm this important observation in light of an increased frequency of transplantation of marginal grafts due to organ shortage.

Authorship

SP: Participated in research design and writing of the manuscript. GM: Participated in data analysis. CJB: Participated in research design and writing of the manuscript. MK: Participated in research design. NP: Participated in data analysis. RZ: Participated in the writing of the manuscript. MG: Participated in research design. K-WJ: Participated in research design. FL: Participated in research design and writing of the manuscript. MKA: Participated in research design and writing of the manuscript.

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Conflict of interest

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