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ORIGINAL ARTICLE

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Coagulation profiles and intraoperative substitution requirements during elective piggyback liver transplantation with prophylactic antifibrinolytic therapy

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Abstract During recent years, piggyback liver transplantation (pOLT) with preservation of the retrohepatic vena cava has been introduced in adults. The objective of this study was to evaluate hemostatic changes associated with this transplantation technique. Fifty-seven patients undergoing elective pOLT for endstage liver disease were studied. Most significant changes were observed after graft reperfusion, when PT showed a 49% decrease and activated partial thromboplastin time (aPTT) as well as TT a 2- to 3-fold prolongation. At the same time, factors of the extrinsic coagulation pathway (II, V, VII) revealed an overall 50% decline. Similar changes were observed for antithrombin III (ATIII) and fibrinogen plasma levels. However, only 42% of all patients required intraoperative substitution with coagulation components. There was an association between preoperative fibrinogen (< 1.7 g/dl) and ATIII ($< 50\%$) plasma levels and the substitution requirement. Multiple linear regression showed a significant correlation between preoperative ATIII activity and intraoperative blood loss. Despite a marked impairment of hemostasis, pOLT can frequently be performed with minimized substitution therapy.

Keywords Coagulation profiles · Substitution therapy · Liver transplantation

Introduction

The hazard of hemostatic imbalances is a well known feature during orthotopic liver transplantation (OLT) in humans, frequently necessitating the intraoperative substitution of rather large quantities of coagulation factors and blood products [3, 12, 17, 19, 23]. In this context, different factors contribute to the abnormalities of the coagulation system, which may sustain intraoperative bleeding. The underlying liver disease with impaired liver function coincides with a deficient hepatic synthesis of coagulation factors and their inhibitors [12, 23]. As a result, abnormal preoperative levels of procoagulants and coagulation factors (I, II, V, VII, IX–XIII) [2, 11, 14, 18, 19, 22], inhibitors (AT-III and alpha-2-antiplasmin) [1, 26, 27] and regulatory proteins (C1 inhibitor and prekallikrein) [7, 27] are frequently observed. In addition, portal hypertension, peripheral vasodilatation, and thrombocytopenia are frequently found in states of liver cirrhosis [12, 23]. Characteristic features of hemostatic disorders during standard OLT are disseminated intravascular coagulation (DIC) and fibrinolysis as well as abnormal platelet counts and function [1, 10, 12, 18, 19, 23]. These changes can be observed during the anhepatic phase of liver transplantation, but particularly after graft reperfusion.

The standard technique of OLT, which involves the resection of recipient liver along with the retrohepatic vena cava [4, 30], may further increase the risk of intraoperative bleeding due to the transient caval occlusion. Although the introduction of veno-venous bypass, which maintains venous blood circulation

during the anhepatic stage with caval occlusion, has reduced hemodynamic instabilities and intraoperative bleeding problems [28, 29], considerable blood loss and hemostatic abnormalities are frequently observed [13, 16, 19]. During recent years, the technique of piggyback liver transplantation (pOLT) without intraoperative occlusion and resection of the retrohepatic vena cava has been developed, maintaining physiologic recirculation of venous blood during all stages of liver transplantation [5, 6, 31]. Although the impact of standard OLT on the coagulation system has been extensively studied, the intraoperative hemostatic imbalances associated with pOLT have not been evaluated. Therefore, we retrospectively analyzed general coagulation profiles with special emphasis on the extrinsic coagulation pathway as well as the substitution requirements during elective pOLT, which was routinely performed with prophylactic antifibrinolytic administration of aprotinin.

Material and method

Between July 1995 and October 1999, a total of 122 liver transplants were performed at our institution. In 113 cases, pOLT was achieved (92.6%). Sixteen patients received multiorgan transplants (liver, pancreas, and/or kidney). Two patients were excluded due to portal vein thrombosis necessitating portal vein reconstruction. Other exclusion criteria were emergency transplantation ($n=17$), liver retransplantation ($n=4$), primary malignant diseases ($n=11$), and other liver diseases (liver cysts, Budd-Chiari syndrome, $n=6$). The remaining 57 patients underwent elective pOLT for endstage liver disease with histologically confirmed liver cirrhosis. Patients' demographics, diagnosis, and Child-Pugh scores [24] are summarized in Table 1.

The pOLT was performed as previously described [5, 31]. Caval anastomosis was performed to the recipient hepatic veins without cross clamping of the recipient vena cava. During the anhepatic phase of liver transplantation, the portal vein of the recipient was cross clamped. No temporary portocaval anastomosis was performed.

Prophylactic antifibrinolytic therapy was routinely employed. A loading dose of 1 million IE aprotinin (Trasylol) was administered after induction of anesthesia followed by 500,000 IE per h throughout the operation. In all cases, a heparin-coated cellsaver system was used. Erythrocyte concentrates were substituted when hemoglobin levels fell below 5 mmol/l (8 g/dl). Coagulation concentrates were substituted when diffuse intraoperative oozing, which could not be controlled by surgical means, was recognized in conjunction with abnormal coagulation profiles. Thus substitution therapy was not guided by strict cutoff values.

Table 1. Clinical characteristics of 57 patients undergoing elective pOLT

	Total, $n=57$
Median age in years (range)	51 (17–69)
Sex (female/male)	17/40
Diagnosis	
Alcoholic cirrhosis	22 (42%)
Hepatitis B/C cirrhosis	18 (31.5%)
Primary biliary cirrhosis	3 (5.2%)
Primary sclerosing cholangitis	4 (7%)
Hemochromatosis	2 (5.5%)
Unknown	6 (10.5%)
Child classification	
A	7 (12.2%)
B	16 (28%)
C	29 (50.8%)

Laboratory monitoring of hemostasis included prothrombin time (PT), activated partial thromboplastin time (aPTT), and thrombin time (TT), which were routinely determined at the following time points of pOLT: at the beginning of surgery (I), 10 min into the anhepatic phase (II), 10 min after reperfusion of the graft (III), and at the end of surgery (IV). In addition, plasma levels of factor I, II, V, and VII and antithrombin III were measured using standard laboratory methods. All data were retrospectively collected and analyzed.

With the exception of PT, which is shown as percent of normal activity (normal range 70–130%), the international system of units (SI) was used. Normal reference values were as follows: factor II, V, VII: 70–130%; ATIII: 80–120%, fibrinogen 1.5–4.5 g/l, platelets 150–380 Gpt/l, aPTT 29–41 seconds (s) and TT 15–22 s.

The intraoperative substitution (units) of erythrocytes (EC), platelets (Pl), and fresh frozen plasma (FFP) was recorded. The amount of collected and autotransfused cellsaver blood was calculated in milliliter (ml). The administration of antithrombin III (ATIII, IE) (Atenativ, Kybernin), fibrinogen (Haemocomplettan, g), and factors of the prothrombin complex (PPSB) (factor II, VII, IX, X, Prothromplex, Beriplex, IE) were determined.

All data was tested at each point in time for normal distribution using the Kolmogorov-Smirnov test (Lilliefors), placing the confidence level at 95%. Since normal distribution was not always confirmed, results are shown as median values and range to provide an objective comparison. The significance of differences between nonparametric data was assessed using the Wilcoxon's signed rank test and the Mann-Whitney U test. The chi-squared test (P values corrected with Yates method) was used to compare qualitative variables. The influence of single coagulation factors on intraoperative blood loss was assessed by one-way regression analysis, multiple regression analysis with backward elimination, and Pearson's correlation. Probability values of $P<0.05$ were regarded as statistically significant.

Results

Changes of the extrinsic coagulation system as generally analyzed by PT are shown in Fig. 1. Preoperatively, PT had a median of 55% (range 25–95%) in all patients. Thereafter, it constantly declined to 28% (range 9–73) after reperfusion of the graft ($P<0.05$). Only marginal improvements were seen at the end of surgery (median 32%, range 12–77).

Profound changes were also found within the intrinsic coagulation pathway (Fig. 1). The aPTT steadily increased from a median of 52.2 s (range 26.4–78.3 s) preoperatively to 110.2 s (range 60.4–237.8 s) after graft reperfusion ($P<0.05$). At this point in time, aPTT could only be measured in 18 of 57 patients (31.5%).

In contrast, TT showed a sharp increase from normal values during the anhepatic phase (median 17.3 s, range 15–25 s) to a median of 38 s (range 16.7–206.0 s) after graft reperfusion ($P<0.05$), when TT could only be determined in 13 of 57 patients (22.8%). At the end of

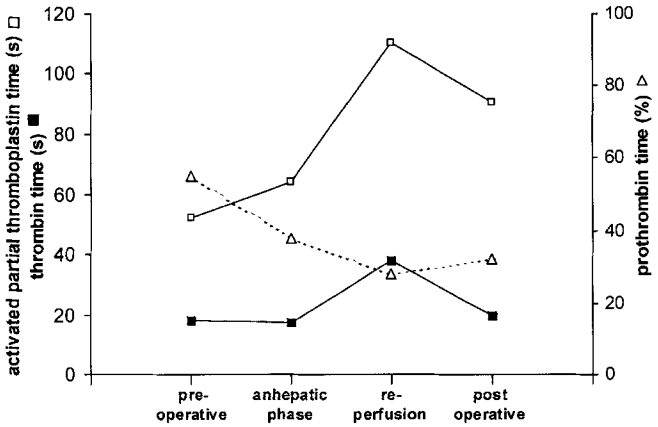

Fig. 1. Intraoperative changes of prothrombin time (%), activated partial thromboplastin time (s) and thrombin time (s) at different time points during pOLT

surgery, TT rapidly improved to almost normal values (median 20 s, range 14.7–33.6 s), whereas aPTT was still significantly prolonged, with a median of 99.5 s (range 41.5–207.8 s). At this point in time, aPTT was measurable in 40 of 57 patients (70%).

The overall intraoperative changes of single factors of the extrinsic coagulation pathway are shown in Fig. 2. Starting with suboptimal plasma levels of 43% to 51% preoperatively, factor II, V, and VII activity further declined to 20% to 25% after liver reperfusion ($P < 0.05$). With the exception of factor V, the plasma levels of factor II and VII slightly recovered at the end of surgery. Similar alterations of plasma activity were documented for ATIII (Fig. 2). In addition, plasma fibrinogen dropped from a median of 2 g/l (range 0.5–5.1) preoperatively to 1.1 g/l (range 0.3–3) after reperfusion ($P < 0.05$) without any improvements to the end of surgery.

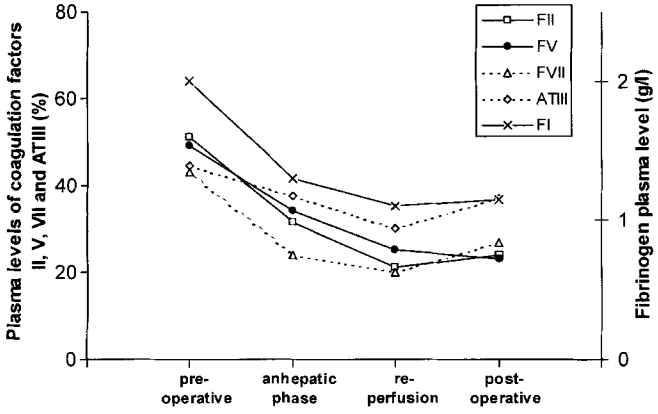

Fig. 2. Intraoperative changes of coagulation factors I (fibrinogen), II, V, and VII and antithrombin III (ATIII) at different time points during pOLT

The overall platelet counts were decreased but stable throughout pOLT ranging between a median of 65 Gpt/l and 73.5 Gpt/l.

Despite deteriorated hemostasis, the overall substitution requirements were low (Table 2). Only 24 of all 57 patients (42.1%) with elective pOLT required an intraoperative administration of coagulation components. Two patients (3.5%) were solely substituted with EC (two units each). Considering a median volume of autotransfused cellsaver blood of 1089 ml and the usual crystalloid infusions (Table 3), the majority of transplants (54.3%) could be performed without any intraoperative substitution of coagulation factors and EC. The quantitative substitution requirements are depicted in Table 3.

The reasons for the intraoperative therapy with coagulation components and EC in 26 patients are shown in Table 4. Substituted patients frequently revealed decreased pre- and intraoperative coagulation profiles as compared to nonsubstituted patients, although both patient groups were comparable with regard to preoperative Child-Pugh score and the preexisting liver disease (data not shown) as well as early postoperative liver graft function (Table 5).

Table 2. Intraoperative substitution therapy in 57 patients undergoing pOLT. *EC* erythrocyte concentrate, *PI* platelet concentrate, *ATIII* antithrombin III, *PPSB* prothrombin complex, *FFP* fresh frozen plasma, *Fib* fibrinogen

Intraoperative substitution	*N* patients
PPSB + ATIII + FFP + EC + PI + Fib	1
PPSB + ATIII + FFP + EC + PI	1
PPSB + ATIII + EC + PI	1
PPSB + ATIII + FFP + PI	1
PPSB + ATIII + FFP + EC	1
PPSB + ATIII + EC	9
PPSB + ATIII + PI	1
PPSB + ATIII	1
PPSB + EC	1
PPSB + Fib	1
ATIII + EC	3
ATIII	2
PPSB	1
EC	2
Total	26 (45.6%)
No substitution	31 (54.3%)

Table 3. Quantitative substitution requirements during pOLT

Components	*N* patients	Median (range)
Cell saver blood	57	1,089 ml (145–3,377)
Crystalloids	57	5,000 ml (1,000–10,000)
Antithrombin III	21	3000 IE (1,000–7,000)
Prothrombin complex	19	2000 IE (500–6,000)
Erythrocyte concentrates	19	3 units (2–8)
Platelet concentrates	5	4.5 units (3–5)
Fresh frozen plasma	4	4.5 units (3–5)
Fibrinogen	2	4 g (3–5)

Table 4. Intraoperative changes of different coagulation parameter in patients with and without intraoperative substitution therapy (PPSB, ATIII, FFP, EC, Pl, Fib)

	Preoperative	Anhepatic phase	Reperfusion	Postoperative
		Prothrombin time (%)		
Nonsubstituted patients	58 (34–95)	45 (24–89)	32 (16–73)	32 (14–77)
Substituted patients	43.5 (25–73)*	32 (15–56)*	21.5 (9–44)*	28.5 (12–65)
		Activated partial thromboplastin time (s)		
Nonsubstituted patients	49.7 (26.4–78.3)	55.8 (41.1–102.7)	100 (60.4–232)	89.6 (41.5–164.5)
Substituted patients	56.6 (33.5–71.4)*	82.4 (39.5–121.8)*	194 (106.9–237.8)	134.7 (55.4–207.8)
		Thrombin time (s)		
Nonsubstituted patients	17.7 (16.2–24.4)	17.1 (15.6–23.7)	33.7 (16.7–148)	19.6 (14.7–33.6)
Substituted patients	18.9 (13.6–22.9)	19 (15.1–25)	62.3 (31.5–206)	22.9 (16–32.6)
		Fibrinogen (Factor I) (g/l)		
Nonsubstituted patients	2.3 (1.1–4.2)	1.7 (0.4–4.6)	1.4 (0.6–3)	1.4 (0.7–3.2)
Substituted patients	1.5 (0.5–5.1)*	1.2 (0.3–3.7)*	1.0 (0.3–2.2)*	1.0 (0.3–3)*
		Prothrombin (Factor II) (%)		
Nonsubstituted patients	56 (11–125)	39 (8–135)	25 (5–84)	21.5 (3–87)
Substituted patients	34.5 (12–103)*	25 (7–80)*	15 (2–72)*	31 (5–115)
		Factor V (%)		
Nonsubstituted patients	55 (32–144)	40.5 (23–119)	28 (17–72)	25 (10–82)
Substituted patients	40.5 (20–168)*	28.5 (13–85)*	18.5 (7–44)*	17 (6–39)*
		Factor VII (%)		
Nonsubstituted patients	50 (15–124)	36.5 (9–119)	25 (5–66)	27 (8–79)
Substituted patients	26 (11–105)*	20.5 (6–57)*	15.5 (3–48)*	26 (10–86)
		Antithrombin III (%)		
Nonsubstituted patients	57.5 (26–135)	39 (18–127)	31 (12–92)	32 (12–95)
Substituted patients	38.5 (12–116)*	24 (9–76)*	29.5 (0–107)	48 (3–118)*
		Thrombocytes (%)		
Nonsubstituted patients	74 (24–294)	92 (33–278)	95 (35–232)	85.5 (36–330)
Substituted patients	60 (10–458)	62 (11–344)*	54.5 (13–314)*	57 (24–442)*

*Statistically significant difference between substituted and nonsubstituted patients (Mann Whitney U test, $P < 0.05$)

Table 5. Early liver graft function (first postoperative day) after pOLT as indicated by aspartate (AST) and alanine (ALT) aminotransferase and glutamate dehydrogenase (GLDH). Differences between both groups were statistically not significant

	AST (μmol/l)	ALT (μmol/l)	GLDH (nmol/l)
Nonsubstituted patients (range)	3.9 (1.8–25)	3.93 (1.5–17.7)	1,261 (433–17,140)
Substituted patients (range)	4.1 (1–10)	3.7 (1.2–14.8)	940 (168–4,009)

With the exception of TT, pre- and intraoperative PT and aPTT were significantly worse in substituted patients (Table 4). At the end of surgery, PT activity reached equal levels in both groups.

Fibrinogen levels and plasma activity of factor V were significantly lower in substituted patients throughout the operation. Probably due to the intraoperative administration of PPSB, factor II plasma activity was higher in substituted patients than in nonsubstituted patients at the end of surgery, although substituted patients had significantly lower factor II plasma activity up to the anhepatic phase. Similar changes were observed for ATIII.

From the anhepatic phase of pOLT onwards, platelet counts were significantly lower in substituted than nonsubstituted patients (Table 4, $P < 0.05$), despite platelet transfusions in five of 26 substituted patients.

An association between preoperative fibrinogen and ATIII plasma levels and the intraoperative substitution therapy was found. Sixteen of 22 patients (73%) with preoperative fibrinogen levels of less than 1.7 g/l intraoperatively required coagulation concentrates and/or EC, as compared to only ten of 34 patients (29%) with fibrinogen levels of more than 1.7 g/l ($P < 0.05$, chi-squared). Furthermore, patients with fibrinogen levels of less than 1.7 g/l and ATIII plasma activity of less than 50% required substitution therapy in 81% (13/16), whereas only four of 22 patients (18%) with higher

plasma activities received similar transfusions ($P < 0.05$, chi-squared). The addition of other factor activities did not improve the predictive value. Cutoff points for fibrinogen and ATIII were deliberately chosen. One way linear regression analysis revealed a weak but significant association between the amount of collected cell saver blood and preoperative fibrinogen levels ($P = 0.026$) as well as ATIII activity ($P = 0.022$) (Fig. 3). This was confirmed by a significant Pearson's correlation (fibrinogen $P = 0.026$, ATIII $P = 0.016$).

However, in multiple regression analysis with backward elimination, only ATIII could be identified as bearing a statistically significant influence on the intraoperative blood loss as indicated by the collected and autotransfused cell saver blood ($P = 0.048$).

Discussion

The preoperative coagulation profiles with subnormal PT and aPTT activity as well as decreased plasma levels of coagulation factor I, II, V, and VII and ATIII underline the preexisting coagulopathy secondary to the liver disease in our patients. This is in line with previous studies in standard OLT [1, 18, 19, 22].

During later stages of liver transplantation, the intraoperative substitution regimen becomes an important aspect. Based on close coagulation monitoring, many transplant centers continuously substitute coagulation components to maintain constant coagulation profiles [1, 12, 13, 19]. Others suggest a more restricted substitution regimen, which in first line is guided by hemodynamic parameters and in second line by coagulation profiles. In this setting, factors of the coagulation system are primarily substituted in case of intraoperative blood loss, which can not be controlled by surgical means [9]. A similar substitution regimen was adopted for our patients. The low plasma levels of all determined coagulation factors throughout the operation reflect this policy. Many times, critically decreased levels of coagulation factors could be tolerated. As a result, the majority of pOLT was performed with substitution of crystalloids and albumin alone. Only 42% of our patients required the intraoperative administration of coagulation concentrates. This can be compared to the Stanford's group experience, who reported FFP substitution in only 30% of their patients undergoing pOLT [5].

In accordance with the experience from standard OLT, coagulopathy progressively develops during pOLT. Maximal alterations are seen after liver reperfusion. The aPTT shows a 2- to 3-fold prolongation, and PT declines to 40% of normal activity. The PT is a sensitive indicator for the hepatic synthetic function [13], which will unequivocally diminish during liver explantation of the recipients. Within the extrinsic coagulation pathway, the decreased factor VII activity after graft reperfusion may particularly influence PT activity.

The aPTT is largely influenced by heparin effects, which occurs on reperfusion due to endogenous release of heparin from the donor [12, 13]. Since FFP and other coagulation components were restrictively substituted in our patients, a still significantly prolonged aPTT at the end of surgery is not surprising. In contrary fashion, if coagulation components are deliberately substituted, aPTT prolongation is seldom found at the end of surgery, as it was demonstrated in standard OLT [1, 14, 18, 19].

Thrombin time, a useful measurement for fibrinogen conversion, stays within the normal range until reperfusion of the graft when a rapid 3-fold increase is recognized. This significant prolongation may also be due to heparin release by the donor liver [23]. Decreased fibrinogen plasma levels probably play a minor role in TT prolongation, since TT rapidly normalizes at the end of surgery although fibrinogen plasma levels are still below the normal range.

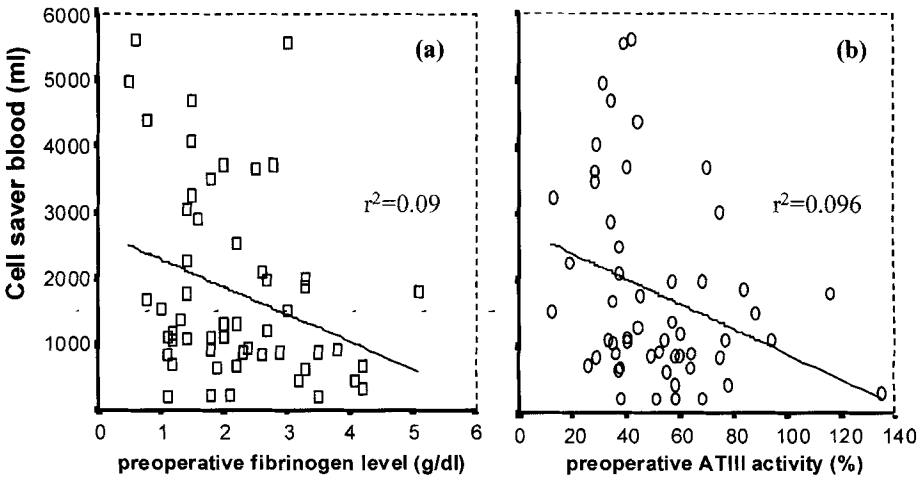

Fig. 3a, b. One way linear regression between preoperative fibrinogen plasma levels (**a**), ATIII plasma activity (**b**), and the intraoperative blood loss as indicated by collected cell saver blood

Disseminated intravascular coagulation (DIC) and fibrinolysis have been described during the anhepatic and reperfusion phase in standard OLT [12, 19, 23]. Consumption of extrinsic coagulation factors (II, V, VII, and X) is considered to be responsible for the pathological PT activity present in 90% of patients with DIC [8]. If DIC progresses, the inhibitory capacity of ATIII is exhausted and plasma activity decreases [20]. Considering these facts, the deteriorated PT, aPTT, and decreased factor II, V, VII, and ATIII activity observed in our patients may implicate DIC as a causative factor for the observed hemostatic disturbances, particularly in substituted patients. However, since fibrin degradation products or thrombin-antithrombin complexes (TAT) have not been measured, a final conclusion cannot be drawn.

Severe fibrinolysis occurs on reperfusion in approximately 40% of patients undergoing standard OLT and becomes clinically apparent by uncontrollable bleeding or generalized oozing [15]. It is mainly caused by release of plasminogen activator (t-PA) from the grafted liver and congested viscera together with a reduction of plasminogen activator inhibitor (PAI) [1, 12, 23, 32]. From our data, which does not include the relevant laboratory analysis (i.e., euglobulin clot lysis time, whole blood clot lysis time), the impact of fibrinolysis on the hemostatic imbalances can not be estimated in our patients.

Contrary to other studies [9, 25], an association between preoperative fibrinogen and ATIII plasma levels and the intraoperative substitution with coagulation components was observed. Furthermore, preoperative ATIII plasma activity correlated with the intraoperative blood loss. Our findings probably have to be attributed to the restrictive substitution regimen applied in our patients. As a result, the influence of single coagulation factors on blood loss and substitution therapy might become evident.

Several studies have implicated a positive effect of prophylactic antifibrinolytic therapy on the intraoperative blood loss during standard OLT [19, 20, 21]. Therefore, a prophylactic regimen with aprotinin (Trasylol) was routinely performed. The low substitution requirements as demonstrated in our patients may further underline this strategy, although no control group has been included. In summary, pOLT is associated with a marked impairment of the coagulation system. The observed hemostatic imbalances during pOLT closely resemble intraoperative coagulopathy known from standard OLT [9, 16, 25]. However, in our experience the majority of pOLT can be performed without any substitution of coagulation components using a restricted substitution policy, which is primarily guided by the coincidence of decreased factor levels and surgically evident diffuse oozing. With this strategy, deteriorated laboratory coagulation profiles can often be tolerated without increasing the risk of uncontrollable bleeding.

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