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A comparative study on changes in hemostasis in orthotopic and auxiliary liver transplantation in pigs

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Abstract. We compared blood loss and hemostasis in pigs which had undergone either orthotopic liver transplantation (OLT) (group A, $n = 12$) or auxiliary heterotopic partial liver transplantation (APLT) (group B, $n = 11$). Blood samples were taken at regular intervals during and after the operations. In both groups, nine animals survived longer than 24 h and data from these animals were used for analysis. Median (range) intraoperative blood loss was 825 ml (250–1500 ml) in OLT and 425 ml (300–750) in APLT ($P < 0.01$). Routine clotting times, as the activated partial thromboplastin time, prothrombin time and thrombin time, showed no major intraoperative changes in either group. Fibrinogen levels decreased in both groups, but no significant difference was found between the two groups. The only significant difference between group A and B was a more sustained increase in fibrinolytic activity after graft recirculation in group A. Postoperatively, restoration of fibrinogen, antithrombin-III and α_2-antiplasmin levels was slightly faster in group B, resulting in significantly higher levels during the first day. We conclude that, in this animal model, APLT is associated with significantly lower blood loss and less severe fibrinolytic activity, than OLT. This difference might result from the lack of an anhepatic period and the reduced surgical trauma in auxiliary heterotopic liver transplantation.

Key words: Liver transplantation, auxiliary, in pigs – Hemostasis, in liver transplantation, in pigs – Auxiliary liver transplantation, hemostasis, in pigs

Although orthotopic liver transplantation (OLT) has become an accepted method to treat patients with end-stage chronic liver disease, it is still associated with massive intraoperative blood loss and the use of large amounts of blood products [9, 17]. Excessive blood loss is associated with an increased perioperative mortality and morbidity [32]. Massive transfusion of blood products also contributes significantly to the total cost of liver transplantation [32].

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Bleeding of surgical origin may be seriously complicated by specific hemostatic deteriorations, which occur especially during the anhepatic and post-anhepatic periods [9, 24]. Disseminated intravascular coagulation (DIC), primary increased fibrinolysis, or a combination of both processes, have been suggested as a major cause of bleeding in orthotopic liver transplantation [12, 13, 21, 24]. Lack of hepatic clearance of activated coagulation factors or activators of the fibrinolytic system may lead to severe disturbances of the hemostasis system in the anhepatic phase of OLT [10, 18].

Auxiliary heterotopic liver transplantation has been proposed as an alternative to hepatic replacement. The main theoretical advantage of auxiliary liver transplantation is avoidance of the technical hazards of recipient hepatectomy and the lack of an anhepatic period [7, 29]. A second advantage may be that the recipient is not, at the outset, totally dependent on the function of the homograft. These differences might contribute to less severe hemostatic disorders and the usage of smaller amounts of blood products. However, information on this technique and its effect on hemostasis is limited.

Auxiliary heterotopic liver transplantation, though attractive, cannot be regarded as an alternative at present, and is probably limited to specific indications. Only a small number of auxiliary liver transplantations have been performed in humans [7, 30]. The initial discouraging results have held up further application of this technique. Recently, many of the technical problems seem to have been resolved by improving the procedure and by using a partial graft [26, 27]. The first clinical applications suggest that this improved technique of auxiliary partial liver transplantation (APLT) can be performed successfully without serious changes in blood coagulation and fibrinolysis, even in patients with poor preoperative hemostatic function [15, 23, 31]. However, objective information on the advantages and disadvantages of both techniques of liver transplantation can only be obtained from studies in which both techniques are evaluated under identical conditions. In addition, comparison of the two techniques can provide interesting information regarding the role of the

Table 1. Body weight, intraoperative blood loss and infusion fluids in pigs that underwent orthotopic (OLT) and auxiliary partial (APLT) liver transplantation. Values are median (range). NS, Not significant

	Group A (OLT) ($n = 9$)	Group B (APLT) ($n = 9$)	Significance
Body weight (kg)	26.4 (18.5–28.0)	22.5 (20.0–30.0)	NS
Blood loss (ml)	825 (250–1500)	425 (300–750)	$P < 0.01$
Ringers solution (ml)	2250 (1500–3300)	1500 (1500–3500)	NS
Haemaccel (ml)	2250 (1500–4000)	1750 (1500–2500)	NS

anhepatic phase and graft reperfusion in the origin of hemostatic disorders during OLT.

Therefore, we undertook a comparative study of OLT and APLT in healthy pigs. The effect of pre-existing differences in coagulation defects, as may be found in liver patients, was thus avoided, which made it possible to study the changes in hemostasis during specific stages of the surgical procedures. This study formed part of a larger comparative study on surgical and anesthetic management in OLT and APLT, part of which has been described elsewhere [3].

Materials and methods

Twenty-three female Yorkshire pigs were used in the experiments. The study was approved by the Committee for Laboratory Animal Research of the Erasmus University, Rotterdam. The animals were randomly allocated to two groups: animals in group A ($n = 12$) underwent OLT and those in group B ($n = 11$) underwent APLT. The donor and recipient were matched according to a negative reaction in the mixed lymphocyte culture test (MLC) [19].

All operations were carried out under general anesthesia and the animals were ventilated using a Siemens 900B Servo ventilator. During the operations, Ringers solution and Haemaccel were given for hemodynamic support as needed. Depending on the amount of blood loss, 1–2 IU whole blood (400 ml each) was given in the period after graft recirculation.

Donor hepatectomy was performed using a conventional technique. After harvesting, the donor liver was perfused ex vivo by portal vein cannulation with 1 l Euro-Collins (4°C) and grafted within 4 h. Details of the surgical technique used are given below.

Orthotopic liver transplantation

In group A, OLT was performed by a standard procedure [28]. During the anhepatic period, blood flow from the operative area and the inferior part of the body was shunted away by a bypass from the portal and femoral vein to the jugular vein, using a heparin-coated extracorporeal circuit [5]. No systemic heparin was given.

Heterotopic, auxiliary liver transplantation

In group B, APLT was performed by using a partial liver graft. During bench surgery the left medial and lateral lobes of the liver were resected as described previously [26]. The partial graft, consisting of about 65% of the donor liver, was placed in the right subhepatic space, anastomosing the suprahepatic vena cava of the graft end-to-side to the infrahepatic vena cava of the recipient. The donor portal vein was anastomosed end-to-side to the recipient portal vein and an end-to-side anastomosis was made between the graft hepatic artery to the recipient's infrarenal aorta. Bile flow was reconstituted by a choledochoduodenostomy. In this type of liver transplantation no shunt is necessary for the decompression of the splanchnic circulation during portal clamping. None of the animals received systemic heparin. No immunosuppressive drugs were given in either group.

Blood loss and blood sampling

Blood loss was quantified by measuring the amount of blood sucked away from the surgical field, and collected in Buleaux bottles during the operation.

Intraoperative blood samples (20 ml) were taken from an arterial line, while in the postoperative period blood was collected from a central venous line or by puncturing the jugular vein. A part of the blood sample (18 ml) was divided into two polystyrene test tubes, containing 1 ml ice-cold trisodium citrate 0.11 mol/l (9 vol + 1 vol) and immediately placed on melting ice. Plasma was collected after centrifugation (2800 g, 4°C, 30 min), snap-frozen and stored in small aliquots at −70°C until used. A smaller part of the blood sample (2 ml) was collected into 0.045 ml 15% solution of 6.75 mg EDTA.

In both groups preoperative blood samples were taken immediately after induction of anesthesia. The other blood samples were taken 5 min after anastomosis of the portal vein (recirculation of the graft), 5 min after anastomosis of the hepatic artery, 2 h and 3 h after transplantation and on postoperative days 1, 2, 7, 10, 14 and 21. In group A (OLT), one extra blood sample was taken 10 min before the end of the anhepatic phase.

Hemostasis studies

Coagulation. The activated partial thromboplastin time (APTT), prothrombin time (PT) and thrombin time (ThT) were measured as described previously [22]. Thrombelastography (TEG) was performed in citrated plasma [20]. The r-value was defined as the time interval between the start of the registration and the first deflection on the TEG recording. The k-value was defined as the time interval after the first deflection until an amplitude of 10 mm was reached.

Table 2. Survival and causes of death after orthotopic (OLT) and auxiliary partial (APLT) liver transplantation

Pig no.	Group A (OLT)		Group B (APLT)	
	Survival (days)	Cause of death	Survival (days)	Cause of death
1	7	Rejection	35	Sacrificed in good health
2	17	Cholangitis	8	Volvulus of jejunum
3	2	Not clear	15	Volvulus of jejunum
4	94	Sacrificed in good health	50	Sacrificed in good health
5	72	Sacrificed, leg abscess	86	Sacrificed in good health
6	33	Not clear	91	Strangulated hernia
7	25	Cholangitis	159	Sacrificed in good health
8	5	Volvulus of jejunum	93	Sacrificed in good health
9	38	Bile leakage	23	Purulent pneumonia

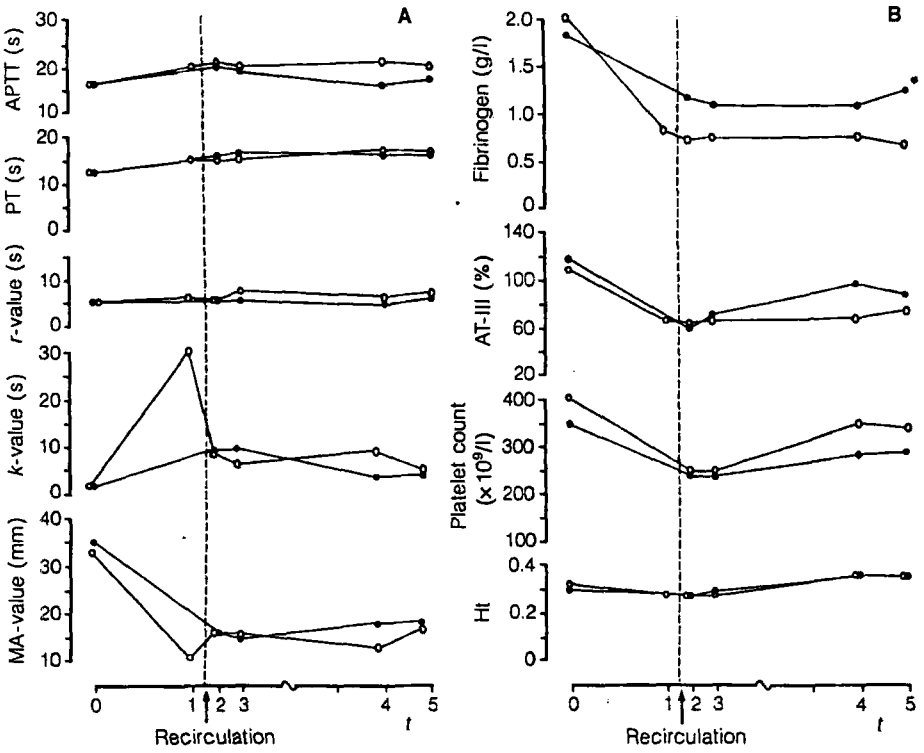

Fig. 1. A *APTT, PT, r-value, k-value* and maximum amplitude *(MA)* of thrombelastogram in animals that underwent liver transplantation. ○ OLT (group A); ● APLT (group B) (median values). **B** *Fibrinogen, AT-III, platelet count* and hematocrit *(Ht)*. ○ OLT (group A); ● APLT (group B) (median values). * $P < 0.05$, comparison between group A and B. *0* Preoperative; *1* end anhepatic phase in OLT; *2* 5 min after recirculation; *3* 5 min after hepatic artery anastomosis; *4* 2 h postoperative; *5* 3 h postoperative. Median (range) time interval between 0 and 2 for OLT, 194 (144–250) min; for APLT, 120 (90–180) min; between 2 and 3 for OLT, 43 (30–70) min; for APLT 40 (25–105) min

The maximum amplitude (MA) represented the maximum deflection on the TEG recording. Fibrinogen was measured according to the method of Clauss [4] and antithrombin-III (AT-III) activity was assayed as described by Abildgaard et al. [1]. The vitamin K dependent factors II, VII and IX were determined by Normotest, according to the manufacturer's instructions (Nyegaard Diagnostica, Oslo, Norway). The hematocrit of each blood sample was measured to detect possible dilution effects.

Fibrinolysis. To determine the euglobulin clot lysis time (ECLT), standard euglobulin fractions of plasma were prepared at pH 5.9 with a plasma dilution of 1:10 [14]. Precipitates were redissolved in Tris/Tween buffer (0.1 *M TRIS*/HCl, containing 0.1% v/v Tween 80, pH 7.5), and to 0.2 ml aliquots of the dissolved euglobulin fractions 0.1 ml portions of calcium thrombin solution ($CaCl_2$ 25 mmol/l and thrombin 10 NIH IU/l) were added to induce clot formation. The lysis time of the clot was recorded. The disappearance of air bubbles was regarded as the endpoint of lysis. α_2-Antiplasmin (α_2-AP) activity was measured according to the method of Friberger et al. [8]. Plasminogen was assayed in acidified plasma using urokinase (Choay, Paris, France) for activation of plasminogen and S-2251 (Kabi Vitrum Haematology, Amsterdam, The Netherlands) as substrate [19].

Statistical analysis

Statistical analysis was performed using the Wilcoxon signed rank test for paired data and the two-sample test for unpaired data. Values at $P < 0.05$ were considered to be significant.

Results

In both groups nine animals survived longer than 24 h after transplantation and the data of these animals were used for analysis. The excluded animals died of secondary complications which needed extensive therapeutic interventions, such as cardiac resuscitation, and which interfered with the standard surgical and anesthetic procedures essential for this study. In Table 1 body weight, blood loss and the amount of infusion fluids in group A (OLT) and group B (APLT) are compared. Median intraoperative blood loss in group A (OLT) was about twice as much as in group B (APLT) ($P < 0.01$) Survival and causes of death in both groups are shown in Table 2. None of the animals died of postoperative hemorrhage. The main causes of early mortality were secondary to surgery and included intestinal strangulations. Autopsy demonstrated vital donor livers, with patency of all vascular anastomoses in all but one case in group A (no. 1). The graft of this animal was firm and signs of intrahepatic cholestasis were present. In group B (APLT), vital grafts with patent vascular anastomoses were found in 5 of 7 animals for which autopsy data were available. In two animals (nos. 6 and 7) a pale, firm and atrophic auxiliary graft was found.

Coagulation

Intraoperatively, none of the investigated coagulation parameters was different between the two groups. A rather stable course of APTT and PT was found in both groups (Fig. 1 A), as also was found for ThT and NT. In fact, the only coagulation parameter that showed important changes during the operations was fibrinogen, for which a more than 40% decrease of the median levels was found during the operations in both groups (Fig. 1 B). This was also reflected by a prolongation of the *k*-value and a decrease of the MA on the TEG recordings (Fig. 1 A).

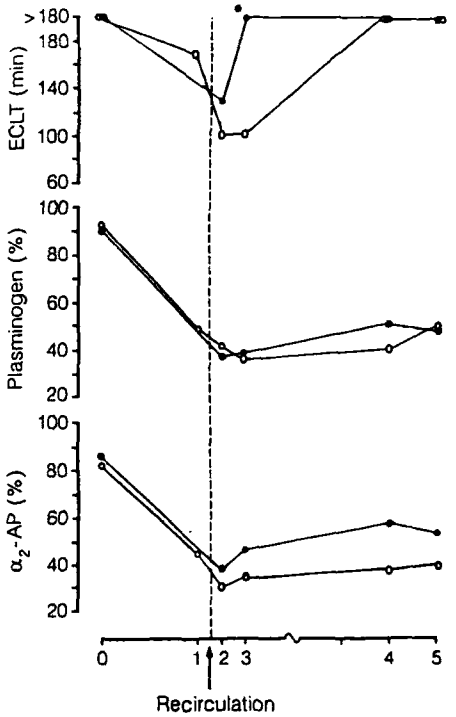

Fig. 2. *ECLT, plasminogen* and α_2-antiplasmin (α_2-AP) in animals that underwent liver transplantation. ○ *OLT* (group A); ● APLT (group B) (median values). * $P < 0.05$, comparison between group A and B. X-axis notation as in Fig. 1

These changes could not be explained by hemodilution since no important changes in hematocrit were found (Fig. 1 B). A slowly decreasing pattern was also seen for AT-III and platelet count (Fig. 1 B).

Fibrinolysis

Important intraoperative changes were found in the investigated fibrinolytic parameters in both groups. Hyperfibrinolysis, as characterized by shortened ECLTs and reduction of α_2-AP and plasminogen concentrations, was found 5 min after graft reperfusion in both OLT and APLT (Fig. 2). During OLT an increased fibrinolytic activity, as measured by ECLT, was already present during the anhepatic period. In group A (OLT) a further increase of fibrinolytic activity was seen during the postreperfusion period, resulting in significantly shorter ECLTs at the time of completion of the arterial anastomosis, compared with group B (APLT) ($P < 0.05$). In both groups, ECLT became normal (> 180 s) 3 h after the operation. At this time plasma levels of plasminogen and α_2-AP were still reduced. Restoration of α_2-AP levels was apparently faster in group B (APLT), but the difference was not statistically significant.

Long-term postoperative changes

In both groups, a recovery of hemostatic parameters was observed during the first postoperative week. There were no differences in APTT, PT and NT. Fibrinogen, AT-III and α_2-AP levels on the first day after surgery were higher in group B (APLT) ($P < 0.01$) (Fig. 3). Fibrinogen levels showed a peak on day 2 in group A (OLT) and on days 1 and 2 in group B (APLT) (Fig. 3). Platelet count reduced further during the first postoperative days, reaching a minimum on the second day in both groups. Thereafter a rapid recovery of platelet count was observed, resulting in a thrombocytosis (median values higher than 500×10^9/l) at the end of the first week (Fig. 3).

Discussion

The anhepatic phase in OLT is associated with serious changes in hemostasis, which may further complicate surgical bleeding and contribute to the need for massive blood transfusions [12, 24]. Auxiliary liver transplantation potentially has benefits over OLT, as the technical hazards of the recipient hepatectomy and the subsequent anhepatic period are avoided. Therefore, auxiliary liver transplantation may, theoretically, be associated with less severe hemostatic deterioration, and it may be an attractive alternative to OLT. However, objective evidence on the potential advantages of auxiliary liver transplantation, with regard to blood loss and disturbances of hemostasis, are lacking. Although a comparison of OLT and auxiliary liver transplantation has been made in a previous study, this was primarily designed to study the effect of graft preservation damage on hemostasis, and insight into the specific changes due to the auxiliary transplantation procedure cannot be obtained from this study [11].

In the present study we investigated hemostasis after OLT and APLT using techniques which are currently used in humans. Both types of liver transplantation were performed in a controlled study in healthy pigs. The effects of pre-existing differences on coagulation defects, as may occur in liver patients, were thus avoided. This made it possible to study the specific changes in hemostasis due to the surgical procedures only. It should be noted that the results obtained in healthy pigs cannot be translated directly to the clinical situation. Liver patients undergoing transplantation usually already have severe hemostatic disorders before the operation, which has an important influence on the tendency for intraopertive bleeding [24]. Still, this study provided information on the hemostatic changes that occur intraoperatively and that are directly related to the transplantation procedure itself.

A lower blood loss was found in the animals that underwent APLT than in those that underwent OLT. This is in accordance with our experience in clinical APLT [31], and can, at least partly, be explained by the difference in surgical trauma, but this may very well be amplified by differences in the degree of intraoperative hemostatic deterioration. When comparing the hemostatic profile of the two groups, differences were not found in the blood coagulation system, but rather in the fibrinolytic system. In fact, the only minor changes in the routine clotting times, found in the OLT group, were comparable to the APLT group, without the anhepatic phase. This demonstrated that the changes are related to the surgical proce-

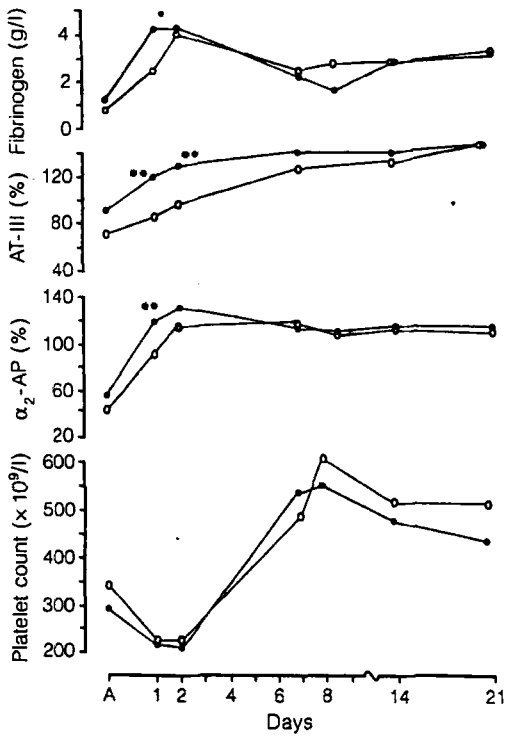

Fig. 3. Postoperative course of *fibrinogen, AT-III,* α_2-AP and *platelet count* in animals that underwent liver transplantation. O OLT (group A); ● APLT (group B) (median values). *A* 2 h after surgery. * $P < 0.05$, ** $P < 0.01$, comparison between group A and B

dures in general, and not specifically due to the anhepatic phase in OLT.

The only coagulation parameter that showed serious alteration was fibrinogen. A decrease in fibrinogen levels and subsequent prolongation of *k* value, representing clot formation rate, and a decrease in the MA value on TEG recordings, representing clot stiffness, were found in both OLT and APLT. Although the intraoperative decrease in fibrinogen levels was apparently more severe in OLT, this difference was not statistically significant. However, an ongoing postoperative decrease in fibrinogen levels after OLT did result in significantly lower levels compared with the APLT group 3 h after the operation. Several investigators have described a reduction of fibrinogen levels in experimental and clinical OLT [10, 12, 13, 16, 18, 21]. Mechanisms of consumption, DIC trapping in the graft, fibrinogenolysis and the effect of hemodilution have been suggested to explain this phenomenon [12, 16, 24]. We did not find convincing evidence for DIC and/or hemodilution. AT-III levels never reached extremely low values and no serious changes in any of the clotting times or hematocrit were observed. The decrease in fibrinogen levels was most probably caused by a local consumption around the surgical wounds.

We also found signs of hyperfibrinolysis, as characterized by a shortened ECLT and decrease in plasminogen and α_2-AP levels after graft recirculation in both groups. However, fibrinolytic activity was more severe and lasted longer in animals that underwent OLT. After recirculation of auxiliary grafts, the ECLT showed a fast normalization, and ECLT was normalized in this group at the time of completion of the hepatic artery anastomosis. Many investigators have stressed the role of hyperfibrinolysis in the origin of bleeding complications in OLT. Recent studies in clinical OLT suggested that increased fibrinolytic activity is predominantly of primary origin [12, 16] and may result from a combination of reduced hepatic clearance and an increased release of tissue-type plasminogen activator [6, 25]. The lack of an anhepatic phase and the remnant clearing function of the host liver might explain why we observed less severe fibrinolytic activation in APLT. In agreement with this, we recently demonstrated, in a clinical study, that signs of hyperfibrinolysis are only found in a minority of patients undergoing APLT [23]. Although the clinical relevance of hyperfibrinolysis in liver transplantation is still under discussion, this may be an important point of difference between OLT and APLT, and it may contribute to less frequent bleeding complications in APLT.

Another difference between OLT and APLT, found in this study, was an earlier restoration of some hemostasis parameters after the operation. Levels of fibrinogen, α_2-AP and AT-III were significantly higher in the APLT group on the first postoperative day. At first sight, this difference can be explained well by the reduced functional capacity of the orthotopically transplanted liver, and the possibility cannot be excluded that this effect is predominantly due to synthesis by the host liver in APLT. However, clinical observations in cirrhotic patients with severe preoperative coagulation defects who underwent APLT showed a similar fast restoration of α_2-AP and AT-III levels [23, 31]. Postoperatively, we observed a further decrease in platelet count in both groups. This is in agreement with clinical findings [21], but the mechanisms underlying this drop in platelet count are still not clear and will be the subject of further research.

The thrombocytosis observed in both groups after the first week can be ascribed to a reactively increased thrombopoiesis. Rebound thrombocytosis occurs because of a lag in the feedback mechanism associated with the platelet/megakaryocyte control mechanism [33]. In cirrhotic patients undergoing liver transplantation, a moderate to severe thrombocytopenia, due to splenomegaly, is usually present preoperatively. This may explain why such a thrombocytosis is less striking after successful clinical liver transplantations.

In conclusion, in comparing OLT and APLT in a controlled study, we observed a halving of intraopertive blood loss in animals that underwent APLT. No differences in the investigated coagulation parameters were found between the two groups. Although an increase in fibrinolytic activity was found during both types of liver transplantation, signs of hyperfibrinolysis were present during a longer period after graft recirculation in OLT. Postoperatively, an earlier normalization of disturbed hemostatic parameters was seen after APLT. It can be concluded that the anhepatic phase and reduced functional capacity of the donor liver during the early postreperfusion period play an important role in the hemostatic deterioration in OLT. Further clinical experience has to be awaited to determine the specific indications and advantages of APLT, compared to OLT.

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