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Increased fibrinolysis in orthotopic but not in heterotopic liver transplantation: the role of the anhepatic phase

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Abstract. The major cause of increased tissue-type plasminogen activator (t-PA) activity during orthotopic liver transplantation (OLT) is still unclear. Both lack of hepatic clearance of t-PA in the anhepatic period and/or increased endothelial release from the graft upon reperfusion have been suggested. Heterotopic liver transplantation (HLT) avoids resection of the host liver and is therefore a useful model to differentiate these two possibilities. The fibrinolytic system was evaluated in ten patients with OLT and in 18 patients with HLT. A marked increment in t-PA activity was observed during the anhepatic period of OLT, which rapidly normalized after reperfusion. In contrast t-PA activity levels remained normal in HLT. As a reflection of the increased t-PA activity fibrin degradation products were markedly elevated during OLT and plasminogen and α_2-antiplasmin decreased simultaneously during the anhepatic period. In conclusion, the lack of hepatic clearance during the anhepatic period is the most important factor in the evolution of increased t-PA activity during OLT.

Key words: Fibrinolysis – Liver transplantation – t-PA activity – Hepatic clearance

During the past decade, the increase in number of orthotopic liver transplantations (OLT) has led to a better understanding of the coagulation problems encountered during the procedure. Especially during the late anhepatic phase of liver transplantation and soon after reperfusion of the allograft, a dangerous period of hypocoagulation is present in many patients. Increased fibrinolytic activity, found during the anhepatic period in many studies, is an important factor in the origin of massive haemorrhage [3]. The mechanism underlying the increased fribrinolysis is not yet well defined. Lack of hepatic clearance of tissue-type plasminogen activator (t-PA) in the anhepatic phase and/or release of t-PA from either vascular endothelium or hepatocytes upon reperfusion trauma have been suggested as causes of hyperfibrinolysis.

Heterotopic liver transplantation (HLT) avoids the anhepatic period and is therefore a useful model to differentiate the single effect of graft reperfusion on the haemostatic changes from the effect of the anhepatic period. We compared the fibrinolytic activity between OLT and HLT in order to address this question. We also studied the single effect of surgery itself on fibrinolysis in patients undergoing partial hepatic resection (PHR).

Patients and methods

In consecutive series of 10 patients undergoing OLT, 21 patients HLT and 10 patients PHR, arterial blood samples were taken at regular intervals during the whole procedure. OLT was divided into three stages; stage I began with the induction of anaesthesia and ended with the occlusion of blood flow to the patient's own liver, stage II was the anhepatic phase and stage III started at the moment of reperfusion. For the comparison, it was decided that in HLT stage II started 120 min after the beginning of surgery. Blood samples were collected from an unheparinized arterial line in plastic tubes and anticoagulated with trisodium citrate. The samples were immediately placed on melting ice and centrifuged for 30 min at 4 °C within 20 min. Plasma was snap-frozen and stored at −70 °C until testing.

Tissue-type plasminogen activator was assayed according to the method of Verheyen et al. [4]. t-PA antigen levels were measured using an ELISA (Biopool IMULYSE t-PA, Umea, Sweden). Tissue plasminogen activator inhibitor (PAI-1) antigen levels were determined by an ELISA (Biopool TINTELIZA, Umea, Sweden). Plasminogen and α_2-antiplasmin levels were assayed according to the method of Friberger et al. [2]. Fibrin degradation products (FbDP) and fibrinogen degradation products (FgDP) were determined by EIA (Organon Technica, Turnhout, Belgium).

The Wilcoxon test for independent samples was used for statistical analysis. Any probability less than 0.05 was considered significant.

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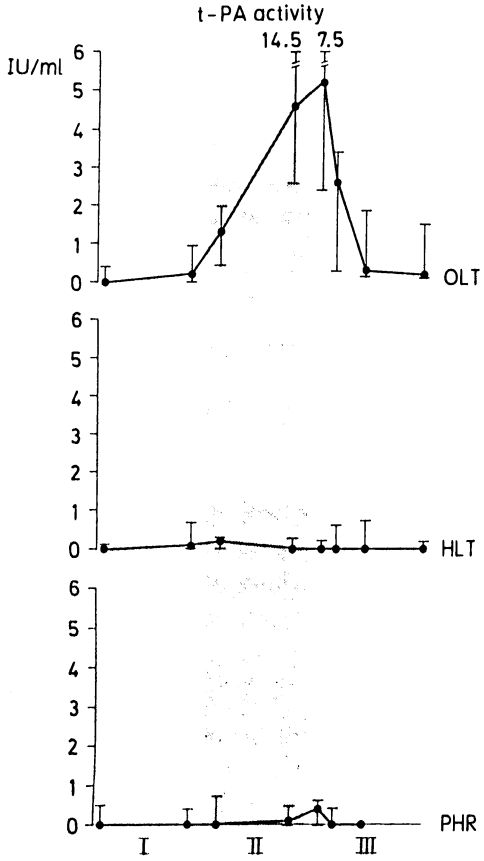

Fig. 1. t-PA activity (IU/ml, median and quartiles) during stage I, II and III of OLT, HLT and PHR. For explanation of I, II and II see text

Results

The median levels of t-PA activity during OLT, HLT and PHR are shown in Fig. 1. In OLT, t-PA activity increased from 0.2 IU/ml to 5.2 IU/ml at the end of the anhepatic period, and returned to a normal value soon after reperfusion. In contrast, t-PA activity remained within the normal range throughout HLT and PHR. t-PA antigen levels increased significantly from 11.5 ng/ml to 23.7 ng/ml during OLT. In HLT and PHR t-PA antigen levels did not change significantly. Concentrations of FbDP and FgDP rose only during OLT. Levels of PAI-1 antigen, plasminogen and α_2-antiplasmin decreased during OLT until reperfusion and remained virtually unchanged during HLT and PHR.

Discussion

The results obtained in this study clearly show that lack of t-PA clearance during the anhepatic period is essential for the development of a fibrinolytic state during liver transplantation. During the anhepatic period of OLT a marked increase in t-PA activity and t-PA antigen levels was found in contrast to no change in the comparable period of HLT. After reperfusion of the graft, t-PA activity returned to normal values within 15 min. Another proof that lack of clearance, and not reperfusion trauma, causes hyperfibrinolysis comes from the observation that the first venous outflow from the allograft after reperfusion did not contain an increased t-PA activity or antigen level (data not shown). Moreover, as no increase in t-PA activity during PHR was observed, manipulation of the liver per se is not an important factor in the pathogenesis of hyperfibrinolysis.

Another explanation for the enhanced fibrinolytic activity could be an inhibition of PAI-1 by protein C. However, during OLT protein C levels did not change (data not shown).

It has been suggested that the veno–venous bypass used in OLT may induce t-PA release from the vascular endothelium [1]. However no difference in t-PA activity was observed between patients with and without a veno–venous bypass.

The presence of an active fibrinolytic process is also demonstrated by a simultaneous decrease in plasminogen and α_2-antiplasmin during the anhepatic phase. As a reflection of the increased t-PA activity fibrin degradation products were markedly elevated during OLT. Fibrinogenolysis was seen in a limited degree during OLT. Although enhanced fibrinolysis occurred during OLT and not during HLT, no significant difference in blood loss was observed between OLT and HLT. Blood loss, however, is influenced by multiple factors which could have neutralized the single effect of the enhanced fibrinolytic state during OLT.

In conclusion, this study shows that the increased fibrinolytic activity observed during OLT is caused by lack of clearance of t-PA during the anhepatic period.

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