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Possible Role of the Phagocytic Proteinases, Cathepsin B and Elastase, in Orthotopic Liver Transplantation

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PREVIOUS studies have suggested that disseminated intravascular coagulation (DIC) is a causal factor for bleeding complications during orthotopic liver transplantation (OLT). It seems likely that inflammatory mediators (eg, proteinases of phagocytes) in the perfusate released by the grafted liver may enter the circulation and induce the deterioration in hemostasis. The aims of our study were (1) to prove the presence of the cystein proteinase cathepsin B from macrophages and the serine proteinase elastase from granulocytes in liver graft perfusate and (2) to evaluate the correlation of these proteinases with coagulopathy in OLT.

MATERIALS AND METHODS

Between August and November 1989, 10 consecutive patients undergoing primary OLT were studied. They received packed red blood cells (RBC) and fresh frozen plasma (FFP), but neither platelets nor concentrates of coagulation factors. Eight blood samples were collected: (1) preoperatively, (2) 5 minutes before and (3) 10 minutes after removal of the liver, (4) 5 minutes before and (5) 5 minutes, (6) 15 minutes, (7) 1 hour, and (8) 12 hours after reperfusion of the liver graft. In addition, a sample of the perfusate was obtained after flushing of the graft with systemic blood. Antigen levels of D-dimer, thrombin-antithrombin III-complex (TAT), von Willebrand factor (vWF), and elastase (in complex with alpha 1-protease inhibitor, EPI), as well as activities of fibrinogen, protein C, antithrombin III (AT III), C_1-inhibitor, and cathepsin B were determined. Wilcoxon's rank-sum test was used to analyze the data. P values $< .05$ were considered to be significant.

RESULTS

Levels of vWF and fibrinogen were lower in the perfusate samples than in the corresponding plasma specimen, collected 5 minutes before reperfusion of the graft (Table 1).

Table 1. Coagulation Profiles of Venous Blood (5 minutes Before Reperfusion) and Perfusate

	Before Reperfusion		Perfusate	
	Mean	Range	Mean	Range
vWF (%)	317	94–405	275	36–446
Fibrinogen (g/L)	1.9	1.1–2.7	1.5*	0.5–2.2
AT III (%)	66	35–89	38*	26–56
C_1-inhibitor (%)	78	55–107	64*	27–92
Protein C (%)	27	8–54	10*	0–24
TAT (ng/mL)	59	15–270	121*	10–324
D-dimer (mg/L)	1.7	0–4.0	3.3	0–16.0
EPI (ng/mL)	452	231–766	553	136–904
Cathepsin B (U/mL)	0.2	0.1–0.2	27.6*	7.0–75.8

*$P < .05$ compared with the value of venous blood sample.

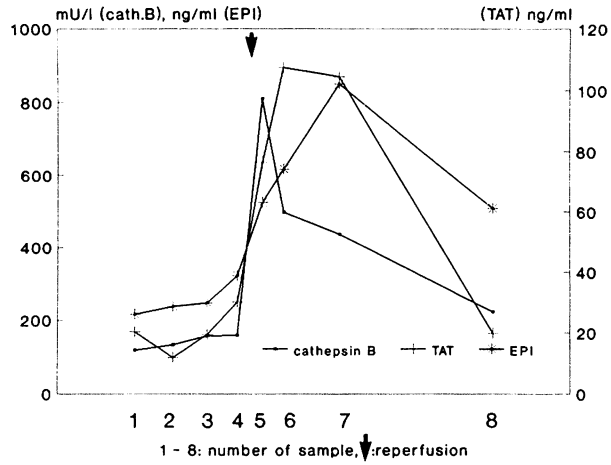

Fig 1. Concentrations of cathepsin B, thrombin-antithrombin complex (TAT), and elastase alpha 1-protease inhibitor complex (EPI) during orthotopic liver transplantation.

These differences, however, were significant only for fibrinogen. In addition, the activities of AT III, protein C, and C_1-inhibitor were significantly reduced in the perfusate. On the other hand, levels of TAT and D-dimer (indicating activated coagulation), as well as EPI and cathepsin B (indicators of activated phagocytes) in the perfusate, were significantly increased (Table 1). Plasma levels of cathepsin B remained unchanged until the reperfusion phase. At that time a significant increase in the extracellularly released phagocytic proteinase cathepsin B was evident. EPI plasma levels increased steadily for up to 60 minutes after reperfusion. At the end of the observation period the plasma concentrations of both phagocytic enzymes—especially of EPI—were significantly greater than the preoperative levels (Fig 1). TAT level slowly increased during the anhepatic phase but showed a highly significant increase, reaching its maximal level 15 to 60 minutes after reperfusion followed by a decrease to the preoperative level 12 hours after reperfusion (Fig 1).

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DISCUSSION

Flushing of the liver graft removes most, but not all, of the preservation fluid. This is demonstrated by the decreased levels of coagulation proteins in the perfusate compared with those in the systemic circulation. On the other hand, significantly elevated levels of phagocytic proteinases, well known as potent inflammatory mediators, were found in the perfusate, and they may enter the systemic circulation. Cathepsin B is an effective lysosomal cysteine proteinase of broad specificity, without an adequate inhibitory potential in plasma.[1] The release of cathepsin B from the liver macrophages, reflected by the excessive elevation in the perfusate, results in a steep and sustained increase in cathepsin B activity in plasma. Therefore, cathepsin B may play an important role in the activation and consumption of plasma factors and may be responsible for the decompensation of preexisting low-grade DIC. Elastase, a lysosomal proteinase from granulocytes,[2] may be released from such cells still sticking in the liver graft vessels. On the other hand, the protracted increase in EPI may reflect an ongoing inflammation response of leukocytes entering the operative field and liver graft. Activation of the coagulation system, demonstrated by the highly significant increases in TAT (Fig 1) and fibrin monomers and D-dimer (not shown), as well as the pronounced decrease in the activities of the coagulation inhibitors, is consistent with the hypothesis that the coagulation system becomes further activated by mediators released from the liver graft.

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