An Increase in Plasma Concentrations of Granulocyte Elastase during and after Bench Surgery of the Liver

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Elastase released from granulocytes has been shown to be involved in a variety of disorders: adult respiratory distress syndrome, sepsis, disseminated intravascular coagulation and ischemia/reperfusion injuries[1–5]. the involvement of granulocytes in reperfusion injuries has been established in almost all organs including the liver[6]. A primary non-function of grafts, which still disturbs successful orthotopic liver transplantation, has been thought to be partly caused by an activation of granulocytes, resulting in a production of active oxygen and a release of proteases[6]. Riess et al. reported changes in plasma granulocyte elastase concentration in 10 patients undergoing liver transplantation[7]. They observed an abrupt rise in granulocyte elastase concentration in plasma after reperfusion. We measured granulocyte elastase concentration in the plasma of a patient undergoing bench surgery of the liver for a metastatic liver tumor.

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Case Report

A 49-yr-old woman (155 cm, 54 kg) underwent abdominoperineal resection for rectal cancer five years ago. A metastatic mass which occupied almost the whole right lobe of the liver beside the portal vein was found. Laboratory tests showed normal liver function except for serum γ-glutamyltranspeptidase of 105 IU$\cdot l^{-1}$ (normal range 5-55 IU$\cdot l^{-1}$). A bench surgery was planned. Anesthesia was induced by thiamylal and pancuronium, and was maintained by diazepam 18 mg, fentanyl 2.2 mg and isoflurane 0.8–2.0%. Dopamine at a rate of 3 μg$\cdot$kg$^{-1}\cdot$min^{-1} and prostaglandin E_1 (Prostandin 500®, Ono Pharmaceutical Co. Ltd., Osaka, Japan) at a rate of 14 ng$\cdot$kg$^{-1}\cdot$min^{-1} were infused intravenously to maintain hepatic blood flow. Urinastatin (Miraclid®, Mochida Pharmaceutical Co. Ltd., Tokyo, Japan), 200,000 U was administered intravenously about 4 hours before the removal of the liver. During the anhepatic period, blood from the right femoral vein and the portal vein

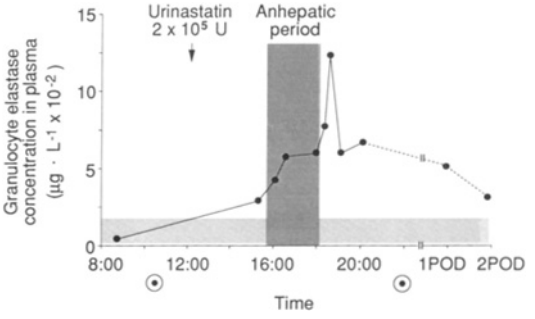

Fig. 1. The changes in plasma concentrations of granulocyte elastase during and after bench surgery of the liver.

The changes in plasma concentrations of granulocyte elastase in a 49-yr-old woman undergoing bench surgery of the liver for a metastatic liver tumor. See text for details of the patient profile, anesthetic management, and operative procedures. Blood samples were taken through a radial arterial cannula, and the concentrations of plasma granulocyte elastase were measured by radio-immunoassay. Heavily and lightly shaded areas indicate the anhepatic period and the normal range of plasma granulocyte elastase, respectively. ◎, the start and the end of operation; 1POD and 2POD, the first and the second post-operative day, respectively.

was diverted to the left axillary vein via Anthron tubes and a biopump. The anhepatic time and the operation time were 157 min and 12.3h, respectively. Blood loss was estimated to be around 3,000g. Human plasma protein fraction (Plasmanate-Cutter®, Bayer, Germany) 3,000 ml, fresh frozen plasma, 700g, fresh whole blood 2,000g, and packed red cells, 700g were infused or transfused during the operation. She recovered satisfactorily, and was discharged a month later. Blood samples were taken through a radial arterial cannula, and the concentrations of plasma granulocyte elastase were measured by radio-immunoassay using the MERCK Immunoassay (Merck, New Jersey). This assay is not affected by the presence of protease inhibitors.

Results and Discussion

The granulocyte elastase consentration in the plasma, which was within normal range before the operation, increased during and after the operation (fig. 1). The elastase concentration had increased before the removal of the liver, and further increased during the anhepatic period. Just after the reimplantation of the liver, the elastase concentration increased sharply, and it returned to the levels observed at the end of the anhepatic period within an hour. It was followed by a slow reduction through the second post-operative day (2POD).

The observed rise in the elastase concentration seemed to be caused by at least three factors: (i) a nonspecific increase associated with surgical trauma[8,9]; (ii) an increase associated with extracorporeal circulation such as cardio-pulmonary bypass[10]; and (iii) an increase induced by reperfusion[5]. Another possible cause of the increase during the anhepatic period is that the elimination of elastase is suppressed due to the absence of the liver and the hepatic reticuloendothelial system. The abrupt increase just after the anhepatic period might be caused by a reperfusion-induced activation of granulocytes. The prompt decline of the elastase concentration after the reperfusion-induced abrupt increase, which coincides with the observation by Riess et al.[7], might reflect a restoration of the hepatic functions. The exact contribution of the liver to the elimination of circulating elastase, however, has not been elucidated. It is also possible that an infusion of plasma protein fraction and blood transfusion has contributed to the observed increase in elastase concentration to some extent. Although endotoxemia, which is expected to activate granulocytes, is reported to be associated with liver transplantation[11], endotoxin was

not detected in plasma from our patient through the 2POD (not shown).

Although alpha$_1$-antitrypsin, an elastase inhibitor, is present abundantly in plasma and its plasma half life has been reported to be 5–6 days[12], its production in the liver and its influx into plasma might be suppressed after bench surgery of the liver or liver transplantation as well as partial hepatectomy[13]. Therefore, a prophylactic administration of urinastatin, a urinary trypsin inhibitor, seems a reasonable precaution to lessen damage to organs including the liver[13]. Elastase directly destroys cellular and interstitial architecture, and modifies a wide variety of enzymes. For example, elastase has been shown to mediate a conversion of xanthine dehydrogenase to oxidase in endothelial cells[14], resulting in deterioration of the overproduction of active oxygen.

In summary, the concentration of granulocyte elastase in plasma was increased during and after bench surgery of the liver. Many factors such as extracorporeal circulation, excision of the liver, ischemia/reperfusion injury of the liver seem to be responsible for this rise. Pharmacological management of the released elastase is recommended in bench surgery of the liver as well as in hepatectomy.

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