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# COAGULATION AND FIBRINOLYSIS IN PIGS DURING EXTRACORPOREAL LIVER PERFUSION

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The authors studied disorders of the blood clotting system and fibrinolysis in pigs, the systemic circulation of which was utilized for perfusion of isolated and previously stored heterogenic livers. Despite of administration of large dises of heparin, the phenomenon of hypercoagulability was observed in the initial period of perfusion. This phase of hypercoagulability resulted in secondary thrombocytopenia and fibrinogenopenia.

One of the most important problems in liver transplantation is coagulation and fibrinolysis disturbances with their clinical sequelae of uncontrollable bleeding (2). Laboratory studies reveal a consumption of coagulation factors, low platelet count, and activation of fibrinolysis. These changes occur as a consequence of increased consumption of coagulation factors and increased fibrinolysis. Their magnitude depends on the function of the transplanted liver (6), and duration of its preservation (7).

The most convenient experimental model for studies of coagulation and fibrinolysis disturbances dependent on liver function is the isolated perfused liver.

In our presentation coagulation and fibrinolysis studies were carried out on extracorporeal porcine liver previously preserved for 3 hours in hypothermia.

## METHODS

The techniques of liver preservation and extracorporeal perfusion were described previously (5). Heparin in a dose of 4 mg/kg was administered intravenously prior to perfusion. The following determinations were performed during perfusion: fibrinogen level, platelet count, and euglobulin lysis time (3) every hour, thrombin clotting time (above 40 u/ml) every 10 minutes. The amount of thrombin used for coagulation studies was adjusted so as to give

the clotting time immediately after heparinization around 5 minutes. Without thrombin, blood clotting time was above 30 minutes. Fifty mg of heparin were administered immediately when thrombin clotting time tended to decrease. In cases of increased fibrinolytic activity fibrinolysis inhibitors were given intravenously. These were EACA 0·1 g/kg, and AMCHA 20 mg/kg.

## RESULTS

Figs 1 and 2 illustrate the average results obtained in five experiments with 3 hr preservation and 3 hr normothermic perfusion, and three experiments with 3 hr preservation followed by 6 hr perfusion. In two cases in which only 4 mg/kg of heparin were given hypercoagulability was observed between the 30th and 60th minute of perfusion, followed 1—2 hours later by hemorrhagic diathesis with fatal bleeding of the animal. During the state of hypercoagulability many clots were found in the tubings, there was also a sharp decrease in blood clotting time. These observations led to more careful hematological studies during the experiment with thrombin clotting time determination every 10 minutes, and heparin administration immediately when a decrease in clotting time was observed. In all cases high plasma anti-heparin activity was found. Clinically heparin had a tendency to disappear from the circulation, and this resulted in low thrombin clotting time. The amount of heparin administered during every experiment is shown on Fig. 1.

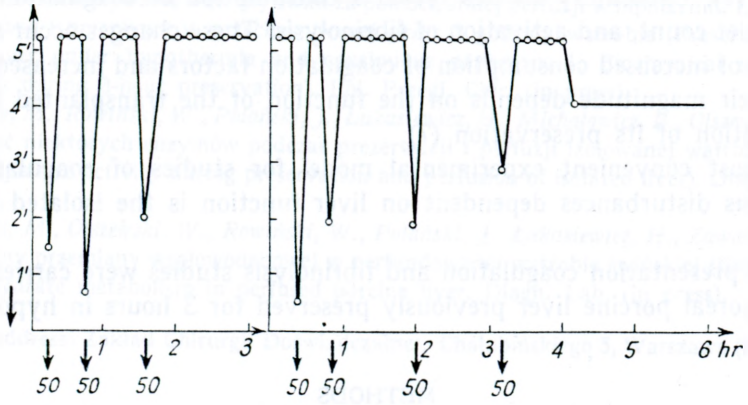


Fig. 1. Thrombin clotting time during extracorporeal liver perfusion.

A tendency toward thrombocytopenia and fibrinogenopenia was observed in course of every perfusion (Fig. 2). That decrease in platelet count and fibrinogen level was accentuated mostly in the first hour of perfusion. Increased fibrinolytic activity was usually seen in the 2nd or 3rd hour of the experiment,

with a decrease of euglobulin lysis time to 90 minutes. In all experiments with perfusion lasting for 6 hr bleeding from the porto-caval shunt, abdominal wall and nasal mucosa were observed.

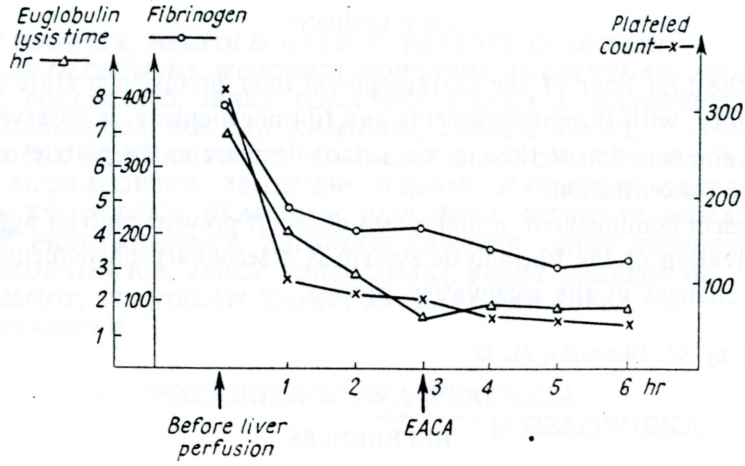


Fig. 2.

## DISCUSSION

Increased plasma anti-heparin activity was found in all cases of extracorporeal liver perfusion. This was probably caused by platelet trapping in the isolated liver with an abundant release of platelet factor 4 (4). Anti-heparin platelet factor is responsible for the decrease of fibrinogen concentration, its consumption during the process of paracoagulation, for the decreased platelet count, and low clotting time. The same changes in the blood coagulation system were observed in rabbits after intravenous injection of the purified platelet factor 4 (1). Administration of heparin even in high doses, does not protect against platelet trapping and aggregation.

The extent of coagulation and fibrinolysis changes in the animal perfusing the isolated liver depends on the function of that liver, blood flow through the liver, blood pressure, hypoxia, acidosis etc.

In the initial phase of hypercoagulation a substantial decrease of fibrinogen level and platelet count is usually observed. This is more pronounced during the following hours of perfusion. Increased fibrinolytic activity is recognized only after 2—3 hours of perfusion. It seems to be a secondary phenomenon caused by the transfusion of blood and electrolytes, and prolonged anesthesia. Administration of fibrinolysis inhibitors has some effect on the activation of the fibrinolytic process. The mechanism of coagulation disturbances during isolated

liver perfusion is a complex one. The intravascular coagulation which takes place during the first hour of perfusion leads to a state of consumption coagulopathy. Activation of the fibrinolytic process and also circulating fibrinogen split products have some more untoward effect on the mechanism of coagulation.

## CONCLUSIONS

1. In the first hour of the extracorporeal liver perfusion a state of hypercoagulability, with thrombocytopenia and fibrinogenopenia, is observed. In the course of the experiment there is a constant decrease in the platelet count and fibrinogen concentration.
2. Heparin administered in high doses does not prevent platelet aggregation.
3. Activation of the fibrinolytic system is a secondary phenomenon leading to more changes in the coagulation process.

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